SURVEY ON PRESCRIPTION FREQUENCY OF SITAGLIPTIN AS AN ANTIDIABETIC AGENT IN HOSPITAL OF BANGLADESH

A dissertation submitted to the Department of Pharmacy, East West University in the partial fulfillment of the requirements for the Degree of Masters of Pharmacy.

Submitted By

Syed Sohidul Haque Shovon
ID: 2013-3-79-027

Submitted To

Md. Anisur Rahman
Senior Lecturer

Department of Pharmacy

East West University

SURVEY ON PRESCRIPTION FREQUENCY OF SITAGLIPTIN AS AN ANTIDIABETIC AGENT IN HOSPITAL OF BANGLADESH

A dissertation submitted to the Department of Pharmacy, East West University in the partial fulfillment of the requirements for the Degree of Masters of Pharmacy.

Submitted By

Syed Sohidul Haque Shovon
ID: 2013-3-79-027

Submitted To

Md. Anisur Rahman
Senior Lecturer

Department of Pharmacy

East West University

DECLARATION BY THE RESEARCH CANDIDATE

I, Syed Sohidul Haque Shovon, ID: 2013-3-79-027, hereby declare that the dissertation entitled "**SURVEY ON PRESCRIPTION FREQUENCY OF SITAGLIPTIN AS AN ANTIDIABETIC AGENT IN HOSPITAL OF BANGLADESH**'' submitted by me to the Department of Pharmacy, East West University and in the partial fulfillment of the requirement for the award of the degree Masters of Pharmacy, under the supervision and guidance of Md. Anisur Rahman, Senior Lecturer, Department of Pharmacy, East West University, Dhaka, Bangladesh.

Syed Sohidul Haque Shovon

ID: 2013-3-79-027

Department of Pharmacy

East West University

Dhaka, Bangladesh.

CERTIFICATION BY THE SUPERVISOR

This is to certify that the dissertation entitled ‘‘**SURVEY ON PRESCRIPTION FREQUENCY OF SITAGLIPTIN AS AN ANTIDIABETIC AGENT IN HOSPITAL OF BANGLADESH**’’ submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Bachelor of Pharmacy is a bonafied record of original and genuine research work carried out by **Syed Sohidul Haque Shovon**, ID: 2013-3-79-027 under my supervision and guidance.

——————————————

Md. Anisur Rahman

Senior Lecturer

Department of Pharmacy

East West University

Dhaka, Bangladesh

ENDORSEMENT BY THE CHAIRPERSON

This is to certify that the dissertation entitled ‘‘**SURVEY ON PRESCRIPTION FREQUENCY OF SITAGLIPTIN AS AN ANTIDIABETIC AGENT IN HOSPITAL OF BANGLADESH**’’ submitted to the Department of Pharmacy, East West University for the partial fulfillment of the requirement for the award of the degree Masters of Pharmacy is a bonafied record of original and genuine research work carried out by **Syed Sohidul Haque shovon**, ID: 2013-3-79-027, under the supervision and guidance of **Md. Anisur Rahman**, Senior Lecturer, Department of Pharmacy, East West University and no part of this project has been submitted to other degree.

Shamsun Nahar Khan, Ph. D

Chairperson & Associate Professor

Department of Pharmacy

East West University

Dhaka, Bangladesh

Acknowledgement

First, all praise and glory are to ALLAH for all the bounties granted to me and only with His guidance and help this achievement has become possible.

I would like to express my deepest gratitude to my supervisor and respected teacher, **Md. Anisur Rahman,** Senior Lecturer, Department of Pharmacy, East West University, for his constantsupervision, intense support, enthusiastic encouragements and constructive criticism during the research work. His timely advice and encouragement have made it possible for me to accomplish the task as per schedule.

I put forward my most sincere regards and profound gratitude to **Dr. Shamsun Nahar Khan, Chairperson & Associate Professor**, Department of Pharmacy, East West University, forher inspiration in my study. She also paid attention for the purpose of my research work and extending the facilities to work.

I am also expressing my gratitude to my honorable teacher **Dr. Repon Kumer Saha**, Assistant Professor, Department of Pharmacy for his help and guidance.

I want to give special thanks to all of my friends and juniors, who gave me support for my research work and for their extended cooperation for my study.

I express my sincere thankfulness to my family for guiding me all through my life, including that for my research project.

This Research paper is

Dedicated

To my beloved Parents

Table of Content

List of Content	Page No.
List of Tables	I
List of Figures	I-II
List of Abbreviations	II
Abstract	III
CHAPTER ONE: INTRODUCTION	2-18
Overview	2
Some terminologies	3
Classification	3
Type 1 Diabetes Mellitus	3
Type 2 Diabetes Mellitus	3
Diabetes Insipidus	5
Gestational Diabetes Mellitus (GDM)	6
Signs and Symptoms of Diabetes Mellitus	7
Management of Diabetes Mellitus	8
Sitagliptin	14
History of Sitagliptin	14
Mechanism of action of Sitagliptin	15
Indications of Sitagliptin	16
Pharmacokinetic profile of sitagliptin	17
Brand Name of Sitagliptin in Bangladesh	18
CHAPTER TWO: LITERATURE REVIEW	19-32
Clinical trials	20

CHAPTER THREE: METHODOLOGY	
Research design	34
Material and methods	34
Procedure	34
CHAPTER FOUR: RESULTS	
Prescription percentage of anti-diabetic drugs in Bangladesh	37
Prescription percentage of Insulin for diabetic patients	38
Prescription percentage of DPP-4 inhibitors for diabetic patients	38
Prescription percentage of anti-diabetic drugs of different companies in Bangladesh	39
DPP-4 inhibitors vs other anti-diabetic drugs prescription percentage in Bangladesh Percentage of prescription of DPP-4 inhibitors vs combination of anti-diabetic agents	40
Prescription percentage of Metformin Hcl vs Sitagliptin	41
Prescription percentage of Sitagliptin vs other combination of anti-diabetic agents in Bangladesh	43
Prescription percentage of Sitagliptin and Linagliptin in Bangladesh Prescription percentage of Insulin vs oral anti-diabetic agents in Bangladesh	43

CHAPTER FIVE: DISCUSSION **44-45**

CHAPTER SIX: CONCLUSION **46-47**

CHAPTER SEVEN: REFERENCES **48-54**

CHAPTER EIGHT: ANNEXURE **55**

List of Figures

Prescription percentage of anti-diabetic drugs in Bangladesh	37
Prescription percentage of Insulin for diabetic patients	38
Prescription percentage of DPP-4 inhibitors for diabetic patients	38
Prescription percentage of anti-diabetic drugs of different companies in Bangladesh	39
DPP-4 inhibitors vs other anti-diabetic drugs prescription percentage in Bangladesh Percentage of prescription of DPP-4 inhibitors vs combination of anti-diabetic agents	40
Prescription percentage of Metformin Hcl vs Sitagliptin	41
Prescription percentage of Sitagliptin vs other combination of anti-diabetic agents in Bangladesh	43
Prescription percentage of Sitagliptin and Linagliptin in Bangladesh Prescription percentage of Insulin vs oral anti-diabetic agents in Bangladesh	43

List of Abbreviation

ADA	American Diabetes Association
AFN	Assembly of First Nations
CDA	Canadian Diabetes Association
FNW	First Nation Women
GDM	Gestational Diabetes Mellitus
GCT	Glucose Challenge Test
HAPO	Hyperglycemia and Adverse Pharmacy Outcomes
MODY	Maturity Onset Diabetes of the Young
NIDDM	Non Insulin Dependent Diabetes Mellitus
OGTT	Oral Glucose Tolerance Test
PCOS	Polycystic Ovary Syndrome
RCTs	Randomized Controlled Trials
T2D	Type 2 Diabetes

WHO World Health Organization

ABSTRACT

Diabetes is a very common disease among the adult people in Bangladesh now-a-days. This is becoming the major cause of death and disability. To treat diabetes different antidiabetic drugs prescribed by the doctors and prescribers. The purpose of this study was to determine the frequency of use of Dipeptidyl-peptidase inhibitor (DPP-4 inhibitors) in the prescription by the doctors. Doctors are not so convinced and familiar with this class of antidiabetic drugs. Therefore, this class specially Sitagliptin, Linagliptin and Vildagliptin require more promotion to increase its market. Another objective was to determine whether this new class of drug is required or the older class is enough to fill up the requirements of the diabetic patients. To work on these two objectives, a survey was performed by collecting 500 prescriptions from Bangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM), Dhaka.

Key Words: Diabetes, Dipeptidyl-peptidase inhibitor (DPP-4 inhibitor), Sitagliptin, Linagliptin, Vildagliptin, BIRDEM.

CHAPTER 1

INTRODUCTION

INTRODUCTION

Overview: Diabetes mellitus is a leading cause of death and disability around the world. Diabetes has recently become a major public health issue in our country. There are different types of diabetes such as- type-1, type-2 & diabetes insipidus. For the treatment of type-1 diabetes insulin is used and there are so many oral anti-diabetic agents which are used to treat type-2 diabetes like: Metformin, Vildagliptin, Linagliptin, Sitagliptin etc. Older molecules or generics are more likely to be prescribed by the physicians till now. But, in recent times it is seen that DPP-4 inhibitors (Sitagliptin, Saxagliptin, Linagliptin, Vildagliptin) are prescribed by the physicians. Here, it can be mentioned that these newer molecules are discovered around 2005 and marketed in Bangladesh after 2010. The objective of our survey is to analyze how frequently these newer generics (like: Vildagliptin, Linagliptin & Sitagliptin) are prescribed by the physicians for the patients who is suffering from diabetes. Another objective of this survey is to observed wheather these newer molecules are required to treat the patients suffering from diabetes or the older molecules are sufficient enough to treat these patients?. My focus for analysis is on the generic Sitagliptin. For this purpose 500 prescription data is collected from the outpatients of BIRDEM hospital with the prior approval from hospital authority. Then these prescription data is analyzed.

Diabetes Mellitus: (McCance*et al*., 1994, Metzger*et al*., 2010)

A heterogeneous group of disorders characterized by high blood glucose levels. A metabolic disorder with hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Chronic hyperglycemia involves with the disturbances of carbohydrate, fat and protein metabolism.

Pancreas which is located between the stomach and spine, it helps in digestion of food and releases a hormone named insulin into the blood. Insulin helps the blood for carrying glucose to the cells. Sometimes the body doesn't make enough insulin or the insulin cannot work properly. Glucose then stays in the blood and doesn't reach within the cells. The blood glucose levels get too high called hyperglycemia and the cells do not get sufficient glucose which causes diabetes. The young diabetic patients with no cardiovascular disease is prescribed DPP-4 inhibitors

without any doubt. Patients with cardiovascular problem or heart failure are prescribed DPP-4 inhibitors with caution.

Some terminologies: (Eschewege *et al*., 2000)

- **Normoglycemia:**
  Normal blood glucose regulation
- **Impaired Fasting Glucose:**
  Describes the difference between the upper limit of normal fasting plasma glucose and the lower limit of the diabetic fasting plasma glucose.
- **Impaired Glucose Tolerance:**
  Involves muscle insulin resistance and defective insulin secretion

  Insulin Resistance:
  A condition in which the body cannot use insulin properly alto sufficient amount of insulin is produced. It can lead to type 2 diabetes due to the destruction of the beta cells of pancreas, they fail to keep up with the body's increased need for insulin. Excess glucose builds up in the bloodstream without enough insulin, leading to diabetes, prediabetes, and other serious health disorders.

Classification

Type 1 Diabetes Mellitus: (Genuth *et al*., 2003)

An autoimmune disease,body's own immune system attacks and destroys the beta cells. This type involves the processes of beta–cell destruction, which results in absolute insulin deficiency. It occurs at the age of less than 30 years.This is also called insulin dependent diabetes or juvenile diabetes mellitus.

Different symptoms with elevated blood glucose levels will develop. If it is not diagnosed properly, ketoacidosis may occur.

Type 2 diabetes: (Fagot et al., 2000)

It is the most common form of diabetes. Type 2 diabetes is often undiagnosed and sometimes when a patient consult with doctor for another medical problems or for the eye or physical examination, suddenly it appeared. diabetes develops most often in middle-aged and older people who are also overweight or obese. It is also called non-insulin dependent diabetes mellitus (NIDDM).

Causes:

- I**nsulin resistance**: when body do not use insulin properly although sufficient quantity of insulin is produced
- Sometimes body cannot produce sufficient quantity of insulin.

Risk Factors:

- Age 45 or older
- Overweight or obese
- Physically inactive
- Family background
- History of gestational diabetes
- High blood pressure: 140/90 or above
- High-density lipoprotein (HDL) level

Table 1: Clinical Features of Type 1 and Type 2 diabetes mellitus (Genuth *et al*., 2003, Ozougwu *et al*., 2013)

Features	Type 1	Type 2
Onset of action	Usually less than 20 years. Acute and symptomatic	Usually greater than 30 years. Slow and often asymptomatic
Clinical picture	Weight loss, polyuria, polydipsia	Obesity, Strong family background, Ethnicity – high prevalence Populations,
Ketoacidosis	Almost always present	Usually absent

Associated auto-immune diseases	Yes	No
Insulin sensitivity Normal Reduced	Normal Reduced	Reduced
Treatment	Insulin invariably	Food habit, lifestyle,drugs such asthiazolidinediones, metformin, sulfonylureas, or insulin

Diabetic insipidus (DI): (Khardori, 2014) Droumaguet *et al*., 2006)

Diabetes insipidus (DI) is a rare disease that causes frequent urination.This is a disease in which large volumes of dilute urine (polyuria) are excreted.Polyuria is characterized by a urine volume in excess of 2 l/m 2 /24 h or approximately 150 ml/kg/24 h at birth, 100–110 ml/ kg/24 h until the age of 2 years and 40–50 ml/kg/24 h in the older child and adult.

