A Survey on Prescription Pattern of Diabetes Mellitus

A Dissertation Submitted to the Department of Pharmacy, East West University in partial fulfillment of the requirement For The Degree Of Masters Of Pharmacy (M.Pharm)

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DECLARATION BY THE CANDIDATE

I, D.M. Wasiuddin Shourov, hereby declare that, **"A Survey on Prescription Pattern of Diabetes Mellitus"** *i*s an authentic and genuine research work done by me under the supervision and guidance of **Abdullah-Al-Faysal**, Lecturer, Department of Pharmacy, East West University, Dhaka, Bangladesh.

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CERTIFICATE BY THE SUPERVISOR

This is to certify that the dissertation entitled **"A Survey on Prescription Pattern of Diabetes Mellitus"** is a research work done by **D. M. Wasiuddin Shourov**, ID NO: 2015-1-79-001 under my supervision and no part of this dissertation has been or is being submitted elsewhere for the award of any Degree.

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ENDORSMENT BY THE CHAIRPERSON

This is to certify that the entitled ***"A Survey on Prescription Pattern of Diabetes Mellitus"*** is a genuine research work carried out by **D. M. Wasiuddin Shourov**, ID NO: 2015-1-79-001 under the supervision of **Abdullah-Al-Faysal**, Lecturer, East West University, Dhaka. I further 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.

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DEDICATION

DEDICATED TO

MY BELOVED PARENTS WHO INSPIRED AND SUPPORTED ME THROUGHOUT MY WORK.

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List of Abbreviation

1. DM-Diabetes Mellitus
2. IDDM-Insulin Dependent Diabetes Mellitus
3. NIDDM-Non-Insulin Dependent Diabetes Mellitus
4. GDM-Gestational Diabetes Mellitus
5. LADA-Latent Autoimmune Diabetes of Adults
6. MRDM-Malnutrition Related Diabetes Mellitus
7. GLP-1-Glucagon Like Peptide-1
8. GIP-Glucose Dependent Insulinotropic Peptide
9. DPP-4-Dipeptidyl Peptidase-4
10. FDA-Food and Drug Administration
11. ACEIs-Angiotensin Converting Enzyme Inhibitors
12. ARBs-Angiotensin Receptor Blockers
13. IDF-International Diabetes Federation
14. WHO-World Health Organization
15. ED-Energy Department
16. TBAD-Type B Aortic Dissection
17. TCM-Traditional Chinese Medicine
18. NHIRD-National Health Insurance Research Database
19. CKD-Chronic Kidney Disease
20. DKA-Diabetic Ketoacidosis
21. OHA-Oral Hypoglycemic Agents
22. BIRDEM-Bangladesh Institute of Research& Rehabilitation in Diabetes, Endocrine and Metabolic Disorders

Abstract

Now a days, diabetes is well known diseases in all parts of the world. About 386 million people is suffered by type 2 diabetes and in 90% cases it is done. Within 2035 year this level will be raised to 592 million. Diabetes at least doubles a person's risk of death. The global economic cost of diabetes in 2014 was estimated to be $612 billion USD. In the United States, diabetes cost $245 billion in 2012. (World Health Organization,2014)

The aim of the study was to observe what kinds of drugs is prescribed to the diabetic patients. In addition, this study was performed to identify the adherence of the given treatment with the new antidiabetic drugs in our country. Furthermore, this study was also focus on how much old antidiabetic drugs is prescribed by physician. If the old antidiabetic drugs is sufficient and very effective than new antidiabetic drugs. So, why we take new antidiabetic drugs? Where previous anti-diabetic drugs is given enough support to the diabetic patient. In future, we have need to develop the new antidiabetic drugs for the patient. Therefore, it will bring a radical change in treatment of diabetic patients.

Chapter One

Introduction

1.1 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. 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 kidney failure, foot ulcers, and damage to the eyes. Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. There are three main types of diabetes mellitus: Type 1 DM results from the pancreas' failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown. 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 Gestational diabetes, is the third main form and occurs when pregnant women without a previous history of diabetes develop a high blood sugar level. Prevention and treatment involve a healthy diet, physical exercise, not using tobacco and being a normal body weight. 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. As of 2014, an estimated 387 million people have diabetes worldwide, with type 2 DM making up about 90% of the cases. This represents 8.3% of the adult population, with equal rates in both women and men. From 2012 to 2014, diabetes is estimated to have resulted in 1.5 to 4.9 million deaths each year. Diabetes at least doubles a person's risk of death. The number of people with diabetes is expected to rise to 592 million by 2035.The global economic cost of diabetes in 2014 was estimated to be $612 billion USD. In the United States, diabetes cost $245 billion in 2012.(World Health Organization.2014)

Fig 1.1: Universal blue circle symbol for diabetes.(International Diabetes Federation, 2006*)*

1.2 History of diabetes:

Fig 1.2: Frederick Banting (right) joined by Charles Best in office, 1924

Diabetes is 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 that the urine would attract ants. The term "diabetes" or "to pass through" was first used in 250 BCE by the Greek Apollonius of Memphis. 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 obesity. The term "mellitus" or "from honey" was added by Thomas Willis in the late 1600s to separate the condition from diabetes insipidus which is also associated with frequent urination.

1.2.1 Further history:

The first complete clinical description of diabetes was given by the Ancient Greek physician Aretaeus of Cappadocia (fl. 1st century CE), who also noted the excessive amount of urine which passed through the kidneys. Diabetes mellitus appears to have been a death sentence in the ancient era. Hippocrates makes no mention of it, which may indicate that he felt the disease was incurable. Aretaeus did attempt to treat it but could not give a good prognosis; he commented that "life (with diabetes) is short, disgusting and painful. The disease must have been rare during the time of the Roman empire with Galen commenting that he had only see two cases during his career. In medieval Persia, Avicenna (980–1037) provided a detailed account on diabetes mellitus in *The Canon of Medicine*, "describing the abnormal appetite and the collapse of sexual functions," and he documented the sweet taste of diabetic urine. Like Aretaeus before him, Avicenna recognized a primary and secondary diabetes. He also described diabetic gangrene, and treated diabetes using a mixture of lupine, trigonella (fenugreek), and zedoary seed, which produces a considerable reduction in the excretion of sugar, a treatment which is still prescribed in modern times. Avicenna also described diabetes insipidus very precisely for the first time, though it was much later that Thomas Willis differentiated it from diabetes mellitus in a chapter of his book Pharmaceutic erationalis (1674). The sweet urine symptom of diabetes is evident in the Chinese name for diabetes, *tángniǎobìng* (糖尿病), meaning "sugar urine disease". This name has also been borrowed into Korean and Japanese. In 1776 Matthew Dobson confirmed that the sweet taste comes from an excess of a kind of sugar in the urine and blood. Although diabetes has been recognized since antiquity, and treatments of various efficacy have been known in various regions since the Middle Ages, and in legend for much longer, pathogenesis of diabetes has only been understood experimentally since about 1900.An effective treatment was only developed after the Canadians Frederick Banting and Charles Best first used insulin in 1921 and 1922. The discovery of a role for the pancreas in diabetes is generally ascribed to Joseph von Mering and Oskar Minkowski, who in 1889 found that dogs whose pancreas was removed developed all the signs and symptoms of diabetes and died shortly afterwards. In 1910, Sir Edward Albert Sharpey-Schafr suggested that people with diabetes were deficient in a single chemical that was normally produced by the pancreas—he proposed calling this substance insulin, from the Latin insula, meaning island, in reference to the insulin-producing islets of