Causes:

- Vasopressin deficiency
- AVP (Arginine Vasopressin) resistance
- Excessive water intake (primary polydipsia)

Symptoms:

- Quickly become dehydrated if they do not drink enough water.
- Children with DI may be irritable
- May have fever, vomiting, or diarrhea.

Treatment:

- Milder forms of DI can be managed by drinking enough water, usually between 2 and 2.5 liters a day.
- ADH substitute to see if the kidneys respond by concentrating the urine volume

Gestational Diabetes: (Landon*et al*., 2009)

It is a form of glucose intolerance diagnosed during the second or third trimester of pregnancy. The third type of diabetes exists which affects only women and is called gestational diabetesmellitus (GDM). During pregnancy, increasing blood glucose levels increase therisk for both mother and fetus and require treatment to reduce problems for the motherand infant. Treatment may include diet, regular physical activity, or insulin.

Causes of Gestational Diabetes Mellitus:(Oster et al., 2009)

Almost all women have some degree of impaired glucose intolerance as a result ofhormonal changes that occur during pregnancy. That means that their blood sugar may be higher than normal, but not high enough to have diabetes. During the third trimester ofpregnancy, these hormonal changes place pregnant woman at risk forgestational diabetes. During pregnancy, increased levels of certain hormones made in theplacenta (the organ that connects the baby by the umbilical cord to the uterus) help shiftnutrients from the mother to the developing fetus. Other hormones are produced by theplacenta to help prevent the mother from developing low blood sugar. They work byresisting the actions of insulin.Over the course of the pregnancy, these hormones lead to progressive impaired glucoseintolerance (higher blood sugar levels). To try to decrease blood sugar levels, the bodymakes more insulin to get glucose into cells to be used for energy. Usually, the mother'spancreas is able to produce more insulin (about three times the normal amount) toovercome the effect of the pregnancy hormones on blood sugar levels. If, however, thepancreas cannot produce enough insulin, blood sugar levels will rise, resulting in gestational diabetes.

Risk Factors:(Godwin *et al*., 1999)

Mild insulin resistance is very normal in the third trimester of pregnancy.

1. Family history of diabetes.
2. High birth weight baby (weighing over 8 pounds).
3. Increases with age and is highest for women 35 years old and older.

4. Obesity.
5. Use of corticosteroids (i.e. drugs used for arthritis).
6. History of polycystic ovary syndrome.

Signs and symptoms of Diabetes Mellitus:(Kelly, 2001)

The most common signs and symptoms of diabetes are:

- Frequent urination
- Excessive thirst
- Disproportionate thirst
- Intense hunger
- Weight gain
- Unusual weight loss
- Increased fatigue
- Irritability
- Blurred vision
- More skin and/or yeast infections

Diagnosis of diabetes

Methods and criteria

With diabetic symptoms: (Metzger *et al.*, 2008)

a random venous plasma glucose concentration ≥ 11.1 mmol/l or a fasting plasma glucose concentration ≥ 7.0 mmol/l (whole blood ≥ 6.1 mmol/l) or two-hour plasma glucose concentration ≥ 11.1 mmol/l two hours after 75g anhydrous glucose in an oral glucose tolerance test (OGTT).

Without symptoms:

Diagnosis should not be based on a single glucose determination but requires confirmatory plasma venous determination. At least one additional glucose test result on another day with a value in the diabetic range is essential, either fasting, from a random sample or from the two-

hour post glucose load. If the fasting random values are not diagnostic the two-hour value should be used.

Diagnosis criteria for Gestational diabetes:

The criteria for diagnosing gestational diabetes is different. Gestational diabetes should be diagnosed if the woman has either:

A fasting plasma glucose level of 5.6mmol/l or above or a 2-hour plasma glucose level of 7.8mmol/l or above.

Haemoglobin A1c (HbA1c) testing to diagnose diabetes: (Edelman *et al*., 2004)

An HbA1c of 48mmol/mol (6.5%) is recommended as the cut off point for diagnosing diabetes. A value of less than 48mmol/mol (6.5%) does not exclude diabetes diagnosed using glucose tests.

Finger-prick HbA1c should not be used unless the methodology and the healthcare staff and facility using it can demonstrate within the national quality assurance scheme that they match the quality assurance results found in laboratories. Finger prick tests must be confirmed by laboratory venous HbA1c in all patients.

In patients without symptoms of diabetes the laboratory venous HbA1c should be repeated. If the second sample is <48mmol/mol (6.5%) the person should be treated as at high risk of diabetes and the test should be repeated in 6 months or sooner if symptoms develop.

Patients whose HbA1c is under 48 mmol/mol: (Pradhan *et al*., 2007)

These patients may still fulfill WHO glucose criteria for the diagnosis of diabetes

WHO glucose testing is used in patients who have symptoms of diabetes or clinically are at very high risk of diabetes. The use of such glucose tests is not recommended routinely in this situation

Management of diabetes: (Knowler *et al*., 2002)

Healthy Food Habit:

- Breads, cereals, rice, and whole grains
- Fruits and vegetables

- Meat and meat substitutes
- Dairy products
- Healthy fats

Monitoring of blood glucose level:

- Prior to meals and snacks
- Occasionally postprandially
- At bedtime
- Prior to exercise
- When low blood glucose is suspected
- After treating low blood glucose until normoglycemic
- Prior to critical tasks (e.g. driving)

Self-care:

- Checking blood glucose level regularly
- Try to maintain lower blood glucose levels.
- Physical exercise such as walking at least 30 minutes every day
- Preventing muscle soreness after physical activity

Table 2: Goals for optimal management (Fuchs*et al*., 2009)

Diet	Normal healthy eating. If concerns regarding cardiovascular risk, advise Mediterranean diet.
Body mass index (kg/m²)	Therapeutic goal is 5–10% loss for people overweight or obese with type 2 diabetes. With BMI >35 and comorbidities or BMI >40, greater weight loss measures should be considered. Note that BMI is a difficult parameter to standardise between different population groups.
Physical activity	At least 30 minutes of moderate physical activity on most if not all days of the week (total ≥150 minutes/week).
Cigarette consumption	0 (per day)
Alcohol consumption	≤2 standard drinks (20 g) per day for men and women.
BGL	6–8 mmol/L fasting and 8–10 mmol/L postprandial. Ongoing self-monitoring of blood glucose is recommended for people with diabetes using insulin, with hyperglycaemia arising from illness, with haemoglobinopathies, pregnancy or other conditions where data on glycaemic patterns is required. Routine self-monitoring of blood glucose in low-risk patients who are using oral glucose-lowering drugs (with the exception of sulphonylureas) is not recommended.
HbA1c (mmol/mol; %)	Needs individualisation according to patient circumstances. Generally: • ≤53 mmol/mol (range 48–58) • ≤7% (range 6.5–7.5). Allowing for normal variation in test accuracy, HbA1c results which range between 6.5 and 7.5% would reflect this goal.
Total cholesterol (mmol/L) <4.0	Initiation of pharmacotherapy is dependent on the assessment of absolute cardiovascular risk (Refer to the Australian absolute CVD risk calculator). This requires using multiple risk factors, which is considered more accurate than the use of individual parameters. Once therapy is initiated the specified targets apply; however, these targets should be used as a guide to treatment and not as a mandatory target.
HDL-C (mmol/L) ≥1.0	
LDL-C (mmol/L) <2.0	
Non-HDL-C (mmol/L) <2.5	
Triglycerides (mmol/L) <2.0	
Blood pressure (mmHg) 130/80	
Urinary albumin excretion	Timed overnight collection (mcg/min): <20 Spot collection (mg/L): <20 Urinary albumin-to-creatinine ratio • Women (mg/mmol): <3.5 • Men (mg/mmol): <2.5
Vaccination	Consider immunisation against influenza and pneumococcal disease, and the dTPa vaccine.

Treatment: (Knowler *et al*., 2002)

Commonly Used Drugs:

- Sulfonylurea
- Insulin
- Thiazolidinedione (TZD)
- Biguanides
- α- Glucosidase inhibitors
- Meglitinides

Newer Drugs:

- GLP-1 receptor agonist (e.g, Exenatide)
- Dipeptidyl peptides -4 (DPP-4) inhibitors (e.g. Sitagliptin, Saxagliptin, Vildagliptin)

Strategy for Antidiabetic Treatment:

- **Oral monotherapy:** Metformin, DPP-4 inhibitors, Sulfonylureas, Glinides, Thiazolidinedione

  (TZD), α- Glucosidase inhibitors

- **Oral Dual Combination Therapy:** Metformin + DPP-4 inhibitors (Sitagliptin)

Metformin + TZD

Sulfonylureas + TZD

Metformin + DPP-4 inhibitors (Sitagliptin)

Metformin + Sulfonylureas

- **Oral Triple Combination Therapy:** Metformin + DPP-4 inhibitors + Sulfonylureas

Metformin +Sulfonylureas + TZD

- **Oral Triple Combination + Basal insulin or + GLP-1 agonist:** Glaring, Levemir, Exenatide

Table 3: Drugs used in type 1 diabetes (Knowler *et al*., 2002)

Pharmacologic therapy	Features
Insulin	• Recommended for most individuals • Treatment with multiple dose insulin injection (3/4 inections/day and prandial insulin) or continuous • Insulin analogs are used to reduce the risk of hypoglycemia • Using sensor augmented low glucose

	suspend threshold pump in patients with frequent nocturnal hypoglycemia
Amylin analog (Pramlintide)	• Delays gastric emptying • Blunts pancreatic secretion of glucagon • Lowers insulin dose • Use only in adults
Investigational agents (Metformin + insulin)	• Reduces insulin requirements

Drugs Used in type 2 Diabetes Mellitus:(Drucker, et al., 2006)

In people with Type 2 Diabetes Mellitus (NIDDM), insulin is indicated in the following situations:

- When diet and oral hypoglycemic drugs fail to control hyperglycemia and achieve
- Therapy targets
- Diabetes during pregnancy when diet alone is inadequate
- When oral hypoglycemic drugs are contraindicated;
- During stressful conditions such as infection and surgery.
- Further guidelines on insulin treatment are included in the section on the management of IDDM (Insulin Dependent Diabetes Mellitus)

Table 4: Drugs used in type 2 diabetes (Crowther *et al*., 2005)

Drugs	Features

Metformin	Preferred initial therapy, if not contraindicated
Insulin therapy with or without other agents	In newly diagnosed diabetic patients with elevated blood glucose level
2nd oral agent is added, GLP-1 receptor agonist, or insulin	If noninsulin monotherapy at maximal tolerated dose does not achieve or maintain A1C target over 3 months

Long-term complications of diabetes: (Pradhan *et al*., 2007)

- **Hypoglycemia:**

If your blood glucose levels drop below 70, you have low blood glucose, also called hypoglycemia.

Table 5: Causes of hypoglycemia (National Institute of Diabetes and Digestive and Kidney Diseases, 2008)

Hypoglycemia	Causes
Below 7mmol/ l	• Taking too much diabetes medicine • Missing or delaying a meal • Being more physically active than usual • Drinking alcoholic beverages

- Retinopathy with potential loss of vision
- Nephropathy leading to renal failure

- Peripheral neuropathy with risk of foot ulcers
- Amputations, and Charcot joints
- Autonomic neuropathy causing gastrointestinal, genitourinary, and cardiovascular symptoms and sexual dysfunction
- Increased incidence of atherosclerotic cardiovascular
- Peripheral, arterial, and cerebrovascular disease
- Hypertension and abnormalities of lipoprotein metabolism

Sitagliptin:(Ahren*et al*., 2005)

A dipeptidyl-peptidase inhibitor (DPP-4 inhibitor) that has recently been approved for the therapy of type 2 diabetes. It is effective in lowering HbA1c, and fasting as well as postprandial glucose in monotherapy and in combination with other oral antidiabetic agents. It stimulates insulin secretion when hyperglycemia is present and inhibits glucagon secretion. In clinical studies it is weight neutral. This article gives an overview of the mechanism of action, the pharmacology, and the clinical efficacy and safety of sitagliptin in type 2 diabetes therapy.

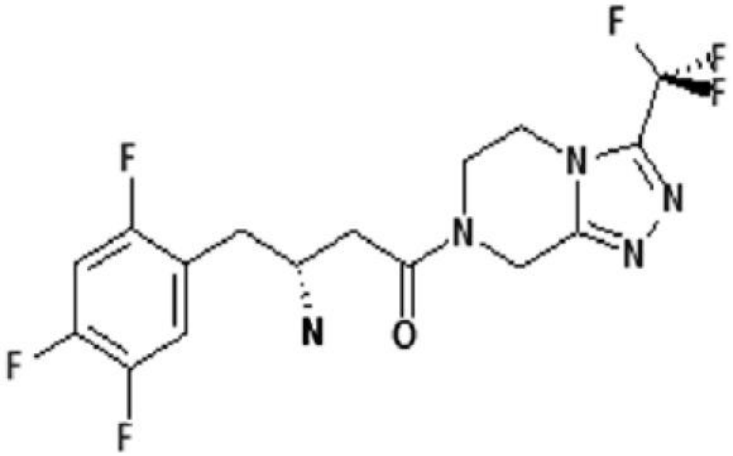


Figure 1: Chemical structure of Sitagliptin (Badyal & Kaur, 2008)

History of Sitagliptin: (Daniel, Chris & Peter, 2007) (Badyal & Kaur, 2008)

In October 2006, the U.S. Food and Drug Administration (FDA) approved Sitagliptin as monotherapy and as add-on therapy to either of two other types of oral diabetes medications,

Metformin or thiazolidinediones to improve blood glucose control in patients with type 2 diabetes when diet and exercise are not enough.

In March, 2007 it was approved in European Union. Sitagliptin is currently approved in 42 countries. The recommended dose of Sitagliptin is 100 mg once daily. It may be taken with or without food. In April, 2007 FDA approved the combination product of Sitagliptin andmetformin for type 2 diabetes.

Mechanism of action: (Dinesh*et al*., 1999)

Sitagliptin prolongs the activity of proteins that increase the release of insulin after blood sugar rises, such as after a meal. Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4), which metabolizes the naturally occurring incretion hormones glucagon-like peptide-1(GLP-1) and glucose dependent insulin tropic polypeptide (GIP) resulting in enhanced glucose dependent insulin secretion from the pancreas and decreased hepatic glucose production. Since GLP-1enhances insulin secretion in the presence of raised blood glucose levels, inhibiting DPPIV

activity will increase and prolong the action of GLP-1 by reducing its rate of inactivation in plasma. Sitagliptin reduces hemoglobin A1C (HbA1c), fasting and postprandial glucose by glucose-dependent stimulation of insulin secretion and inhibition of glucagon secretion. GLP-1 has other widespread effects including delaying gastric emptying, significantly reducing glucagon levels and possible central effects on the appetite.

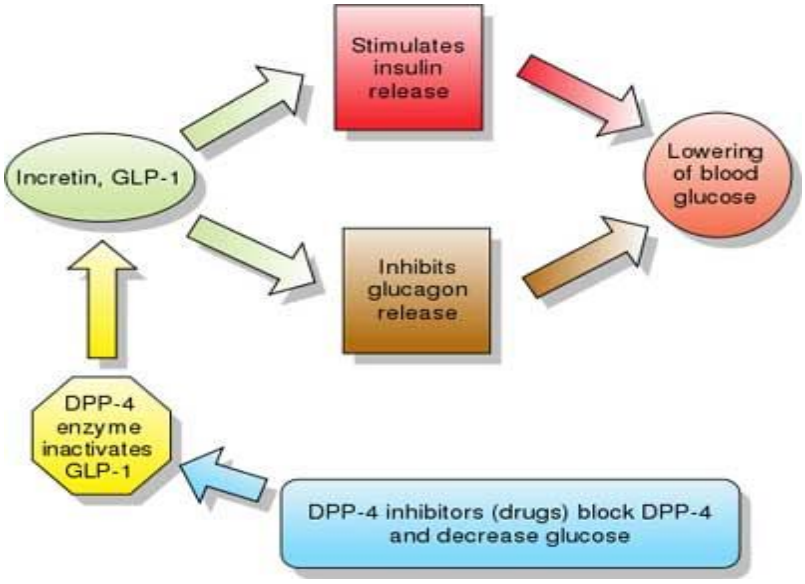


Figure 2: Mechanism of action; DPP-4 (Dipeptidyl-Peptidase) GLP-1(Glucagon like Peptide-1) ((Dinesh *et al.*, 1999)

Indications of Sitagliptin: (Gadsby, 2009)

The use of Sitagliptin is approved in the following medical conditions:

- To improve glycemic control in combination with metformin when diet and exercise plus metformin alone do not provide adequate glycaemic control.
- To improve glycemic control in combination with a sulphonylurea when diet and exercise plus maximal tolerated dose of a sulphonylurea alone does not provide adequate glycemic control and when metformin is inappropriate due to contraindication or intolerance.
- To improve glycemic control in combination with a sulphonylurea and metformin when diet and exercise plus dual therapy with these agents do not provide adequate glycemic control.
- For patients with type 2 diabetes in whom the use of a thiazolidinedione is appropriate,Sitagliptin is indicated
- In combination with the thiazolidinedione when diet and exercise plus the thiazolidinedione agonist alone does not provide adequate glycemic control.

Sitagliptin may be preferable to a thiazolidinedione for the people of

- In whom further weight gain would cause or exacerbate psychological or medical problems associated with high body weight.
- In whom a thiazolidinedione is contraindicated.
- Who have previously had a poor response to or were intolerant of thiazolidinedione Therapy.

Pharmacokinetic profile of Sitagliptin: (White, 2008)

- Bioavailability is approximately 87%
- Half-life is between 8-14 hours
- It is 38% bound to plasma proteins
- It is eliminated through urine

Side Effects:(Bekur *et al*., 2010)

- Nosignificant changes in body weight
- Upper respiratory tract infection
- Stuffy or running nose
- Sore throat
- Headache
- Diarrhea is very rare with sitagliptin

Drug interactions(Reutter, 2002)

- Plasma concentration of sitagliptin may be increased with the interaction of cyclosporine.
- Digoxin plasma levels may be increased slightly
- Care should be taken with drugs that can potentially lower blood sugar such as: Probencid, NSAIDs, MAO inhibitors, β- blockers

Contraindications: (Reutter, 2002)

- Dosage adjustment is needed in patients with moderate or severe renal impairment
- Should be used cautiously during pregnancy
- It is Contraindicated in diabetic ketoacidosis.

Table 6: Brand name of Sitagliptin in Bangladesh (Bergman *et al*., 2002)

Brand Name	Manufacturer/Marketer	Composition	Dosage Form
GLIPITA 100MG	Beximco Pharmaceuticals Ltd	Sitagliptin Phosphate INN eq. to Sitagliptin 100mg	Film Coated Tablet
GLIPITA 50MG	Beximco Pharmaceuticals Ltd	Sitagliptin Phosphate INN eq. to Sitagliptin 50mg	Film Coated Tablet
SIGLITA 100	Square Pharmaceuticals Ltd.	Sitagliptin 100mg (as Sitagliptin Phosphate Monohydrate INN)	Film coated tablet
SIGLITA 50	Square Pharmaceuticals Ltd.	Sitagliptin 50mg (as Sitagliptin Phosphate Monohydrate INN)	Film coated tablet
Sitagil 100	Incepta Pharmaceuticals Limited	Sitagliptin Phosphate INN eq.to Sitagliptin 100mg	Tablet
Sitagil 25	Incepta Pharmaceuticals Limited	Sitagliptin Phosphate INN eq.to Sitagliptin 25mg	Tablet
Sitagil 50	Incepta Pharmaceuticals Limited	Sitagliptin Phosphate INN eq.to Sitagliptin 50mg	Tablet

CHAPTER 2

LITERATURE REVIEW

Survey on prescription frequency of Sitagliptin as an antidiabetic agent in hospital of Bangladesh

DPP-4 inhibitors (Sitagliptin, Saxagliptn, Linagliptn, Vildagliptin) are now currently used as monotherapy or in combination with Metformin or thiazolidinedione or sulfonylurea. The young diabetic patients with no cardiovascular disease is prescribed DPP-4 inhibitors without any doubt. Patients with cardiovascular problem or heart failure are prescribed DPP-4 inhibitors with caution.The purpose of the study on DPP-4 inhibitors is to identify whether this class is required or the previous antidiabetic drugs are sufficient to satisfy the requirements of the diabetic patients with less side effects and more efficacy. In 2006, clinical trials of sitagliptn were practiced on different specific condition. Some trials are performed in combination with other antidiabetic and some are performed alone.Different clinical trials are practiced under specific conditions. Adverse reactions, safety and efficacy are measured through these clinical trials.

Clinical trials:

From January 2005 to August 2011, extensive research was performed with the generic names "sitagliptin", "vildagliptin", "saxagliptin", "alogliptin" and "linagliptin. These trials were performed for 24-26 weeks on 100 type 2 diabetic patients it was considered for 12 weeks. In one trial, type 2 patients who were treated with diet and exercises and in another trial patient treated with metformin, sitagliptin was given in the both type of patients. Both of these trials showed that DPP-4 inhibitors decreased HbAlc (Glycosylated haemoglobin) and also reduced fasting plasma glucose and postprandial glucose levels without inducing hypoglycemic condition, less weight gaining and well tolerability that did not differ from the placebo controlled trial (Fakhoury *et al.*, 2010) (Monami *et al.*, 2011)

Again in 2005, Some interesting features were revealed when type 2 patients were treated with sitagliptin and Metformin combination. Here 100 mg sitagliptin was used and 1000 mg Metformin were used in clinical trial and a mean reduction in HbA1c of 0.6-0.8% was found. This trial exposed that adding any gliptin was superior to a placebo (Scheen *et al.*, 2010)

In 2006, When sitagliptin was compared with Sulfonylureas, reduced HbA1c levels and an increase in the proportion of patients achieving HbA1c levels < 7% (53 mmol/mol) and a remarkable incident of blood glucose level. Generally, sulfonylurea treated patients have a

problem of weight gaining in initial use of drugs but when gliptin was uesd, there was no weight change or even modest weight loss. In the two longest-running trials, secondary increase in HbA1c levels after performing trial of 24 and 104 weeks following a good initial HbA1c reduction. In case of weight gaining, The Sulfonylureas such as glipizide (5-20 mg/day) or glimepiride (1-6 mg/day) was significantly less effective than sitagliptin 100 mg or vildagliptin 100 mg. This trial was performed on 1172 patients.

Again in 2006, When DPP-4 was compared with a Thiazolidinedione (TZD), initial observations suggested that DPP-4 inhibitors may be less potent than TZDs. Three head-to-head trials comparing a DPP-4 inhibitor and TZD such as two with pioglitazone 30 mg and one with rosiglitazone 8mg were performed. Overall, the reduction in HbA1c was similar with the two pharmacological approaches, with a low incidence of hypoglycaemic events. A significant weight increase was observed in all trials with TZDs in contrast to the weight neutrality seen with DPP-4 inhibitors terms of body-weight changes. A significant weight increase was observed in all trials with TZDs in contrast to the weight neutrality seen with DPP-4 inhibitors. The five studied DPP-4 inhibitors have the ability to reduce HbA1c levels by almost 1% and increase the proportion of patients with HbA1c levels < 7% (53 mmol/mol) by 15-20% when they added to pioglitazone but there was increasing hypoglycaemic episodes with minimal weight increases. All these studies compared the effect of adding a DPP-4 inhibitor vs a placebo. Sitagliptin 100 mg and pioglitazone 30 mg trial was performed for 18 weeks on 273 patients. And sitagliptin 100 mg and rosiglitazone 8mg trial was performed for 24 weeks on 514 patients (Rosenstock *et al*., 2007) (De Fronzo *et al*., 2009) (Rosenstock *et al*., 2010)

The team of University of Liège of Belgium performed another trial on vidagliptin 50 mg and acarbose. One trial compared vildagliptin 50 mg with alpha-glucosidase inhibitor such as acarbose (up to 300 mg) and reported similar HbA1c reductions with the two compounds, but some the other trial performed like linagliptin (5 mg/day or l0mg/day) had greater efficacy than voglibose (3 × 0.2 mg/day) in improving glycaemic control. In these both studies, drug-related gastrointestinal disorders were more common with the acarbose, voglibose than with the DPP-4 inhibitors. In case of vildagliptin and acarbose, 661 patients were treated and reduced HbA1c level was 1.3-1.4% and an increase in the proportion of patients achieving HbA1c levels < 7%

(46mmol/mol), and in case of linagliptin and voglibose 481 patients were prescribed (Pan *et al*., 2008) (Kawamori *et al*., 2010).