Langerhans in the pancreas. The endocrine role of the pancreas in metabolism, and indeed the existence of insulin, was further clarified in 1921, when Sir Frederick Grant Banting and Charles Herbert Best repeated the work of Von Mering and Minkowski, and went further to demonstrate they could reverse induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs.The islets of Langerhans was discovered in 1869 by an anatomist named Paul Langerhans. He identified the keys cells in the pancreas which produce the main substance that controls glucose levels in the body. Banting, Best, and colleagues (especially the chemist Collip) went on to purify the hormone insulin from bovine pancreases at the University of Toronto. This led to the availability of an effective treatment—insulin injections—and the first patient was treated in 1922. The first successful patient treated was a 14-year-old boy who weighed only 65 pounds. When he was given the extract on January 23, his ketonuria and glycosuria were almost eliminated. His blood sugar levels dropped as low as 77%. Six more patients were treated in February of 1922 and quickly experienced an improved standard of life. A pharmaceutical firm named Eli Lilly and Company, with the University of Toronto, began the mass production of insulin by the fall of 1923, 25,000 patients were being treated in Canada and the United States.For this, Banting and laboratory director John MacLeod received the Nobel Prize in Physiology or Medicine in 1923; both shared their Prize money with others in the team who were not recognized, in particular Best and Collip. Banting and Best made the patent available without charge and did not attempt to control commercial production. Insulin production and therapy rapidly spread around the world, largely as a result of this decision. Banting is honored by World Diabetes Day which is held on his birthday, November 14.The distinction between what is now known as type 1 diabetes and type 2 diabetes was first clearly made by Sir Harold Percival (Harry) Himsworth, and published in January 1936.

Other landmark discoveries include:

- Development of the long acting insulin NPH in the 1940s by Novo-Nordisk
- Identification of the first of the sulfonylureas in 1942

- Reintroduction of the use of biguanides for Type 2 diabetes in the late 1950s. The initial phenformin was withdrawn worldwide (in the U.S. in 1977) due to its potential for sometimes fatal lactic acidosis and metformin was first marketed in France in 1979, but not until 1994 in the US.

- The determination of the amino acid sequence of insulin (by Sir Frederick Sanger, for which he received a Nobel Prize). Insulin was the first protein that the amino acid structure was determined.

- The radioimmunoassay for insulin, as discovered by Rosalyn Yalow and Solomon Berson (gaining Yalow the 1977 Nobel Prize in Physiology or Medicine)

- The three-dimensional structure of insulin (PDB: 2INS)

- Dr. Gerald Reaven's identification of the constellation of symptoms now called metabolic syndrome in 1988

- Demonstration that intensive glycemic control in type 1 diabetes reduces chronic side effects more as glucose levels approach 'normal' in a large longitudinal study and also in type 2 diabetics in other large studies

- Identification of the first thiazolidinedione as an effective insulin sensitizer during the 1990s

In 1980, U.S. biotech company Genentech developed biosynthetic human insulin. The insulin was isolated from genetically altered bacteria (the bacteria contain the human gene for synthesizing synthetic human insulin), which produce large quantities of insulin. The purified insulin is distributed to pharmacies for use by diabetes patients. Initially, this development was not regarded by the medical profession as a clinically meaningful development. However, by 1996, the advent of insulin analogues which had vastly improved absorption, distribution, metabolism, and excretion (ADME) characteristics which were clinically meaningful based onthis early biotechnology development.

1.3 Signs and Symptoms:

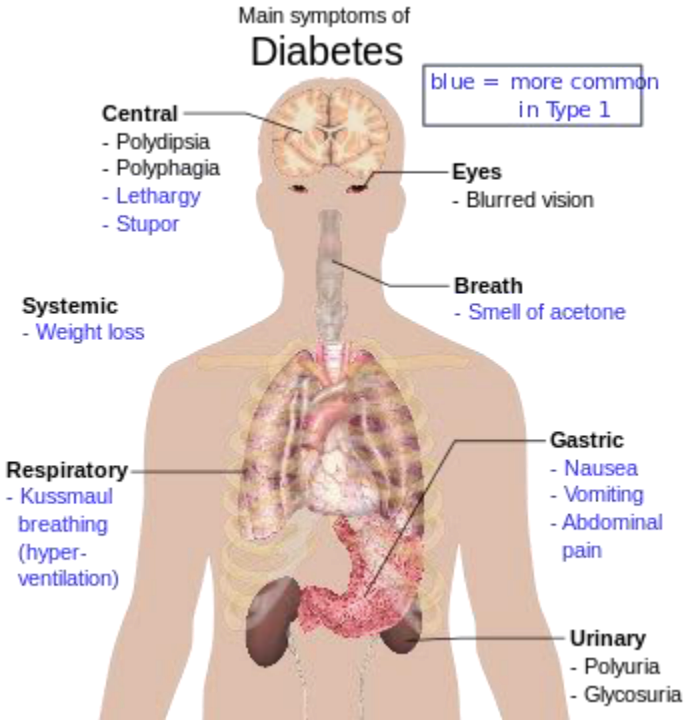

Fig 1.3: Overview of the most significant symptoms of diabetes.

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 dermadromes.

1.4 Classification:

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 Diabetes causes. The term "diabetes", without qualification, usually refers to diabetes mellitus.

1.4.1 Type 1 DM

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in 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-mediated autoimmune attack leads to the loss of beta cells and thus insulin. 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."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. 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 (e.g., Addison's disease).These phenomena are believed to occur no more frequently than in 1% to 2% of persons with type 1 diabetes. Type 1 diabetes is partly inherited, with multiple genes, including certain HLA genotypes, known to influence the risk of diabetes. In genetically susceptible people, the onset of diabetes can be triggered by one or more environmental factors, such as a viral infection or diet. There is some evidence that suggests an association between type 1 DM and Coxsackie B4 virus. Unlike type 2 DM, the onset of type 1 diabetes is unrelated to lifestyle.

1.4.2 Type 2 DM

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.

1.4.3 Gestational diabetes

Gestational diabetes mellitus (GDM) resembles type 2 DM in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2–10% of all pregnancies and may improve or disappear after delivery. However, after pregnancy approximately 5–10% of women with gestational diabetes are found to have diabetes mellitus, most commonly type 2. Gestational diabetes is fully treatable, but requires careful medical supervision throughout the pregnancy. Management may include dietary changes, blood glucose monitoring, and in some cases insulin may be required. Though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital heart and central nervous system abnormalities, and

skeletal muscle malformations. Increased levels of insulin in a fetus' blood may inhibit fetal surfactant production and cause respiratory distress syndrome. A high blood bilirubin level may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A Caesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

1.4.4 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 cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to the pancreas 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 the current taxonomy was introduced in 1999.Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes.

1.4.5 Comparison of type 1 and 2 diabetes:

Table-1:

Feature	Type 1	Type 2
Onset	*Sudden*	*Gradual*
Age at onset	*Mostly in children*	*Mostly in adults*
Body size	*Thin or normal*	*Often obess*
Ketoacidosis	*Common*	*Rare*
Autoantibodies	*Usually present*	*Absent*
Endogenous Insulin	*Low or absent*	*Normal, decreased or increased*
Concordance in identical twins	*50%*	*90%*
Prevalence	*~10%*	*~90%*

1.5 The following is a comprehensive list of other causes of diabetes:

Table-2:

• Genetic defects of β-cell function • Maturity onset diabetes of the young • Mitochondrial DNA mutations • Genetic defects in insulin processing or insulin action • Defects in proinsulin conversion • Insulin gene mutations • Insulin receptor mutations • Exocrine pancreatic defects • Chronic pancreatitis • Pancreatectomy • Pancreatic neoplasia • Cystic fibrosis • Hemochromatosis • Fibrocalculous pancreatopathy	• Endocrinopathies • Growth hormone excess (acromegaly) • Cushing syndrome • Hyperthyroidism • Pheochromocytoma • Glucagonoma • Infections • Cytomegalovirus infection • Coxsackievirus B • Drugs • Glucocorticoids • Thyroid hormone • β-adrenergic agonists • Statins

1.6 Anti-diabetic Drugs:

Drugs used in diabetes treat diabetes mellitus by lowering glucose levels in the blood. With the exceptions of insulin, exenatide, liraglutide and pramlintide, all are administered orally and are thus also called oral hypoglycemic agents or oral anti-hyperglycemic 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. Treatments include-

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

b) agents that increase the sensitivity of target organs to insulin, and

c) 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.