In 2009, a clinical trial was performed to review the efficacy and safety of sitagliptin and discuss its place in therapy. A team using previous published reviews and papers gathered some information and used the guideline recommendations and discussions for sitagliptin and DPP4 inhibitors. Evidence from a Cochrane review and meta-analysis of 14 trials or study arms suggests that sitagliptin lowers HBA1c by 0.7% in sitagliptin versus placebo trials. Evidence from a pooled safety database of 3415 people taking sitagliptin, and the Cochrane review show that the drug is well tolerated, causes no hypoglycaemia and is weight neutral. No specific signals of concern for the safety of sitagliptin have so far arisen in the pooled database. Guidelines recommend its use in triple therapy with metformin and sulphonylurea in dual therapy with metformin or sulphonylurea or thiazolidinedione in certain circumstances (Gatsby, 2009)

In 2008, a trial of a combination of metformin and saxagliptin as initial therapy for type 2 diabetes. In this multicenter randomized double blind study 1306 treatment naive patients who had uncontrolled T2DM with a HgA1c between 8%–12%. Patients were allocated to one of four treatment arms: saxagliptin 5 mg + metformin 500, saxagliptin 10 mg + metformin 500 mg, saxagliptin 10 mg + placebo, and metformin 500 mg + placebo. Saxagliptn was dosed once daily. Metformin groups had this dose titrated to 1000 mg after one week and this titration continued to a max of 2000 mg daily with split dosing or until the fasting glucose was ,6.11 mmol.L. The initial combined therapy improved HgA1c (-2.5%) as well as fasting and PPG-AUC. The saxagliptin + placebo group saw a 1.7% reduction and the metformin + placebo group had a HgA1c reduction of 2.0%. In addition, 60.3% of patients reached a goal HgA1c ,7%, significantly higher than saxagliptin alone (32.2%) and metformin alone (41.1%) with a P, 0.0001 for combination therapy compared to each monotherapy. Finally, the saxagliptin and metformin combination provided significant improvements in B-cell function (HOMA-2B) compared to saxagliptin alone (P, 0.0001) and metformin alone (P # 0.0004) (Jadinsky *et al*., 2008)

Again in 2008, another trial examined the effect of saxagliptin added to a group individual with poorly controlled type 2 diabetes who were using TZD as monotherapy. Patients on TZD therapy had HbA1c's ≥ 7.0% and ≥10.5% (mean 8.3%). Participant age varied from 18–77 years and included both genders. Results accrued after a TZD 2-week lead in period when patients were randomized to different groups of a dose-response curve of 2.5 mg/d; 5 mg/d, and placebo (PBO) in addition to the background TZD. Patients were treated for 24 weeks on this regimen. Patients randomized to saxagliptin 2.5 mg and 5 mg daily had improvements from baseline in endpoints measured when compared with PBO (i.e, A1C values, AUC for FPG and PPG) and improved oral glucose tolerance and postprandial insulin surges as shown by AUC (area under the curve) modeling for HbA1c and C-peptide. Baseline reductions for 2.5 and 5 mg saxagliptin plus TZD vs. TZD alone were -436 and -514 vs. -149 mmol·in/L, respectively (P, 0.0001 for each comparison between saxagliptin plus TZD vs. TZD monotherapy). Compared to PBO (25.6%), a greater proportion of patients achieved a target HbA1c of ,7% at 24 weeks on saxagliptin (42% at 2.5 mg, P = 0.001; 42% at 5 mg, P = 0.005%). Saxagliptin treatment increased postprandial insulin and C-peptide AUC compared with PBO (P, 0.05) (Jay *et al*., 2011).

In 2010, an another clinical trial was performed with adult type 2 diabetes mellitus patients. 801 patients with glycated haemoglobin (HbA1c) 6.5-10% on stable metformin doses (1500-3000 mg/day) were randomized 1:1 to add-on 5 mg saxagliptin or 100 mg sitagliptin once daily for 18 weeks. The primary efficacy analysis was a comparison of the change from baseline HbA1c at week 18 in per-protocol patients. Non inferiority was concluded if the upper limit of the two-sided 95% confidence interval of the HbA1c difference between treatments was <0.3%. The adjusted mean changes in HbA1c following the addition of saxagliptin or sitagliptin to stable metformin therapy were -0.52 and -0.62%, respectively. The between-group difference was 0.09% (95% confidence interval, -0.01 to 0.20%), demonstrating noninferiority. Both treatments were generally well tolerated; incidence and types of adverse events were comparable between groups. Hypoglycaemic events, mostly mild, were reported in approximately 3% of patients in each treatment group. Body weight declined by a mean of 0.4 kg in both groups. Last ofall it was decided that Saxagliptin combined with metformin therapy was effective in improving glycaemic control in type 2 diabetic patients insufficiently controlled by metformin alone; saxagliptin plus

metformin was no inferior to sitagliptin plus metformin, and was generally well tolerated. (Scheen *et al*., 2010)

Within 2010-2011,this trial was performed on saxagliptin. Some information is taken from American Diabetic Association (ADA) and European Association for the Study of Diabetes (EASD) websites. Two double blind studies were conducted to evaluate the safety and efficacy of saxagliptin as well as to develop pharmacokinetic/pharmacodynamic (PK/PD) data. In the first, subjects age 18–70 years with type 2 diabetes were assigned to one of five dose panels. Within each panel, subjects (n = 6) were randomized to 2.5, 5, 15, 30, or 50 mg of saxagliptin or placebo (n = 2). In the second study, 50 age-matched healthy subjects (HS) were randomized to each of five dose panels. Within each panel, subjects were randomized to a higher dose of saxagliptin 100, 150, 200, 300, or 400 mg, 40 mg saxagliptin or placebo. All subjects underwent laboratory testing, ECG monitoring, and observation for adverse effects. No ECG aberrancies, abnormal labs, or hypoglycemic episodes were observed at any dose exposure. Systemic exposures were dose-proportional and similar on days 1 and 14. PK parameters were comparable between the two study groups (HS and T2DM). Saxagliptin inhibited, in dose-dependent fashion, plasma DPP-4 (pDDP-4) with doses 150 mg a day showing the same levels of inhibition. There was also a dose-related increase of 1.5–3.0 times the plasma GLP-1 concentration due to saxagliptin after breakfast, lunch, and dinner in both groups (T2DM and healthy subjects) on days 13 and 14.32 The authors concluded that saxagliptin was safe and effective at the doses tested. Orally administered saxagliptin at doses from 2.5 to 400 mg a day for 2 weeks were safe, well-tolerated, and effective. (Boulton *et al*., 2007) (Jay *et al*., 2011)

In the same year (2010) there was a 24-week monotherapy study performed, saxagliptin was compared with placebo both as a fixed-dose and with dose titration: quantified as 2.5 mg QAM, 5 mg QAM, 5 mg daily after noon (QPM), and 2.5 mg titrated to 5 mg QAM (2.5/5 mg QAM) in 365 treatment-naive patients with Type 2 diabetes mellitus with inadequate glycemiccontrol (mean baseline HbA1c 7.9%) using diet and exercise. Statistically significant mean changes from baseline HbA1c were seen for 2.5 mg QAM (-0.71%; P = 0.0023), 5 mg QAM (-0.66%; P = 0.0059), 2.5/5 mg QAM (-0.63%; P = 0.0119), and 5 mg QPM (-0.61%; P = 0.0157) vs. placebo (-0.26%). Respective reductions in FPG were -0.63 (P = 0.0204), -0.59 (P = 0.0271), -0.69 (P =

0.0130), -0.44 (P = NS), vs. 0.18 mmol-min/L. The percentages of patients achieving HbA1c ,7% with 2.5 mg QAM, 5 mg QAM, 2.5/5 mg QAM, and 5 mg QPM, vs. placebo were 35.8, 44.9, 43.5, and 38.6% vs. 35.3%, respectively (Mest *et al*., 2010)

In 2011, In clinical trials with the combination of vildagliptin + metformin, 0.4% of patients withdrew due to adverse reactions in the vildagliptin 50 mg once daily + metformin treatment group and no withdrawal due to adverse reactions was reported in either the vildagliptin 50 mg twice daily + metformin or the placebo + metformin treatment groups. In clinical trials, the incidence of hypoglycaemia was uncommon in patients receiving vildagliptin 50 mg once daily in combination with metformin (0.9%), patients receiving vildagliptin 50 mg twice daily in combination with metformin (0.5%) and in patients receiving placebo + metformin (0.4%). No severe hypoglycaemic events were reported in the vildagliptin arms. Vildagliptin is weight neutral when administered in combination with metformin. In combination with glimepiride again in 2011, vildagliptin 50 mg + glimepiride was taken as sample. The overall incidence of withdrawals due to adverse reactions was 0.6% in the vildagliptin 50 mg + glimepiride treatment group versus 0% in the placebo + glimepiride treatment group.In clinical trials, the incidence of hypoglycemia when vildagliptin 50 mg once daily was added to glimepiride was 1.2% versus 0.6% for placebo + glimepiride. No severe hypoglycaemic events were reported in the vildagliptin arms.At the recommended dose of 50 mg, Vildagliptin is weight neutral when administered in combination with glimepiride.In clinical trials with the combination of vildagliptin and a thiazolidinedione, 0.7% of patients withdrew for adverse reactions in the vildagliptin 50 mg once daily + pioglitazone group and there were no withdrawals due to adverse reactions reported in either the vildagliptin 50 mg twice daily + pioglitazone or the placebo + pioglitazone treatment groups. In clinical trials, no hypoglycaemia events were reported in patients receiving vildagliptin 50 mg once daily + pioglitazone 45 mg, hypoglycaemia was uncommon in patients receiving vildagliptin 50 mg twice daily + pioglitazone 45 mg (0.6%) but common in patients receiving placebo + pioglitazone 45 mg (1.9%). No severe hypoglycaemic events were reported in the vildagliptin arms. In the pioglitazone add-on study, the change in body weight compared to placebo was +0.1 kg and +1.3 kg for Vildagliptin 50 mg daily and Vildagliptin 50 mg twice daily, respectively. The incidence of peripheral oedema when

vildagliptin was added to a maximum dose of background pioglitazone (45 mg once daily) was 8.2% as 50 mg once daily and 7%, as 50 mg twice daily compared to 2.5% for background pioglitazone alone. The incidence of oedema when vildagliptin was added to pioglitazone as dual initial therapy in drug naive patients was, however, less than for pioglitazone alone (50 mg once daily 3.5%, 50 mg twice daily 6.1% versus pioglitazone 30 mg 9.3%). In clinical trials, there was no increased risk of hypoglycaemia regarding the incidence or severity of hypoglycaemia compared to placebo when Vildagliptin was added to insulin. (Vildagliptin + insulin: 22.9% versus placebo + insulin: 29.6%). Vildagliptin 50 mg twice daily in combination with insulin had a mean change in body weight of +0.9 kg versus placebo. (Block *et al*,2011)

This multicentred, randomized, parallel group, phase III study compared linagliptin treatment (5 mg once daily, n=336) with placebo (n=167) for 24 weeks in type 2 diabetes patients. Before randomization, patients pretreated with one OAD (Oral Antidiabetic Drug) underwent a washout period of 6 weeks, which included a placebo run-in period during the last 2 weeks. Patients previously untreated with an OAD underwent a 2-week placebo run-in period. The primary endpoint was the change in HbA1c from baseline after 24 weeks of treatment. Linagliptin treatment resulted in a placebo-corrected change in HbA1c from baseline of −0.69% ($p < 0.0001$) at 24 weeks. In patients with baseline HbA1c≥9.0%, the adjusted reduction in HbA1c was 1.01% ($p < 0.0001$). Patients treated with linagliptin were more likely to achieve a reduction in HbA1c of ≥0.5% at 24 weeks than those in the placebo arm (47.1 and 19.0%, respectively; odds ratio, OR=4.2, $p < 0.0001$). Fasting plasma glucose improved by −1.3 mmol/l ($p < 0.0001$) with linagliptin vs. placebo, and linagliptin produced an adjusted mean reduction from baseline after 24 weeks in 2-h postprandial glucose of−3.2 mmol/l ($p < 0.0001$). Statistically significant and relevant treatment differences were observed for proinsulin/insulin ratio ($p =0.025$), Homeostasis Model Assessment-%B ($p=0.049$) and disposition index ($p=0.0005$). There was no excess of hypoglycaemic episodes with linagliptin vs. placebo and no patient required third-party intervention. Mild or moderate renal impairment did not influence the trough plasma levels of linagliptin (Prato *et al*., 2011)

Another scientist examined the safety and efficacy of saxagliptin in two cohorts (high and low dose) of antidiabetic drug naive type 2 diabetic patients with a baseline HbA1c $ 6.8 to 9.7%.

This multicenter, randomized, parallel group, double-blind, placebo controlled trial examined a dose-response (anti-hyperglycemic effects) of six doses of saxagliptin following a 2-week dietary/placebo wash out phase. Patients were randomized in a 1:1 fashion, across doses, to 2.5, 5, 10, 20, 40 mg or placebo for a 12-week period. These were the low dose cohorts (n = 338). Results showed that, in all treatment arms, there was a 0.7%–0.9% reduction from the average baseline HbA1c of 7.9% vs. placebo (0.3% reduction). The low dose cohorts had a placebo-subtracted HbA1cs reduction of 0.45%–0.63%. Saxagliptin also showed significant placebo-subtracted reductions in fasting serum glucose (14–25 mg/dl) and 1-hour postprandial glucose levels. Adverse effects, including hypoglycemia, were similar between all groups and saxagliptin was weight neutral. The incidence of confirmed hypoglycemia was of low incidence across dose-range. (Rosenstock *et al*., 2008)

In the same year (2010) another trial was done by the same scientist. The study used saxagliptin on a 24-week schedule with a 2-week run-in period. There were 401 treatment naive patients (baseline HgA1c 7%–10%) randomized into 2.5, 5.0 and 10 mg saxagliptin or placebo. An additional open label cohort (n = 66) had baseline HbA1c 10% but not 12%. Statistically significant lowering of HbA1c and FPG (Fasting Plasma Glucose) relative to baseline and PBO (placebo) with saxagliptin treatment at all doses. There was also significant lowering of the area under the curve (AUC) for fasting plasma glucose (FPG) and postprandial glucose (PPG). (Rosenstock *et al*., 2010)

Again in 2010, another group of scientist performed a trial on the combination therapy of Metformin and saxagliptin. In a randomized placebo-controlled study38 743 patients with an average baseline HbA1c of 8.0% ± 0.9% with type 2 diabetes that were uncontrolled with metforminreceived saxagliptin in escalating doses of 2.5, 5, and 10 or placebo as well as metformin dosed between 1500–2550 mg/day. Patients in all saxagliptin plus metformin groups improved HbA1c's of 0.73%, 0.83%, and 0.71%, respectively at the end of 24 weeks (P, 0.0001). Saxagliptin added to metformin was also significantly more effective than metformin plus placebo in achieving HbA1c, 7.0. 38. (DeFronzo *et al*., 2010).