1.6.1 Categories of Anti-Diabetic Drugs:

a) Insulin
b) Oral anti-diabetic drugs
    - Alpha-glucosidase inhibitors (starch inhibitors)
    - Sulfonylureas
    - Biguanides
    - Thiazolidinediones
    - Insulin Secretagogues

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.

Examples of rapid acting insulins include

- Regular insulin (Humulin R, Novolin R)
- Insulin lispro (Humalog)
- Insulin aspart (Novolog)
- Insulin glulisine (Apidra)
- Prompt insulin zinc (Semilente, Slightly slower acting)

Examples of intermediate acting insulins include

- Isophane insulin, neutral protamine Hagedorn (NPH) (Humulin N, Novolin N)
- Insulin zinc (Lente)

Examples of long acting insulins include

- Extended insulin zinc insulin (Ultralente)
- Insulin detemir (Levemir)
- Insulin glargine (Lantus)

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

Sensitizers

Insulin sensitizers address the core problem in Type II diabetes—insulin resistance. It may be upto 10 years prior to the diagnosis of DM and can continue to the progress throughout of the course of the disease. Resistance to insulin occurs mostly in liver and skeletal muscle. Insulin resistance in the liver poses a double threat because the liver becomes non-responsive to insulin for glucose uptake and hepatic production of glucose during the fed state does not cease.

Oral Antidiabetic drugs

Alpha-glucosidase inhibitors (starch inhibitors)

Block intestinal starch absorption. 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%.

- Miglitol
- Acarbose
- Voglibose

These medications are rarely used in the United States because of the severity of their side-effects (flatulence and bloating). They are more commonly prescribed in Europe. They do have the potential to cause weight loss by lowering the amount of sugar metabolized.

Sulfonylureas

Sulfonylureas were the first widely used oral anti-hyperglycemic medications. They are *insulin secretagogues*, triggering insulin release by inhibiting the K_{ATP} 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%.

First-generation agents

- Tolbutamide (Orinase, Rastinon brand name)
- Acetohexamide (Dymelor)
- Tolazamide (Tolinase)
- Chlorpropamide (Diabinese)

Second-generation agents

- Glipizide (Glucotrol, Minidiab, Glibenese)
- Glyburide or glibenclamide (Diabeta, Micronase, Glynase, Daonil, Euglycon)
- Glimepiride (Amaryl)
- Gliclazide (UniDiamicron)
- Glycopyramide
- Gliquidone (Glurenorm)

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** (Glucophage) may be the best choice for patients who also have heart failure, but it should be temporarily discontinued before any radiographic procedure involving intravenous iodinated contrast, as patients are at an increased risk of lactic acidosis.
- **Phenformin** (DBI) was used from 1960s through 1980s, but was withdrawn due to lactic acidosis risk.
- **Buformin** also was withdrawn due to lactic acidosis risk.

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

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:

- **Rosiglitazone(Avandia):** The European Medicines Agency recommended in September 2010 that it be suspended from the EU market due to elevated cardiovascular risks.
- **Pioglitazone (Actos)**
- **Troglitazone(Rezulin):** Used in 1990s, withdrawn due to hepatitis and liver damage risk.

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.

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 panelvoted, 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.

Insulin Secretagogues–

Nonsulfonylurea hypoglycemic agents (meglitinides)

Secretagogues are drugs that increase insulin output from the pancreas. Sulfonylureas are insulin secretagogues, triggering insulin release by direct action on the K_{ATP} channel of the pancreatic beta cells. Blockage of this channel leads to depolarization and secretion of vesicles.

Meglitinides

Meglitinides help the pancreas produce insulin and are often called "short-acting secretagogues." They act on the same potassium channels as sulfonylureas, but at a different binding site. By closing the potassium channels of the pancreatic beta cells, they open the calcium channels, thereby enhancing insulin secretion.

They are taken with or shortly before meals to boost the insulin response to each meal. If a meal is skipped, the medication is also skipped.

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

- Repaglinide (Prandin, NovoNorm)
- Nateglinide (Starlix)

Adverse reactions include weight gain and hypoglycemia.

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.

Exenatide (also Exendin-4, marketed as Byetta) is the first GLP-1 agonist approved for the treatment of type 2 diabetes. Exenatide is not an analogue of GLP but rather a GLP agonist. Exenatide has only 53% homology with GLP, which increases its resistance to degradation by DPP-4 and extends its half-life. Typical reductions in A1C values are 0.5–1.0%.

Liraglutide, a once-daily human analogue (97% homology), has been developed by Novo Nordisk under the brand name Victoza. The product was approved by the European Medicines Agency (EMEA) on July 3, 2009, and by the U.S. Food and Drug Administration (FDA) on January 25, 2010.

Peptide analogs

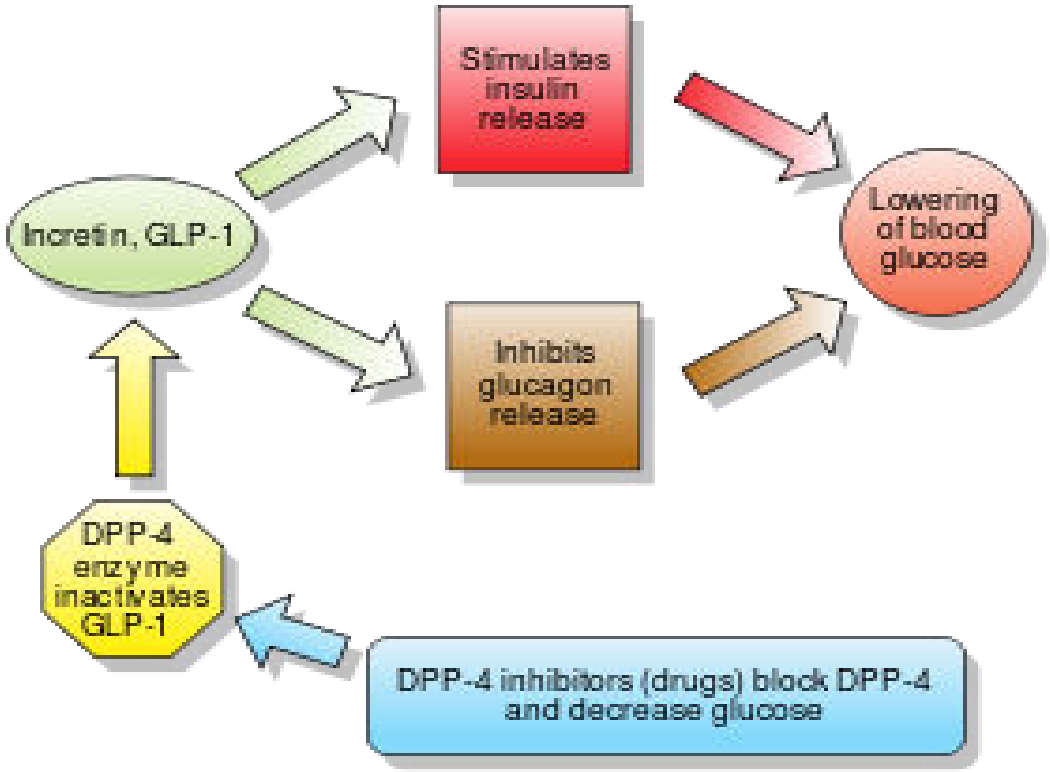

Fig 1.6: Overview of insulin secretion

- Taspoglutide is presently in Phase III clinical trials with Hoffman-La Roche.
- Lixisenatide (Lyxumia) Sanofi Aventis

These agents may also cause a decrease in gastric motility, responsible for the common side-effect of nausea, and is probably the mechanism by which weight loss occurs.

Gastric inhibitory peptide analogs

None are FDA approved

Dipeptidyl Peptidase-4 Inhibitors

GLP-1 analogs resulted in weight loss and had more gastrointestinal side-effects, while in general DPP-4 inhibitors were weight-neutral and increased risk for infection and headache, but both classes appear to present an alternative to other antidiabetic drugs. However, weight gain and/or hypoglycemia have been observed when DPP-4 inhibitors were used with sulfonylureas; effect on long-term health and morbidity rates are still unknown.

Dipeptidyl peptidase-4 (DPP-4) inhibitors increase blood concentration of the incretin GLP-1 by inhibiting its degradation by dipeptidyl peptidase-4.

Examples are:

- vildagliptin (Galvus) EU Approved 2008
- sitagliptin (Januvia) FDA approved Oct 2006
- saxagliptin (Onglyza) FDA Approved July 2009
- linagliptin (Tradjenta) FDA Approved May 2, 2011
- alogliptin
- septagliptin

DPP-4 inhibitors lowered hemoglobin A1C values by 0.74%, comparable to other antidiabetic drugs.

A result in one RCT comprising 206 patients aged 65 or older (mean baseline HgbA1c of 7.8%) receiving either 50 or 100 mg/d of Sitagliptin was shown to reduce HbA1c by 0.7% (combined result of both doses).A combined result of 5 RCTs enlisting a total of 279 patients aged 65 or older (mean baseline HbA1c of 8%) receiving 5 mg/d of Saxagliptin was shown to reduce HbA1c by 0.73%. A combined result of 5 RCTs enlisting a total of 238 patients aged 65 or older (mean baseline HbA1c of 8.6%) receiving 100 mg/d of Vildagliptin was shown to reduce HbA1c by 1.2%. Another set of 6 combined RCTs involving Alogliptin (not yet approved, might be

released in 2012) was shown to reduce HbA1c by 0.73% in 455 patients aged 65 or older who received 12.5 or 25 mg/d of the medication.

Injectable Amylin analogues

Amylin agonist analogues slow gastric emptying and suppress glucagon. They have all the incretins actions except stimulation of insulin secretion. As of 2007, pramlintide is the only clinically available amylin analogue. Like insulin, it is administered by subcutaneous injection. The most frequent and severe adverse effect of pramlintide is nausea, which occurs mostly at the beginning of treatment and gradually reduces. Typical reductions in A1C values are 0.5–1.0%.

Glycosurics

SGLT-2 inhibitors block the re-uptake of glucose in the renal tubules, promoting loss of glucose in the urine. This causes both mild weight loss, and a mild reduction in blood sugar levels with little risk of hypoglycemia. Urinary tract infection is a common side effect. Examples of SGLT-2 inhibitors include:

- Canagliflozin (Invokana - FDA approved March 2013)
- Dapagliflozin (marketed in Europe as Forxiga) *(*Steven *et al,*2008*)*

1.7 Diabetic Emergencies:

Low blood sugar is common in persons with type 1 and type 2 DM. Most cases are mild and are not considered medical emergencies. Effects can range from feelings of unease, sweating, trembling, and increased appetite in mild cases to more serious issues such as confusion, changes in behavior, seizures, unconsciousness, and (rarely) permanent brain damage or death in severe cases. Mild cases are self-treated by eating or drinking something high in sugar. Severe cases can lead to unconsciousness and must be treated with intravenous glucose or injections with glucagon. People (usually with type 1 DM) may also experience episodes of diabetic ketoacidosis, a metabolic disturbance characterized by nausea, vomiting and abdominal pain, the smell of acetone on the breath, deep breathing known as Kussmaul breathing, and in severe cases

a decreased level of consciousness. A rare but equally severe possibility is hyperosmolar nonketotic state, which is more common in type 2 DM and is mainly the result of dehydration.

1.8 Complications:

All forms of diabetes increase the risk of long-term complications. These typically develop after many years (10–20), but may be the first symptom in those who have otherwise not received a diagnosis before that time. The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease and about 75% of deaths in diabetics are due to coronary artery disease. Other "macro vascular" diseases are stroke, and peripheral vascular disease. The primary complications of diabetes due to damage in small blood vessels include damage to the eyes, kidneys, and nerves. Damage to the eyes, known as diabetic retinopathy, is caused by damage to the blood vessels in the retina of the eye, and can result in gradual vision loss and blindness. Damage to the kidneys, known as diabetic nephropathy, can lead to tissue scarring, urine protein loss, and eventually chronic kidney disease, sometimes requiring dialysis or kidney transplant. Damage to the nerves of the body, known as diabetic neuropathy, is the most common complication of diabetes. The symptoms can include numbness, tingling, pain, and altered pain sensation, which can lead to damage to the skin. Diabetes-related foot problems (such as diabetic foot ulcers) may occur, and can be difficult to treat, occasionally requiring amputation. Additionally, proximal diabetic neuropathy causes painful muscle wasting and weakness. There is a link between cognitive deficit and diabetes. Compared to those without diabetes, those with the disease have a 1.2 to 1.5-fold greater rate of decline in cognitive functio*n.*

1.9 Pathophysiology:

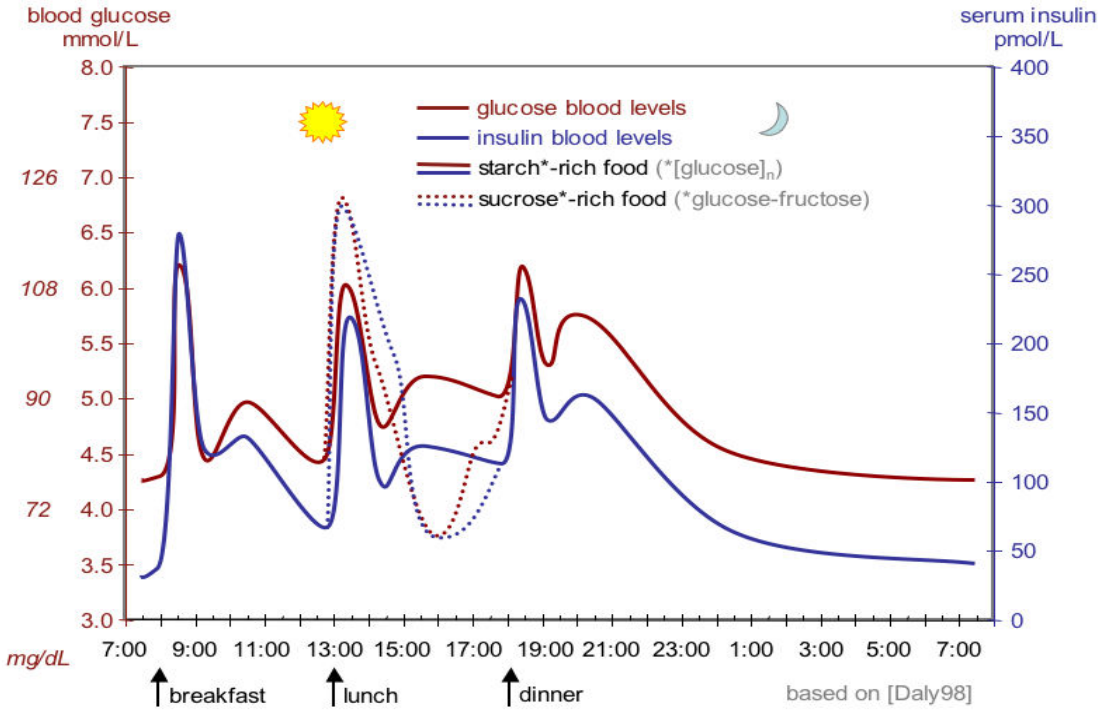

Fig 1.9: The fluctuation of blood sugar (**red**) and the sugar-lowering hormone **insulin** (**blue**) in humans during the course of a day with three meals — one of the effects of a **sugar**-rich vs a **starch**-rich meal is highlighted.(Daily,1998)