In 2011, Linagliptin was also studied in a triple combination as add on to an existing oral combination therapy with metformin and a sulfonylurea in patients with a baseline HbA1c

between 7.0% and 10.0%. At study end, after 24 weeks, the linagliptinadjusted and placebo-corrected mean change from baseline HbA1c was -0.62% (95% CI: -0.73 to -0.50%, P, 0.0001). Fasting plasma concentrations were reduced by linagliptin relative to placebo (-0.7 mmol/l, 95% CI: -1.0 to -0.4, P, 0.0001). Improvements in beta-cell function were seen with linagliptin when measured with the HOMA model (P, 0.001). The occurrence of severe adverse events was low in both groups (linagliptin 2.4%; placebo 1.5%) and, in most cases, due to severe hypoglycemia, which was less frequent in the linagliptin group. Symptomatic hypoglycemia occurred in 16.7% and 10.3% of the linagliptin and placebo groups, respectively. Hypoglycemia was generally mild or moderate; severe hypoglycemia was reported in 2.7% and 4.8% of the participants experiencing hypoglycemic episodes in the linagliptin and placebo groups, respectively. The most common nonmetabolic adverse events were infections and infestations (upper respiratory tract infection, urinary tract infection, nasopharyngitis); here, a lower incidence was observed in the linagliptin group (28.9% vs 21.5%, placebo vs linagliptin). No significant weight changes were noted (Owens *et al*., 2011)

This time a trial was done on the combination of Pioglitazone and linagliptin in 2011. This was investigated in a 24-week study with a total of 389 patients in a three-arm study who received either the combination of 30 mg pioglitazone with 5 mg linagliptin once daily, 30 mg pioglitazone as monotherapy, or placebo. After 24 weeks' treatment, HbA1c was reduced by -1.06% in the patients with the initial combination therapy, whereas the patients on pioglitazone monotherapy showed an HbA1c reduction of -0.56%. The reductions of fasting plasma concentrations were significantly greater for linagliptin plus pioglitazone than with placebo plus pioglitazone (-1.8 and -1.0 mmol/L, respectively), corresponding to a treatment difference of -0.8 mmol/L (95% CI: -1.2 to -0.4, P, 0.0001). The rate of mild hypoglycemic events was low, at 1.2%, and all episodes occurred in the linagliptin plus pioglitazone group; no severe hypoglycemia was reported. Additionally, HOMA-insulin resistance (HOMA-IR) and the disposition index as parameters of beta-cell function improved compared to placebo. At the end of the 24-week study, HOMA-IR was -2.9 for linaglitpin plus pioglitazone and -2.58 for placebo plus pioglitazone. The difference between the linagliptin and placebo arms was -0.32 (95% CI: -0.77 to 0.13, P = 0.16). The ratio of relative change in geometric mean HOMA-IR showed a

difference for linagliptin plus pioglitazone versus placebo plus pioglitazone of 0.85 (95% CI: 0.75–0.96, P = 0.0076). The adjusted mean change from baseline in HOMA-β (-2.17 for linagliptin plus pioglitazone and -1.44 for placebo plus pioglitazone) was -0.73 (95% CI: -9.16 to 7.70, P = 0.86) (Gomis *et al*., 2011)

This open label, parallel group, single centre study enrolled patients with mild (n = 8), moderate (n = 9) or severe (n = 8) hepatic impairment and healthy subjects (n = 8). Groups were matched with regard to age, weight and gender. Primary endpoints were linagliptin exposure following 5 mg linagliptin once daily for 7 days in patients with mild and moderate hepatic impairment vs. healthy subjects or after a single 5 mg dose for patients with severe hepatic impairment vs. healthy subjects. In mild hepatic impairment, steady-state linagliptin exposure was slightly lower than in healthy subjects [AUCt,ss geometric mean ratio (GMR) 75.5%, 90% confidence interval (CI) 61.6%, 92.5%, and $C_{max,ss}$ GMR 64.4%, 90% CI 43.2%, 96.0%]. Exposure also tended to be lower in moderate hepatic impairment ($AUC_{t,ss}$ GMR 85.5%, 90% CI 70.2%, 104.2% and $C_{max,ss}$ GMR 92.3%, 90% CI 62.8%, 135.6%). After a single dose, AUC (0,24 h) in patients with severe hepatic impairment was similar to that in healthy subjects (GMR 100.4%, 90% CI 75.0%, 134.3%) and C_{max} was lower (GMR 77.0%, 90% CI 44.9%, 132.3%). Accumulation based on AUC or C_{max} and renal excretion of unchanged linagliptin (7%) were comparable across groups. Median plasma DPP-4 inhibition was similar in healthy subjects (91%), and patients with mild (90%) and moderate (89%) hepatic impairment at steady-state trough concentrations, and in patients with severe hepatic impairment 24 h after a single dose (84%). Linagliptin was well tolerated (Cusi *et al*., 2012)

An expert committee performed a clinical trial between linagliptin and comparators in 2012. These comparators were placebo, glimepiride (1-4 mg), voglibose (0.6 mg). Total 5239 type 2 patients were treated with different comparators as well as linaglipin. This was a pre-specified meta-analysis of CV events in linagliptin and comparator-treated patients with type 2 diabetes mellitus from eight Phase 3 studies. Risk estimates were calculated using several statistical methods including Cox regression analysis. 5239 treated patients (mean ± SD HbA1c 65 ± 10 mmol/mol, age 58 ± 10 years, Body Mass Index (29 ± 5 kg/m2), 3319 received linagliptin once daily (5 mg, 3159; 10 mg, 160) and 1920 received comparators (placebo, 977; glimepiride,781;

voglibose, 162). Cumulative exposure (patient-years) was calculated, 2060 for linagliptin and 1372 for comparators. Primary CV events occurred in 11 (0.3%) patients receiving linagliptin and 23 (1.2%) receiving comparators. The final decision was that this large Phase 3 programme supported the hypothesis that linagliptin might have CV benefits in diabetic patients (Johansen *et al*., 2012)

Again in 2012, 133 patients with type 2 diabetes (HbA1c 7.0–10.0%) and severe RI (estimated glomerular filtration rate [eGFR] ,30 mL/min/1.73 m2) at screening were randomized to linagliptin 5 mg (n = 68) or placebo (n = 65) once daily, added to existing background therapy. The primary efficacy end point was HbA1c change from baseline to week 12. Efficacy and safety end points were assessed after 1 year. At week 12, adjusted mean HbA1c decreased by 20.76% with linagliptin and 20.15% with placebo (treatment difference, 20.60%; 95% CI 20.89 to 20.31; P, 0.0001). HbA1c improvements were sustained with linagliptin (20.71%) over placebo (0.01%) at 1 year (treatment difference 20.72%, 21.03 to 20.41; P, 0.0001). Mean insulin doses decreased by 26.2 units with linagliptin and 20.3 units with placebo. Overall adverse event incidence was similar over 1 year (94.1 vs. 92.3%). Incidence of severe hypoglycemia with linagliptin and placebo was comparably low (three patients per group). Linagliptin and placebo had little effect on renal function (median change in eGFR, 20.8 vs. 22.2 mL/min/1.73 m2), and no drug related renal failure occurred. In patients with type 2 diabetes and severe RI (Renal impairment), linagliptin provided clinically meaningful improvements in glycemic control with very low risk of severe hypoglycemia, stable body weight, and no cases of drug-related renal failure. The potential for linagliptin to spare insulin and provide long-term renal safety warrants further investigations (Mcgill et al., 2013).

In 2013, Phase III clinical trial was performed on linagliptin. In obese patients with type 2 diabetes and a baseline HbA1c ranging from 6.8%–7.3%, GLP-1 plasma concentrations were raised up to fourfold during meal tests with linagliptin administration in a randomized, double-blind, placebo-controlled trial. Plasma glucagon was suppressed by 24%. As a result of these effects, linagliptin therapy resulted in a significant reduction of the meal-related glucose excursions. The placebo-corrected reductions of HbA1c were -0.31%, -0.37%, and -0.28% for the doses of 2.5 mg, 5 mg, and 10 mg linagliptin, respectively (Baptist *et al*., 2013)

Another clinical trial was also performed in 2014-2015 with sitagliptin phosphate 100 mg which included studies of different adverse reactions with combination or alone. In recent trials, when sitagliptinmonotherapy and combinations such as sitagliptin + Pioglitazone, sitagliptin+ Metformin + Rosiglitazone were given to any treatment group for 18-24 weeks comparing to the placebo controlled trials, they got the following results of

Table 7: Adverse drug reactions (excluding hypoglycemia):(Deacon *et al*., 2010)(Fuchs *et al*., 2009)

	Adverse reactions	**Sitagliptin 100 mg**	**Placebo**
Monotherapy (18 or 24 weeks)	Naso pharyngitis	N= 443 23 (5.2)	N = 363 12 (3.3)

		Sitagliptin 100 mg + Pioglitazone	**Placebo + Pioglitazone**
Combination with Pioglitazone (24 weeks)	Upper Respiratory Tract Infection	N = 175 11 (6.3)	N = 178 6 (3.4)
	Headache	9 (5.1)	7 (3.9)

		100 mg + Metformin + Rosiglitazone	**Placebo + Metformin + Rosiglitazone**
Combination with Metformin + Rosiglitazone (18 weeks	Upper Respiratory Tract Infection	N = 181 10 (5.5)	N = 97 5 (5.2)
	Nasopharyngitis	11 (6.1)	4 (4.1)

		Sitagliptin 100 mg + Glimepiride (+/- Metformin)	**Placebo + Glimepiride (+/- Metformin)**
Combination with Glimepiride (+/- Metformin) (24 weeks	Nasopharyngitis	N =222 14 (6.3)	N = 219 10 (4.6)
	Headache	13 (5.9)	5 (2.3)

Within 2015, a study of clinical trial of monotherapy on sitagliptin was performed. A total of 701 patients with type 2 diabetes participated in a 24-week, randomized, double-blind, placebo-controlled study designed to assess the efficacy of sitagliptin in combination with metformin. Patients already on metformin (N=431) at a dose of at least 1500 mg per day were randomized after completing a 2-week single-blind placebo run-in period. Patients on metformin and another antihyperglycemic agent (N=229) and patients not on any antihyperglycemic agents (off therapy for at least 8 weeks, N=41) were randomized after a run-in period of approximately 10 weeks on metformin (at a dose of at least 1500 mg per day) in monotherapy. Patients with inadequate glycemic control (A1C 7% to 10%) were randomized to the addition of either 100 mg of sitagliptin or placebo, administered once daily. Patients who failed to meet specific glycemic goals during the studies were treated with pioglitazone rescue. In combination with metformin, sitagliptin provided significant improvements in A1C, Fasting Plasma Glucose, and 2-hour Post Prandial Glucose compared to placebo with Metformin. Rescue glycemic therapy was used in 5% of patients treated with sitagliptin 100 mg and 14% of patients treated with placebo. A similar decrease in body weight was observed for both treatment groups. (Huttner *et al.*, 2015)

Survey on prescription frequency of Sitagliptin as an antidiabetic agent in hospital of Bangladesh

CHAPTER 3

METHODology

Methodologies

Research Design:

The study was a descriptive study; in which 500 outcome patients (Age between 15 to 72 years) prescription with diabetes were taken. Treatment information were collected retrospectively from patients' diabetic books prescription and new patients initial form prescription of Bangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM.)

Materials and Methods:

Diabetic Books prescription and new patients initial form prescription of Bangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM.)
Camera or Mobile phone camera Windows 2007(Microsoft Excel).

Sample characteristics:

The sample was collected from the BIRDEM hospital Shahabag, Dhaka from 15 March, 2015 to 15December 2015. 500 prescriptions were collected retrospectively.