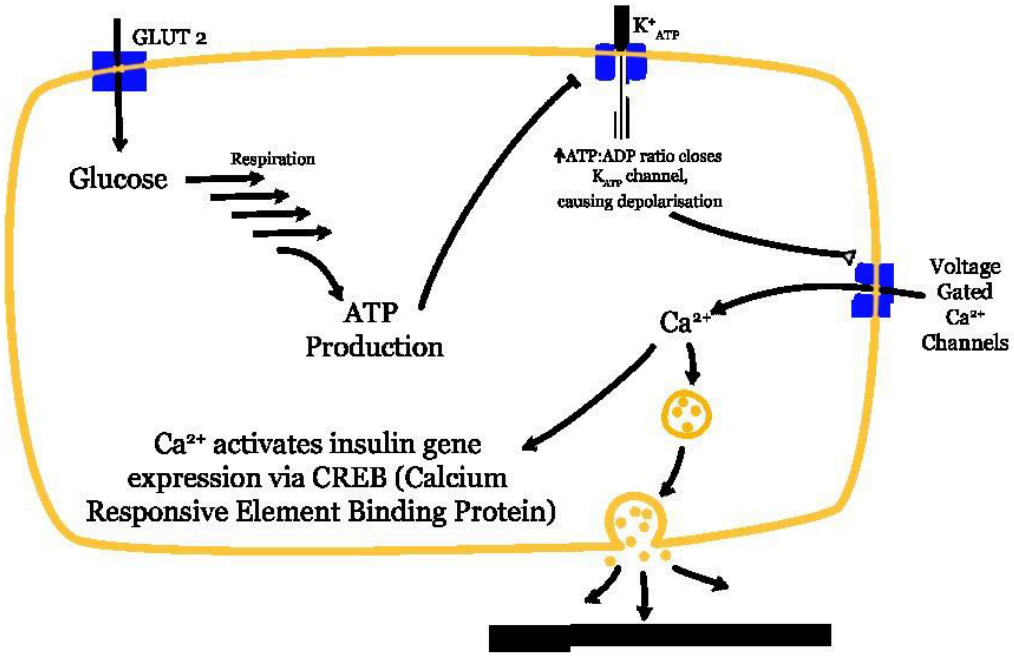

Fig 1.10: Mechanism of insulin release in normal pancreatic beta cells — insulin production is more or less constant within the beta cells. Its release is triggered by food, chiefly food containing absorbable glucose.

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

glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen. Insulin is released into the blood by beta cells (β-cells), found in the islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other

needed molecules, or for storage. Lower glucose levels result in decreased insulin release from the beta cells and in the breakdown of glycogen to glucose. This process is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin. If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or insulin resistance), or if the insulin itself is defective, then glucose will not be absorbed properly by the body cells that require it, and it will not be stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis. When the glucose concentration in the blood remains high over time, the kidneys will reach a threshold of reabsorption, and glucose will be excreted in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst (polydipsia).

1.10 Diagnosis:

Table -3 (World Health Organization,2006)

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

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

- Fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl)

- Plasma glucose ≥ 11.1 mmol/l (200 mg/dl) two hours after a 75 g oral glucose load as in a glucose tolerance test

- Symptoms of high blood sugar and casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl)

- Glycated hemoglobin (HbA_{1C}) ≥ 48 mmol/mol (≥ 6.5 DCCT %).

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

1.10.1 Prevention:

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

saturated fat can also help in the prevention of diabetes. Tobacco smoking is also associated with an increased risk of diabetes, so smoking cessation can be an important preventive measure as well.

1.10.2 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 HbA_{1C} level of 6.5%, but should not be lower than that, and may be set higher. Attention is also paid to other health problems that may accelerate the negative effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise. Specialized footwear is widely used to reduce the risk of ulceration, or re-ulceration, in at-risk diabetic feet. Evidence for the efficacy of this remains equivocal, however.

1.10.3 Lifestyle:

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

1.10.4 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.

1.10.5 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 2 diabetes is often an effective measure. Many are able to maintain normal blood sugar levels with little or no medications following surgery and long-term mortality is decreased. There however is some short-term mortality risk of less than 1% from the surgery. The body mass index cut offs for when surgery is appropriate are not yet clear. It is recommended that this option be considered in those who are unable to get both their weight and blood sugar under control.

1.10.6 Epidemiology:

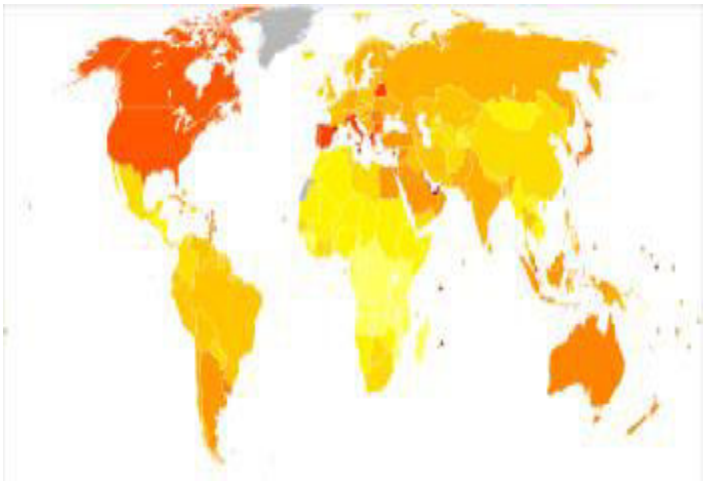

Fig 1.11: Rates of diabetes worldwide in 2000 (per 1,000 inhabitants) — world average was2.8%

Table-4 (WHO, 2009)

no data	45–52.5
≤ 7.5	52.5–60
7.5–15	60–67.5
15–22.5	67.5–75
22.5–30	75–82.5
30–37.5	≥ 82.5
37.5–45	

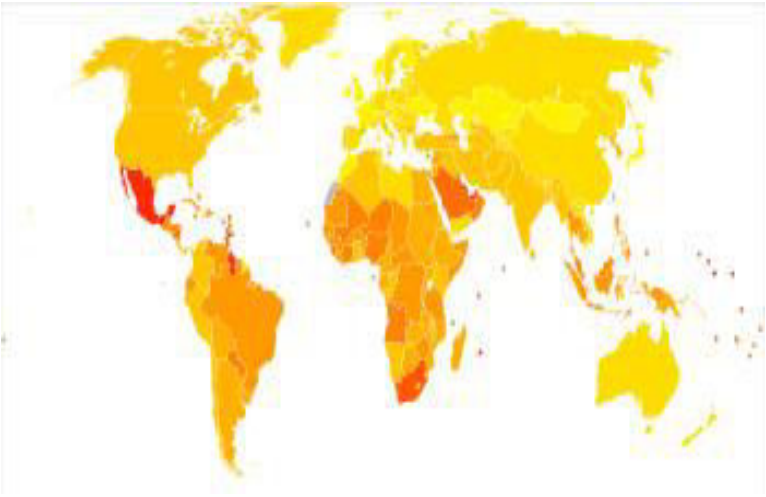

Fig 1.12: Disability-adjusted life year for diabetes mellitus per100,000 inhabitants in 2004

Table-5 (Death and Daily estimates, 2004)

No data	600–700
<100	700–800
100–200	800–900
200–300	900–1,000
300–400	1,000–1,500
400–500	>1,500
500–600	

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; the IDF uses modelling to estimate the amount of deaths that could be attributed to diabetes. More than 80% of diabetic deaths occur in low and middle-income countries. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in more developed countries. The greatest increase in rates was expected to occur in Asia and Africa, where most people with diabetes will probably live in 2030.The increase in rates in developing countries follows the trend of urbanization and lifestyle changes, including a "Western-style" diet. This has suggested an environmental (i.e., dietary) effect, but there is little understanding of the mechanism(s) at present.