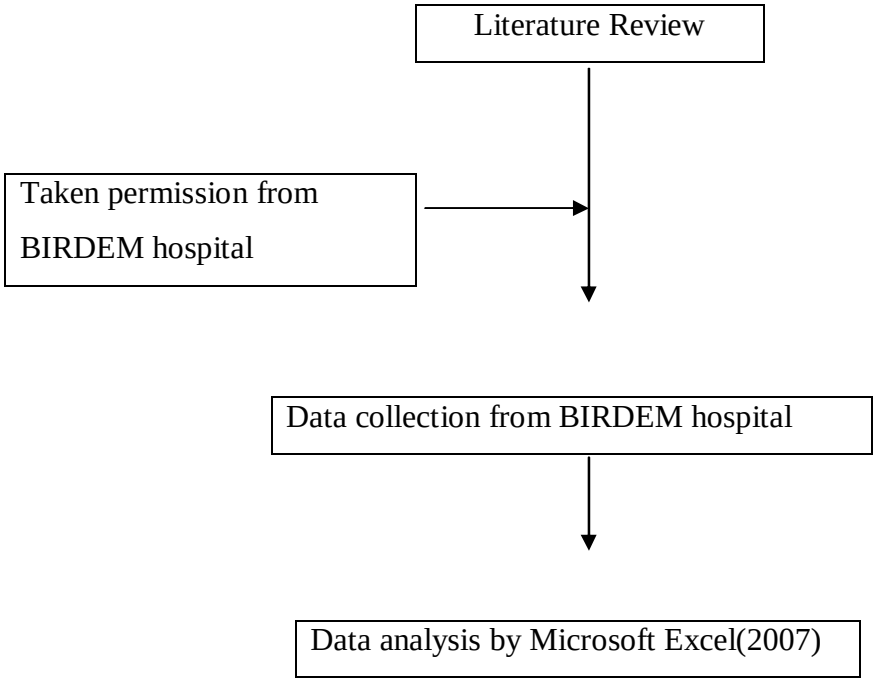
Exclusion criteria:

500 outcome diabetic patients age between 15 to 72 years was excluded for the study.

Procedure:

The study was performed by completing 3 stages of the procedure. In the beginning literature review was done from 40 online literatures regarding diabetic treatment on prescription basis. The aim of the literature review was to observe the situations of the prescription of outcome diabetic patients. Followed by the literature review data collection step was executed by collecting data with the help of diabetic treatment on prescription basis. Data regarding treatment given to the outcome diabetic patients were collected by survey retrospectively from outcome patients' diabetic prescriptions of BIRDEM hospital, Shahabag, Dhaka. Data collection periods

were March 15, 2015 to 15 December, 2015. In the final stage data analysis was made with the help of analytical software Windows 2007(Microsoft Excel).



CHAPTER 4

RESULTS

Result: Prescription pattern of anti-diabetic drugs in Bangladesh

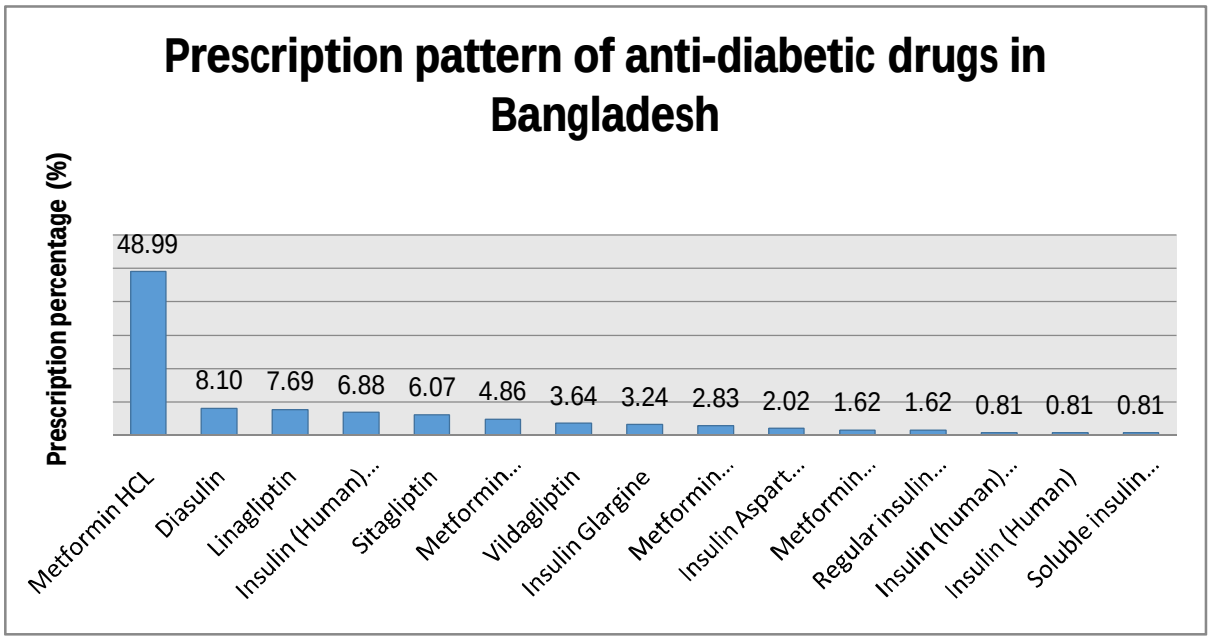


Figure 01: Prescription percentage of anti-diabetic drugs in Bangladesh

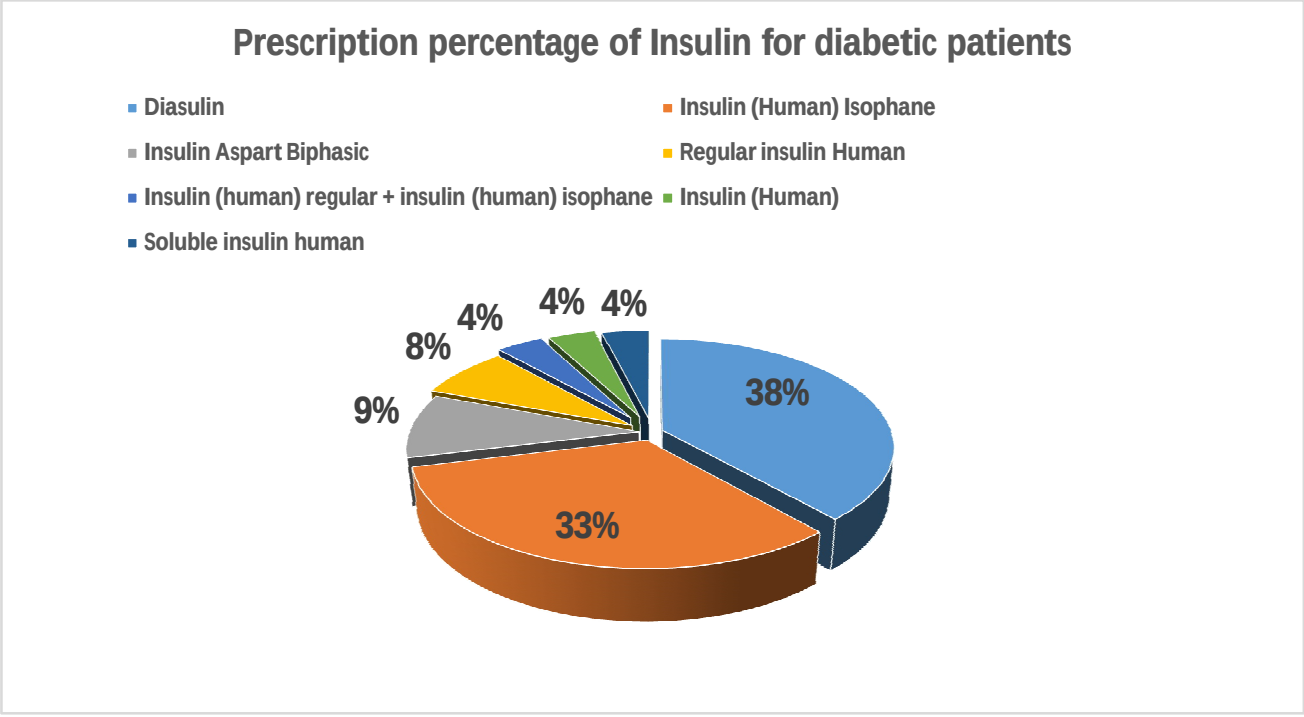


Figure 02: Prescription percentage of Insulin for diabetic patients

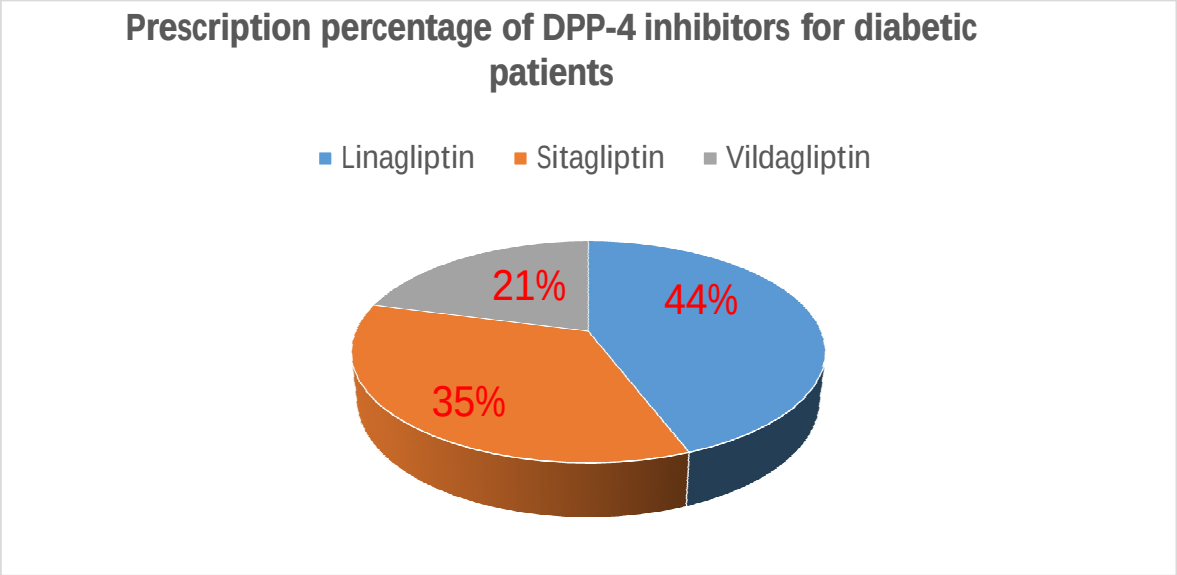


Figure 03: Prescription percentage of DPP-4 inhibitors for diabetic patients

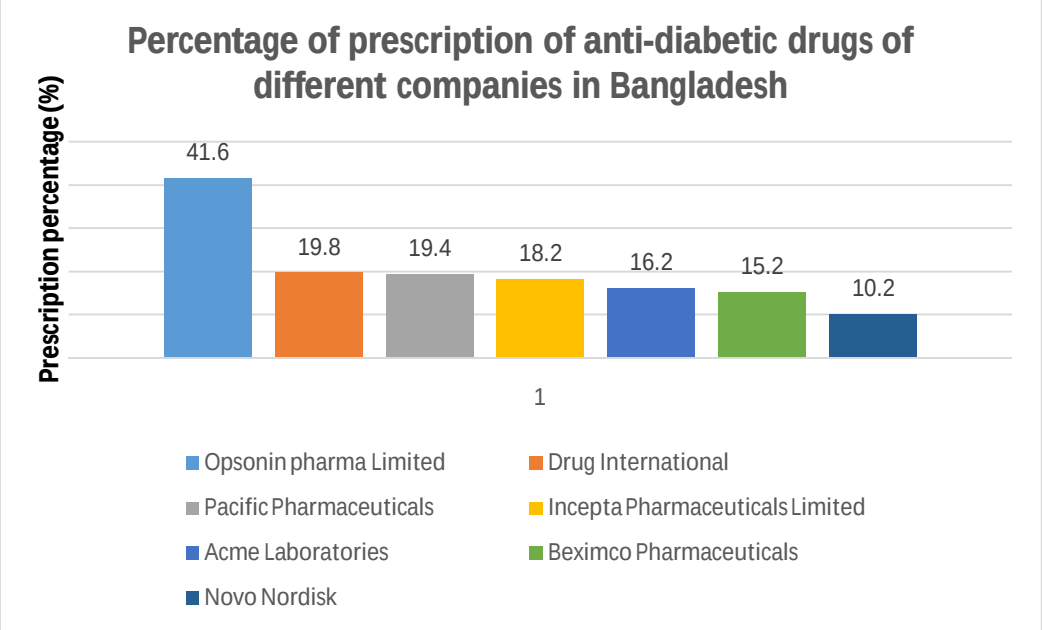


Figure 04: Prescription percentage of anti-diabetic drugs of different companies in Bangladesh