1.10.7 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.

1.10.8 Other Animals:

In animals, diabetes is most commonly encountered in dogs and cats. Middle-aged animals are most commonly affected. Female dogs are twice as likely to be affected as males, while according to some sources, male cats are also more prone than females. In both species, all breeds may be affected, but some small dog breeds are particularly likely to develop diabetes, such as Miniature Poodles. The symptoms may relate to fluid loss and polyuria, but the course may also be insidious. Diabetic animals are more prone to infections. The long-term complications recognized in humans are much rarer in animals. The principles of treatment (weight loss, oral antidiabetics, subcutaneous insulin) and management of emergencies (e.g. ketoacidosis) are similar to those in humans.

1.10.9 Society and Culture:

The 1989 "St. Vincent Declaration was the result of international efforts to improve the care accorded to those with diabetes. Doing so is important not only in terms of quality of life and life expectancy, but also economically—expenses due to diabetes have been shown to be a major drain on health—and productivity-related resources for healthcare systems and governments. Several countries established more and less successful national diabetes programmers to improve treatment of the disease.

People with diabetes who have neuropathic symptoms such as numbness or tingling in feet or hands are twice as likely to be unemployed as those without the symptoms. In 2010, diabetes-related emergency department (ED) visit rates in the United States were higher among people from the lowest income communities (526 per 10,000 population) than from the highest income communities (236 per 10,000 population). Approximately 94% of diabetes-related ED visits were for the uninsured.

1.10.10 Research:

Inhalable insulin has been developed. The original products were withdrawn due to side effects. Afrezza, under development by pharmaceuticals company Man Kind Corporation, was approved by the FDA for general sale in June 2014.An advantage to inhaled insulin is that it may be more convenient and easy to use.

1.11 Dietary Recommendation:

A diabetic diet should focus on healthy carbohydrates, including whole grains, vegetables, fruits and legumes along with low-fat or fat-free dairy products. Fiber-rich plant foods are also beneficial and can help to control blood sugar levels. Dietary fiber contains some parts that cannot be digested or absorbed by the body, which improves digestion. High-fiber foods include beans, lentils, peas, fruits, nuts, wheat bran and whole wheat flour.

The inclusion of heart-healthy fish in the diet at least twice each week can be beneficial for diabetics. Fish is better for the body than high-fat meats. Choose from cod, halibut and tuna, or

go for sardines, mackerel and salmon, which are also rich in Omega-3 fatty acids. Steer clear of fish with high mercury levels, such as swordfish.

Some diabetics may benefit from paying special attention to the glycemic index. Foods with a low glycemic load may provide better blood sugar control.

Foods containing good fats, including pecans, olives, avocados and healthy cooking oils are ideal for diabetics. These foods contain polyunsaturated and monounsaturated fats. However, these foods should be limited, since they have high caloric content.

1.12 Recommended by Doctor:

Doctors generally recommend that diabetics eat healthy carbohydrates, fiber-rich foods, heart-healthy fish and good fats, according to Mayo Clinic.

The goal of a diabetic diet is to keep blood sugar levels within appropriate ranges, usually by counting carbohydrates and calories or by using the glycemic index to select foods.

Doctors usually recommend that diabetics consume no more than 2,300 milligrams of sodium and 300 milligrams of cholesterol per day.

1.13 Community Approach:

Table-6: 2005 Demographic Profile of Patients with Diabetes at Four Saint Mary's Community Health Centers and 13 Advantage Health Commercial Primary Care Physician Offices

	Four Urban Clinics	***13 Suburban Primary Care Physician Offices***	**P Values**
	2005	2005	
No and % 0f patients with primary and secondary diabetes diagnosis	736	3,952	

No and % 0f patients with Type 2 diabetes	624(85%)	3,636 (92%)	
Mean age patients with diabetes	54	60.5	<.05 *
No and % males with diabetes	301(41%)	1,992 (50.4%)	<.05 *
% females with diabetes	433(59%)	1,960 (49.6%)	<.05 *
Ethnicity (%)	184 (25%)	316 (8%)	<.05**
African American	330 (45%)	316 (8%)	<.05**
Latino/Hispanic	147 (20%)	3,162 80%)	<.05**
Caucasian	73 (10%)	158 (4%)	<.05**
Other (Asian, unknown)			

Table 6 shows the demographic composition of patients at both the Community Health Centers and commercial Advantage Health offices. The Community Health clinics serve primarily racial and ethnic minority populations and at-risk Caucasian patients, many of whom are uninsured or underinsured. The 13 suburban physician offices provide services to a primarily Caucasian population, and some type of health insurance covers most of these patients.

Table-7: 2004 and 2005 Quality Indicator Data for Four Community Health Centers That Serve Primarily Racial and Ethnic Minority and Other At-risk Populations

	2004	**2005**	**% Change**	**P values**
Number of patients with diabetes	511	736	+44	
% having annual	337(66%)	623(85%)	+25	<.05*

HbA1c				
% with HbA1c <7%	158(31%)	288(39%)	+22	<.05*
% with HbA1c > 9%	61(12%)	142(19%)	-50	<.05*
% with LDL measured annually	271(51%)	658((90%)	+66	<.05*
% with LDL < 100	97(19%)	303(41%)	+115	<.05*
% with retinopathy screen past year	26(5%)	233(32%)	+440	<.05*
% with microalbumin test past year	122(24%)	452(62%)	+145	<.05*

****All are improvements except A1c > 9.

Table 7 shows performance data for an aggregate of the four Community Health Centers. Data for 2004 are baseline figures captured from medical records at each clinic. These data were shared with physicians and personnel at each Community Health Center, and deliberate steps were initiated as outlined above to improve outcomes.

After implementation of systems-based changes at the Community Health Centers, outcomes for 2005 showed dramatic improvement (Table 7). The Community Health Centers showed a larger number of patients with diabetes. There was improvement in every indicator with the exception

of the percent of patients with HbA1c >9%. Mean outcomes in diabetes quality measures in the Community Health Centers ranged from +22% improvement in the percent of patients with HbA1c below 7% to over +400% mean improvement in the percent of patients who had a retinopathy screen in the past year.

1.14 Goals of Therapy:

DM treatment goals include-

i. Reducing long term microvascular and macrovascular complications,

ii. Preventing acute complications from high blood glucose levels,

iii. Minimizing hypoglycemic episodes and

iv. Maintaining the patients overall quality of life.

To achieve these goals, near normal blood glucose levels are fundamental. Two landmark trials showed that lowering blood glucose levels decreased risk of developing chronic complications. A near normal blood glucose level can be achieved with appropriate patient education.

Proper care of DM requires-

i. Goal setting and assessment for glycemic control,

ii. Self-monitoring of blood glucose levels,

iii. Monitoring of blood pressure and lipid levels,

iv. Regular monitoring for the development of complications,

v. Dietary and exercise lifestyle modification and

vi. Proper medication use

1.15 Aims and Significance of The Study:

The aim of the study is to find out what kinds of drugs are prescribed for the diabetic patients. In addition, this study is performed to identify the adherence of the given treatment with the new anti-diabetic drugs in our country. Furthermore, this study also focus on how much old anti-

diabetic drugs is prescribed by physician. If the old antidiabetic drugs insufficient and very effective than new antidiabetic drugs. So, why we take new anti-diabetic drugs? Where previous antidiabetic drugs is given enough to support diabetic patient.

1.16 Conclusion:

Now a days, diabetes is well known diseases in all parts of the world. About 386 million people is suffered by type 2 diabetes and in 90% cases it is done. Within 2035 year this level will be raised to 592 million. This research will bring the list of old antidiabetic drugs which are commonly prescribed in hospital of Bangladesh to the patient. If the outcome of the study is not sufficient for new ant diabetic drugs this will be indicated that old antidiabetic drugs is sufficient for diabetic patient. And the old antidiabetic drugs is better than new antidiabetic drugs. In future, we have need to develop the new antidiabetic drugs for the patient. Therefore, it will bring a radical change in treatment of diabetic patients.

CHAPTER TWO

Literature Review

2.1 Literature Review

There are substantial amount of research on diabetic patients in various countries. Different studies showed different treatment protocol to treat diabetes unlikely.

2.1.1 A retrospective observational study to assess prescription pattern in patients with Type B aortic dissection and treatment outcome

Aortic dissection is a life-threatening condition. However, the use of medication to treat it remains unclear in our population, particularly in patients with a type B aortic dissection (TBAD) who do not receive surgery. This retrospective cohort study evaluated antihypertensive prescription patterns and outcomes in patients with nonsurgical TBAD. We reviewed the hospital records of patients with TBAD at a medical center in Taiwan from January 2008 to June 2013 to assess the baseline information, prescribing pattern, event rate, and clinical effectiveness of different antihypertensive treatment strategies. A Cox proportional hazards model was used to estimate outcomes in different antihypertensive strategies. The primary endpoints were all-cause mortality and hospital admission for an aortic dissection. We included 106 patients with a mean follow-up period of 2.75 years. The most common comorbidity was hypertension followed by dyslipidemia and diabetes mellitus. Study endpoints mostly occurred within 6 months after the index date. Over 80% of patients received dual or triple antihypertensive strategies. Patients treated with different treatment strategies did not have a significantly increased risk of a primary outcome compared with those treated with a monotherapy. We found no significant difference in the primary outcome following the use of different antihypertensive medication regimes. (Biomed Res Int. 2016).

2.1.2 Association of traditional Chinese medicine therapy and the risk of vascular complications in patients with Type II diabetes mellitus

With an increasing use of traditional Chinese medicine (TCM) in type 2 diabetes mellitus (T2DM), evidence of long-term benefit with adjunctive TCM treatment is limited. This study investigated whether the concurrent TCM treatment reduces the risk of vascular complications in T2DM patients by using a large population from National Health Insurance Research Database (NHIRD). We identified 33,457 adult patients with newly diagnosed T2DM using anti-diabetic

agents from a random sample of one million beneficiaries in the NHIRD between January 1, 2000 and December 31, 2011. We recruited 1049 TCM users (received TCM over 30 days with a diagnosis of T2DM) and randomly selected 4092 controls as the non-TCM cohort at a ratio of 1:4 frequency-matched by age, sex, hypertension, hyperlipidemia, and index year. We investigated the prescriptionpattern of TCM and conducted a Cox proportional hazards regression to calculate the hazard ratios (HRs) of stroke, chronic kidney diseases (CKD), and diabetic foot between the 2 cohorts. In the TCM cohort, the prescriptionpattern of TCM was different between insulin and noninsulin patients. The most common herbs were Dan-Shen (Radix SalviaeMiltiorrhizae) in noninsulin group and Da-Huang (Radix et RhizomaRhei) in insulin group. The most common formulae were Liu-Wei-Di-Huang-Wan in noninsulin group and Yu-Quan-Wan in insulin group. Although no significant reduction in the hazard ratio of CKD and diabetic foot, the incidence rate of stroke was 7.19 per 1000 person-years in the TCM cohort and 10.66 per 1000 person-years in the control cohort, respectively. After adjustment of age, sex, hypertension, hyperlipidemia, and anti-diabetes agent use (including sulfonylureas, α-glucosidase, metformin, meglitinide, thiazolidinediones, and insulin), TCM cohorts were found to have a 33% decreased risk of stroke (95% CI=0.46-0.97; $P<0.05$).This population-based retrospective study showed that the complementary TCM therapy might associate with the decreased risk of stroke in T2DM, suggesting TCM as an adjunctive therapy for T2DM to prevent subsequent stroke.Medicine (Baltimore 2016 Jan.)

2.1.3 Age- and sex-related prevalence and drug utilization pattern in the management of Type 2 diabetes mellitus and its comorbidity with cardiovascular diseases

A cross-sectional study of 250 cases of type 2 diabetes management was conducted in a governmental tertiary care hospital of urban south India to determine the comparative prevalence of type 2 diabetes and its comorbidity with cardiovascular diseases in diabetic population, core drug use indicators and drug utilization pattern in the management of diabetics entirely and with cardiovascular diseases. Highest prevalent age group for type 2 diabetes/cardiovascular diseases (greater incidence in female than male) was 51-60 years. The 62.8% prevalence of cardiovascular diseases in the diabetic population ascertained in the study could provide an evidence-based rationale for the World Health Organization guidelines for the management of hypertension in type 2 diabetics. Incidence of polypharmacy (6.06, the mean number of total

drug products prescribed); 59.26% of encounters prescribed antibiotics; 17.6 and 18.5 min of average consultation and dispensing time, respectively; 100% of drugs actually dispensed and adequately labeled; 81.26% of patients having knowledge of correct dosage and average drug cost of Indian Rupees 145.54 per prescription were the core drug use indicators found mainly. Moreover, drugs prescribed from the Essential Drug List were more than 90% and thereby indicated the drug use in this set-up quite rational. Around 71.09% of cardiovascular agents prescribed by generic name revealed the cost effective medical care. Among the agents in type 2 diabetes management, Actrapid(®) (35.43%) was the highest. Among the cardiovascular agents prescribed, lasix (19.37%) was the highest. Cardiovascular agents prescribed orally by 76.48% signified the good prescription habit indicating the improved patients' adherence to the treatment. The present study emphasizes the need of early detection of hypertension as a preliminary diagnostic parameter of cardiovascular diseases in diabetics and appropriate management through concomitant therapy of cardiovascular drugs to minimize the risks of death. (Indian J Pharm 2015 Jul-Aug)

2.1.4 Insulin dosing and outcomes among commercially insured patients with type 2 diabetes in the United States.

The purpose of this study was to examine costs, resource use, adherence, and hypoglycemic events among patients with type 2 diabetes mellitus (T2DM) treated with increasing doses of 100-U/mL (U-100) insulin regimens.

The study focused on 101,728 individuals with T2DM who received an outpatient prescription for U-100 insulin. In general, costs and resource use are highest among patients treated with the highest dose of insulin (>300 U/d). For example, all-cause and diabetes-related hospitalizations and office visits were highest in the highest-dose cohort. Costs generally followed the same pattern. Patients who were prescribed the lowest dose of insulin (10-100 U/d) generally had higher all-cause or diabetes-related inpatient and emergency department costs and resource use compared with those patients with an index dose >100 to 150, >150 to 200, and >200 to 300 U/d. There were generally no significant differences in rates of hypoglycemic events based on index dose.