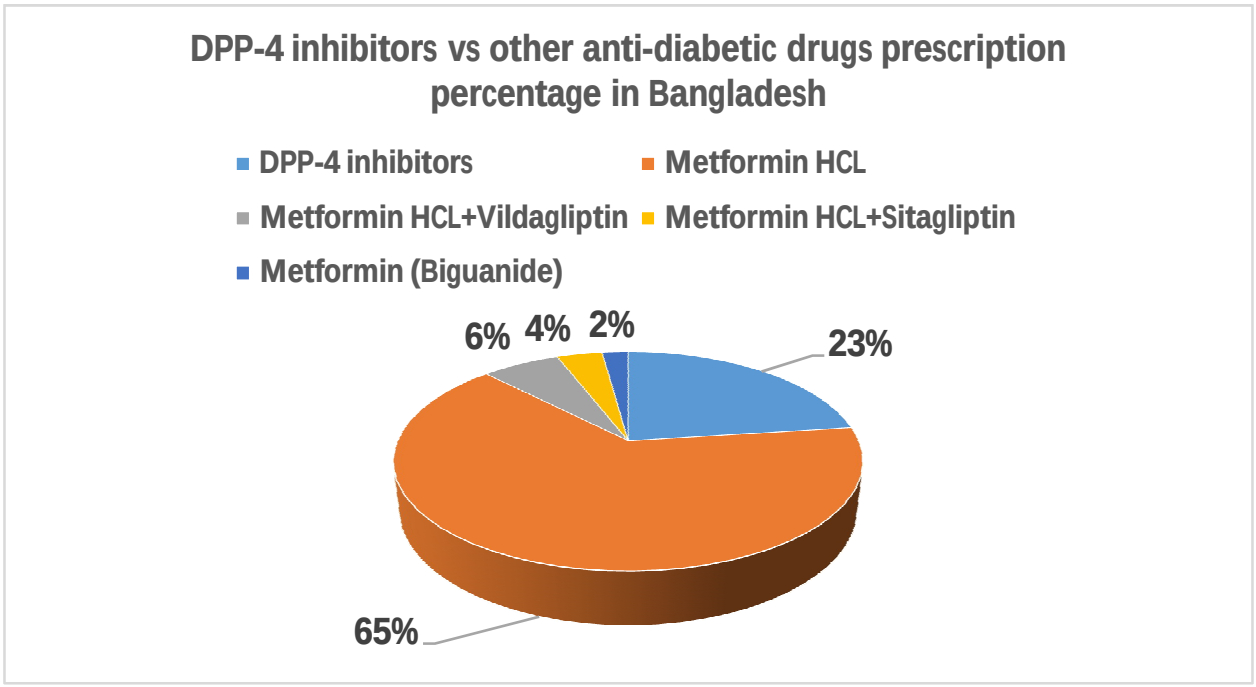


Figure 05: DPP-4 inhibitors vs other anti-diabetic drugs prescription percentage in Bangladesh

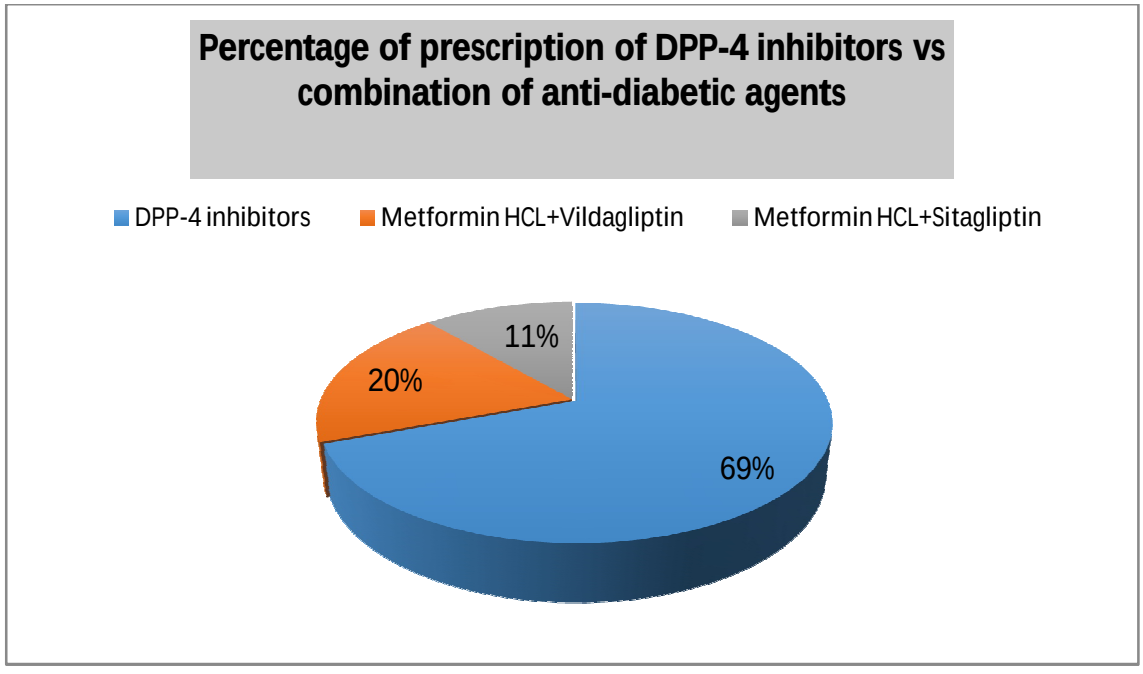


Figure 06: Percentage of prescription of DPP-4 inhibitors vs combination of anti-diabetic agents

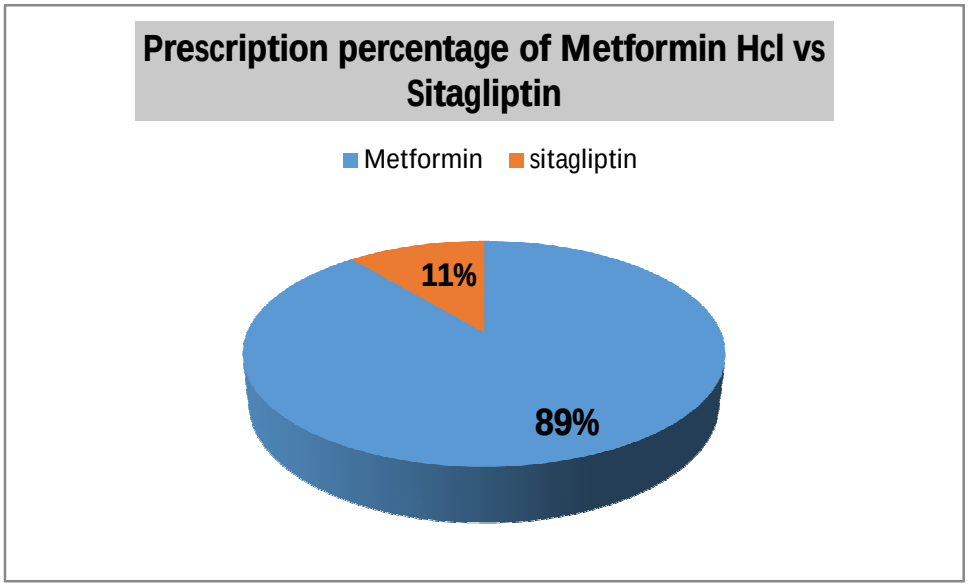


Figure 07: Prescription percentage of Metformin Hcl vs Sitagliptin

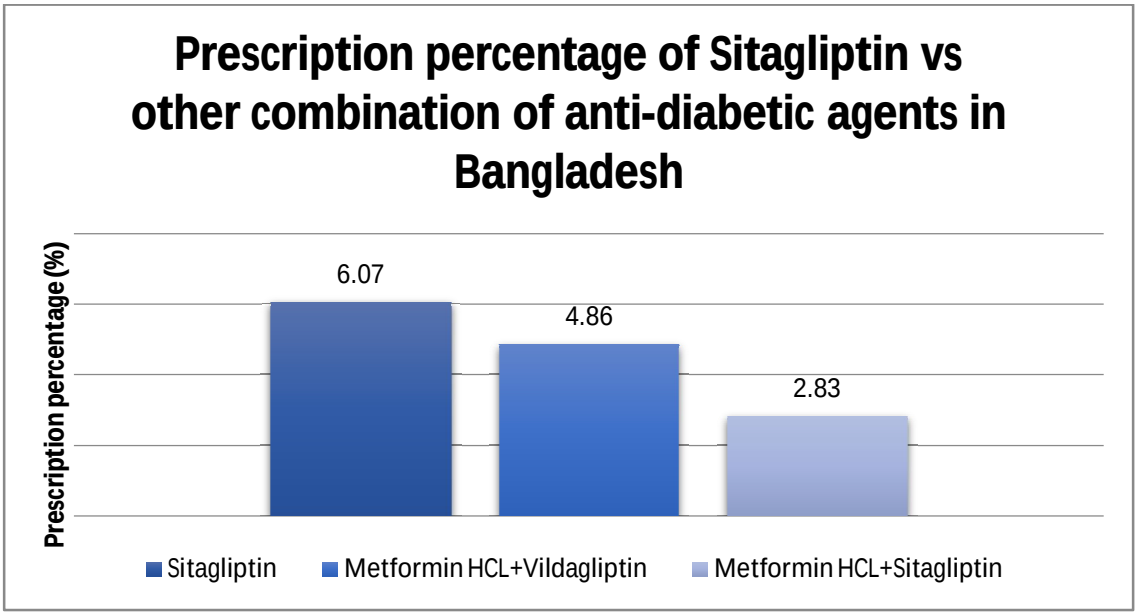


Figure 08: Prescription percentage of Sitagliptin vs other combination of anti-diabetic agents in Bangladesh

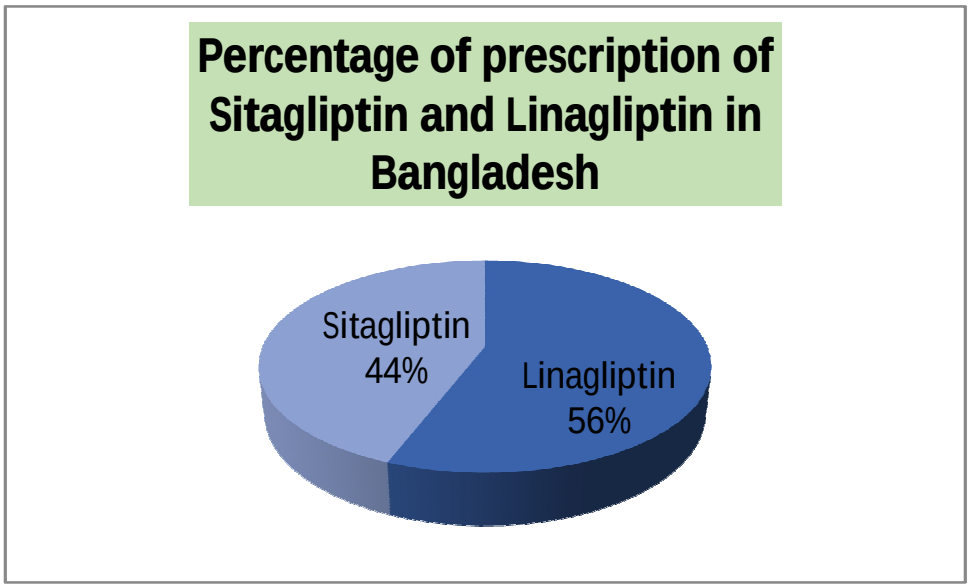


Figure 09: Prescription percentage of Sitagliptin and Linagliptin in Bangladesh

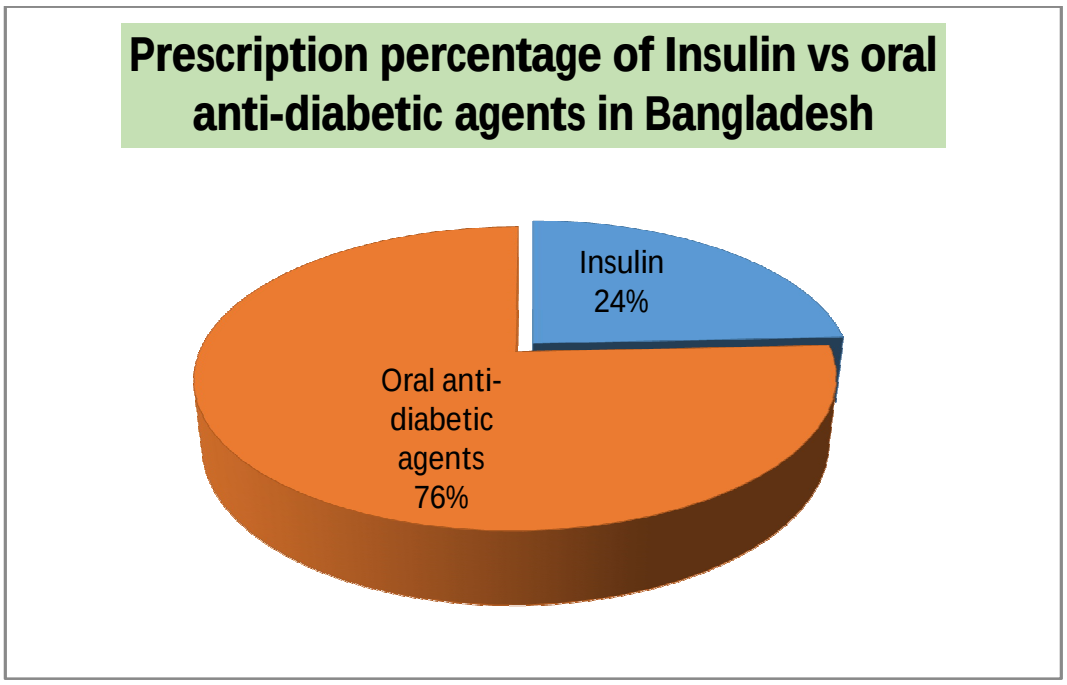


Figure 10: Prescription percentage of Insulin vs oral anti-diabetic agents in Bangladesh

CHAPTER 5

Discussion

After analyzing 500 prescription data of diabetic patients, it has been seen that highest prescribing anti-diabetic agent is Metformin Hcl and the prescription percentage is almost 50% (from figure: 01). Then, there is frequent presence of insulin in prescription and the prescription percentage is 21.05% (from figure: 02). Here, it can be mention that Metformin is an older molecule to treat the patients suffering from diabetes and insulin is used to treat type-1 diabetes. From the analyzed data it can be said that doctors are more likely to prescribe these these two anti-diabetic agents. It has also been seen that doctors are much more rely on top-most companies of Bangladesh Pharmaceuticals market in case of prescribing anti-diabetic drugs for their patients. Name of the topmost companies to which doctors rely most are: Opsonin Pharma Limited, Beximco Pharma Limited, Incepta Pharmaceuticals Limited, Drug International, Acme Laboratories etc. (from figure: 04). In recent times, it seen that a newer anti-diabetic class drugs are used to treat type-2 diabetes that is DPP-4 inhibitors (like:Vildagliptin, Linagliptin, Sitagliptin). From results, it is seen that prescription percentage of DPP-4 inhibitors is 17.40% (from figure: 06) which is significant enough. Among these prescriptions, the prescription percentage of Sitagliptin is 6.07% (from figure: 07) which implicates that doctors are getting

good feedback by prescribing this generic. It is also seen that doctors are preferring DPP-4 inhibitors (prescription percentage is 17.4%) than combination therapy of Metformin+Vildagliptin and Metformin+Sitagliptin (prescription percentage is 4.86% & 2.83% accordingly) (from figure: 08). Recent study suggests that, DPP-4 inhibitors are more efficacious as well as safer than the older antidiabetic agent to treat the patients suffering from diabetes. If the Pharmaceutical companies vigorously promote DPP-4 inhibitors like especially Sitagliptin in doctor's front, then doctors will definately convinced to prescribe Sitagliptin for their patients. For this, Pharmaceutical companies have to provide updated information about molecular superiority of the sitagliptin to the doctors.

CHAPTER 6

Conclusion

Proper marketing practice can convince the doctors to prescribe DPP-4 inhibitors for the patients suffering from diabetes. There are lots of clinical trials which suggests that DPP-4 inhibitors (like: Vildagliptin, Linagliptin and Sitagliptin) are better option to treat patients who are suffering from diabetes. These molecules have the molecular superiority and the potentiality to treat diabetes effectively. These newer molecules will lead the anti-diabetic market in near future undoubtedly. To make it happen Pharmaceutical companies have to provide updated information about molecular superiority of the Sitagliptin to the doctors on a regular basis through literature and by arranging scientific seminar. World diabetes day is celebrated 14th November worldwide. This day can be a great platform to make this promotion smoother. Finally, S

Survey on prescription frequency of Sitagliptin as an antidiabetic agent in hospital of Bangladesh

CHAPTER 7

REFERENCES

References:

Ahren, B. (2005) What mediates the benefits associated with dipeptidyl peptidase-IV inhibition.*Diabetologia*, 48, 605–7

Baptist, G. (2013) Emerging DPP-4 inhibitors: focus on linagliptin for type 2 diabetes. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, 6, 1–9

Bergman, A.J., Stevens, C., Zhou, Y. (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, 55–78.

Bray, G.M. (2006) Exenatide. *Am J Health Syst Pharm*, 63, 411–8

Chapell, R., Gould, A.L., Alexander, C.M. (2009) Baseline differences in A1 C explain apparent differences in efficacy of sitagliptin, rosiglitazone and pioglitazone. *Diabetes Obes Metab*, 11, 1009-16

Crowther, C.A., Hiller, J.E., Moss, J.R., McPhee, A.J., Jeffries, W.S., Robinson, J.S. (2005)/Effect of treatment of gestational diabetes mellitus on pregnancy outcomes. *N Engl J Med*, 352, 2477–2479

Cusi K. (2012) Nonalcoholic fatty liver disease in type 2 diabetes mellitus. *Curr Opin EndocrinolDiabetes Obese*, 16, 141–9.

Deacon, C.F., Holst, J.J. (2002) Dipeptidyl peptidase IV inhibition as an approach to the treatment and prevention of type 2 diabetes: a historical perspective. *Biochem Biophys Res Commune*, 294, 1–4.

Deacon, C.F., Host, J.J. (2010) Linagliptin, a xanthine-based dipeptidyl peptidase-4 inhibitor with an unusual profile for the treatment of type 2 diabetes. *Expert Opin Investig Drugs*, 19, 133–140

DeFronzo, R.A., Hissa, M., Garber, A.J. (2009) The Efficacy and Safety of Saxagliptin when added to metformin therapy in patients inadequately controlled type 2 diabetes on metformin alone. *Diabetes Care*, 32(9), 1649–55

DeFronzo, R.A., Storehouse, A.H., Han, J., Wintel, M.E. (2010) Relationship of baseline HbA1c and efficacy of current glucose-lowering therapies: a meta-analysis of randomized clinical trials. *Diabet Med*, 27, 309-17.

Demuth, H.U., McIntosh, C.H., Pederson, R.A. (2005) Type 2 diabetes—therapy with dipeptidyl peptidase IV inhibitors. *Biochim Biophys Act*, 1751, 33–44

Dinesh, K., Badyal, J.K. (1999) Sitagliptin: 'a New Class of Oral Drug for Type 2 Diabetes'. *JKSCIENCE*, 97-99

Droumaguet, C., Balkan, B., Simon, D., Cases, E., Ticket, J., Charles, M.A., Eschwege, E. (2006) The DESIR Study Group. Use of HbA1c in predicting progression to diabetes in French men and women: data from an Epidemiological Study on the Insulin Resistance Syndrome (DESIR) *Diabetes Care*, 29, 1619–1625

Drucker, N. (2006) The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*, 368, 1696–1705

Edelman, D., Olsen, M.K., Dudley, T.K., Harris, A.C., Oddone, E.Z. (2004) Utility of hemoglobin

A1c in predicting diabetes risk. *J Gen Intern Med*, 19,1175–1180

Eschwege, E., Charles, M.A., Simon, D., Thibult, N., Balkan, B. (2000) From policemen to policies: what is the future for 2-h glucose? The Kelly West Lecture. *Diabetes Care*, 24, 1945–1950.

Fakhoury, W.K., Lereun, C., Wright, D. (2010) A meta-analysis of placebo-controlled clinical trials assessing the efficacy and safety of incretinbased medications in patients with type 2 diabetes. *Pharmacology*,86, 44-57.

Feinglos, M.N., Saad, M.F., Pi, S.F.X. (2005) Effects of liraglutide (NN2211), a long-acting GLP-1 analogue, on glycaemic control and bodyweight in subjects with Type 2 diabetes. *Diabet Med*, 22, 1016–23

Fuchs, H., Tillement, J.P., Uriene, S., Greischel, A., Roth, W. (2009) Concentrationdependent plasma protein binding of the novel dipeptidyl peptidase 4 inhibitor BI 1356 due to saturable binding to its target in plasma of mice, rats and humans. *J Pharm Pharmacol.*, 61, 55–62

Gadsby, R. (2009) Efficacy and Safety of Sitagliptin in the Treatment of Type 2 Diabetes. *Clinical Medicine: Therapeutics*, 1, 53–62

Gallwitz, B. (2006) Therapies for the treatment of type 2 diabetes mellitus based on incretin action. *Minerva Endocrinol*, 31, 133–47

Geiss, L.S., Pan, L., Caldwell, B., Gregg, E.W., Benjamin, S.M., Engelgau, M.M. (2006) Changes in incidence of diabetes in U.S. adults. *Am J Prev Med*, 30, 371–377

Genuth, S., Albert, K.G., Bennett, P., Buse J, Defronzo, R., Kahn, R., Kitzmiller, J., Knowler, W.C., Lebovitz, H., Lernmark, A., Nathan, D., Palmer, J., Rizza, R., Saudek, C., Shaw, J., Steffen, M., Stern, M., Tuomilehto, J., Zimmer, P. (2003) Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care*, 26, 3160−3167

Gomis, R., Espadero, R.M., Jones, R., Woerle, H.J., Dugi, K.A. (2011) 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. *Diabetes Obes Metab.*, 13, 653–661

Herman, G.A., Bergman, A., Yi, B. (2006) Tolerability and pharmacokinetics of metformin and the dipeptidyl peptidase–4 inhibitor sitagliptin when co-administered in patients with type 2 diabetes. *Curr Med Res Opine*, 22, 1939–47

Huttner, S., Graefe-Mody, E.U., Withopf, B., Ring, A., Dugi, K.A. (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, 1171–1178**.**

Jadinsky M, Pfutzner A, Paz-Pacheco E, et al. for CV181-039 Investigators. Saxagliptin given in combination with metformin as initial therapy improves glycaemic control in patients with type

diabetes compared with either monotherapy: a randomized controlled trial. Diab Obes Metab. 2009;11(6): 611–22.

Janet B. M., Lance, S., Jennifer, N., Sanjay, P., Christophe, S.A., Maximillian, V.E., Hans-juergen, W. (2013)Long-Term Efficacy and Safety of Linagliptin in Patients with Type 2 Diabetes and Severe Renal Impairment. *Diabetes Care*, 36, 237–244

Jay, S., Randall, C., Aili, G., Frank, S. (2011) saxagliptin: A selective Dpp-4 Inhibitor for the Treatment of Type 2 Diabetes Mellitus. *Clinical medicine insights: Endocrinology and diabetes*, 4, 1-12

Kawamurai, R., Inagaki, N., Araki, E., Watada, H., Hayashi, N., Horne, Y. (2010) Linagliptin provides superior glycémie control compared to voglibose as monotherapy in Japanese patients with type 2 diabetes. *Diabetes*, 59(l), 172-3

Khardori, R. (2014) Diabetes insipidus. *Medscape*, 60(5), 1106-08

Knowles, W.C., Barrett, C.E., Fowler, S.E., Harmman, R.F., Lachine, J.M., Walker, E.A., Nathan,D.M. (2002) Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*, 346, 393–403

Landon, M.B., Sponge, C.Y., Thom, E., Carpenter, M.W., Raman, S.M., Casey, B., Wapner, R.J., Varner, M.W., Rouse, D.J., Thorpe, J.M., Catalano, P., Harper, M., Sade, G., Lain, K.Y., Sorokin, Y., Placemat, A.M., Tolosa, J.E., Anderson, G.B. (2009) A multicenter,randomized trial of treatment formild gestational diabetes. *N Engl J med*,361, 1339–1348

Mest, H.J., Mentlein, R. (2005) Dipeptidyl peptidase inhibitors as new drugs for the treatment of type 2 diabetes. *Diabetologia*., 48, 616–2

Metzger, B.E., Lowe, L.P., Dyer, A.R., Trimble, E.R., Chaovarindr, U., Constant, D.R., Haden, D.R., McCance, D.R., Hod, M., McIntyre, H.D., Oats, J.J., Persson, B., Rogers, M.S., Sacks, D.A. (2008) Hyperglycemia and adverse pregnancy outcomes. *N Engl J Med*, 358, 1991–2002

Monami, M., Cremasco, F., Lasagna, C., Marchionni, N., Mannucci, E. (2011) Predictors of response to dipeptidyl peptidase-4 inhibitors: evidence from randomized clinical trials. *Diabetes Metab Res Rev*, 27, 362-72.

Owens, D.R., Swallow, R., Dugi, K.A., Woerle, H.J. (2011) Efficacy and safety of linagliptin in persons with type 2 diabetes inadequately controlled by a combination of metformin and sulphonylurea: a 24-week randomized study. *Diabet Med.*, 28, 1352–1361

Pan, C., Yang, W., Barona, J.P., Wang, Y., Niggli, M., Mohideen, P. (2008) Comparison of vildagliptin and acarbose monotherapy in patients with Type 2 diabetes: a 24-week, double-blind, randomized trial. *Diabet Med*, 25, 435-41.

Pradhan, A.D., Rifai, N., Burning, J.E., Rider, P.M. (2007) Hemoglobin A1c predicts diabetes

but not cardiovascular disease in nondiabeticwomen. *Am J Med*, 120, 720–72

Rosenstock, J., Aguilar-Salinas, C., Klein, E., Nepal, S., List, J., Chen, R. (2009) Effect of saxagliptin monotherapy in treatment-naive patients with type 2 diabetes. *Curr Med Res Opin*, 25, 2401-2411.

Rosenstock, J., Kim, S.W., Baron, M.A., Camisasca, R.P., Crosier, F., Couturier, A. (2007) Efficacy and tolerability of initial combination therapy with vildagliptin and pioglitazone compared with component monotherapy in patients with type 2 diabetes. *Diabetes Obes Metab*, 9, 175-85.

Rosenstock, J., Sanko, S.L. (2008) Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug –naïve patients with type 2 diabetes. *Diabetes Obes Metab.*,10, 376–86.

Scheen, A.J., Radermecker, R.P. (2010) Addition of incretin therapy to metformin in type 2 diabetes. *Lancet*, 375, 1410-2.

Stefano, D. P. (2011) Effect of linagliptin monotherapy on glycaemic control and markers of β-cell function in patients with inadequately controlled type 2 diabetes: a randomized controlled trial. *DIABETES, OBESITY AND* METABOLISM, 13, 258–267

Stulc, T. & Sedro, A. (2010) Inhibition of multifunctional dipeptidyl peptidase-IV: is there a risk of oncological and immunological adverse effects? *Diabetes Res Clin Pact*, 88, 125–131

White, R. (2008) Dipeptidyl Peptidase-IV Inhibitors: Pharmacological Profile and Clinical Use.

American diabetes association, 26, 53-57