These results suggest significant differences in patient outcomes based on dosing of insulin. Those patients with T2DM using insulin at the highest and lowest dose ranges have the highest costs and resource use. (Clin Ther. 2015 Oct)

2.1.5 Influence of metformin intake on the risk of bladder cancer in type 2 diabetes patients.

The aim of this study was to look at the influence of metformin intake and duration, on urinary bladder cancer (UBC) risk, with sulfonylurea (SU) only users as control using a new user design (inception cohort).

The inception cohort included 165,398 participants of whom 132,960 were metformin users and 32,438 were SU only users. During a mean follow-up time of more than 5 years 693 patients developed UBC, 124 of the control group and 461 of the all metformin users. There was no association between metformin use and UBC risk (HR = 1.12, 95% CI 0.90, 1.40) compared with SU only users, even after adjustment for diabetes duration (HR = 1.13, 95% CI 0.90, 1.40). We found a pattern of decreasing risk of UBC with increasing duration of metformin intake, which was statistically not significant.

Metformin has no influence on the risk of UBC compared with SU in type 2 diabetes patients using a new user design. (Br J Clin Pharmacol. 2015 Dec)

2.1.6 Integrative traditional Chinese medicine therapy reduces the risk of diabetic ketoacidosis in patients with type 1 diabetes mellitus.

Life-long insulin is the standard treatment for type 1 diabetes mellitus (T1DM). The role of traditional Chinese medicine (TCM) in T1DM is still not clear. The aim of this study is to explore the prescriptionpattern of TCM and its impact on the risk of diabetic ketoacidosis (DKA) in patients with T1DM.

Overall, 416 subjects were TCM users, whereas a total of 1608 matched subjects were classified as non-TCM users. The most common Chinese herbal formula and single herb is Liu-wei-di-huang-wan (Six-ingredient pill of Rehmannia) and Huang-qi (Radix Astragali; Astragalusmembranaceus (Fisch.) Bunge, Astragalusmembranaceus var. mongholicus (Bunge)

P.K.Hsiao), respectively. Compared with non-TCM users, we found a 33% reduction in DKA incidence for all TCM users (aHR 0.67, 95% CI 0.56-0.81, p <0.000) and a 40% reduction for users receiving TCM treatment for more than 180 days (aHR 0.58, 95% CI 0.41-0.82, p <0.01). There were no significant differences between TCM users and non-users in the frequency and medical costs of emergency visits and hospitalizations.

Integrative TCM use may reduce the risk of DKA in patients with T1DM. Our results suggest that TCM may have a substantial positive impact on the management of TIDM. (J Ethnopharmacol. 2016 Sep)

2.1.7 Prescribing pattern and efficacy of anti-diabetic drugs in maintaining optimal glycemic levels in diabetic patients.

The aim was to study the prescribing pattern and efficacy of anti-diabetic drugs in maintaining optimal glycemic levels in diabetic patients attending tertiary care teaching hospital in Navi Mumbai.

Average number of anti-diabetic drugs per prescription was 1.4. Sulfonylureas were the most commonly prescribed class, but metformin (biguanide) was the commonest prescribed individual drug among oral hypoglycemic agents (OHA). Fixed dose combination of biguanide and sulfonylurea was prescribed commonly. Monotherapy dominated over polytherapy and there was a higher percentage of use of insulin in Type 2 diabetics. Only 41% of patients on anti-diabetic therapy had optimal glycemic control. The association between anti-diabetic therapy along with lifestyle modification and glycemic control was statistically significant (P = 0.0011).

OHAs still dominate the prescribing pattern, but there was a shifting trend toward the use of insulin preparations in the management of Type 2 diabetes mellitus. In achieving optimal glycemic control, the efficacy of the anti-diabetic drugs was only 41%; therefore intensification of current drug treatment as well as planning multiple drug interventions with lifestyle modification is necessary. (J Basic Clin Pharm. 2014 Jun)

2.1.8 Drug use evaluation of diabetes mellitus in hospitalized patients of a tertiary care referral hospital.

Many drugs are available for the treatment of diabetes mellitus and are sometimes prescribed in combination. The aim of this study was to determine patient demographic characteristics, analyze prescription patterns of antidiabetic drugs, distribution of complications of diabetes, distribution of co-existing illnesses, distribution of common symptoms of diabetes and distribution of adverse drug reactions.

The pattern of drug prescription in diabetes shows that insulin (80.5%) was most frequently prescribed followed by biguanides (23%), sulfonylureas (22.5%), thiazolidinediones (11%), dipeptidyl peptidase-IV (DPP-4) inhibitors (9.5%) and meglitinides (5.5%). The percentage of patients on diet control therapy was found to be 3%. Combination therapy was prescribed to 26.5% and monotherapy to 65% of patients; 47.5% of these patients were male and 52.5% were female. The most common co-existing illness was found to be hypertension (53.5%). In addition, 67% of patients had irregular blood sugar monitoring and the remaining 33% had regular (either 4 or 6 hourly) monitoring.

It is concluded that the prescribing trend is moving away from monotherapy with insulin and sulfonylureas and towards combination therapies. There is also a significant increase in prescriptions of newer oral antidiabetic drugs, such as DPP-4 inhibitors and insulin analogs. Most inpatients had their blood glucose checked irregularly and haphazardly by ward staff. This study strongly highlights the need for patient education or counseling on use of antidiabetic and concomitant drugs, monitoring of blood glucose and glycosylated hemoglobin (HbA1c) levels, diet control and correction of diabetic complications. (J Basic Clin Physiol Pharmacol. 2012)

2.1.9 Refractive errors in type 2 diabetic patients.

The aim of the study is to determine the prevalence and pattern of refractive errors among African type 2 diabetes mellitus patients and establish the relationship between baseline refractive status and degree of glycemic control.

Ninety six patients aged 28 to 76 years were examined. The male to female ratio was 1:1.5 and about half of the patients (52.1%) had good glycemic control. The prevalence of myopia was 39.5% and that of hypermetropia was 19.0%. Twenty two percent of the study patients had mild diabetic retinopathy (DR). Of the eyes with DR, 20% (15/75) were myopic, 19.4% (7/36) were hypermetropic and 26.6% (21/79) were emmetropic. There was no statistically significant correlation between baseline refractive status with DR (p = 0.358), or HBA1C (glycosylated haemoglobin) (rho = 0.130, p-value = 0.249 among myopes) or FBS (fasting blood sugar) (rho =0.089, p-value = 0.438 among myopes and rho = 0.158, p-value = 0.350 among hyperopes). However, there was a statistically significant correlation between baseline hypermetropic refractive status and HBA1C (rho = 0.401, p-value = 0.014).

Refractive errors were seen in 58.5% of the patients with myopia being the most common type (39.5%) followed by hypermetropia 19.0%. There was no statistically significant relationship between baseline refractive status and indicators of glycemic control except for hypermetropic refractive status and HBA1C. According to the results of this study, it is not mandatory to ask for HBA1C or FBS results before issuing spectacle prescription to adult patients with type 2 diabetes mellitus who are already on treatment. However, there is need to emphasize the need for good glycemic control to minimize the other ocular complications. A similar study should be done on young people with type I diabetes mellitus. (East Afr Med J. 2007 Jun)

2.1.10 Variation in antidiabetic medication intensity among Medicare beneficiaries with diabetes mellitus.

Recent guidelines for treating older patients with diabetes mellitus (DM) and significant disease burden place less emphasis on glycemic control and stress the potential harms that may arise from adherence to strict regimens with antidiabetic medications. However, there are few empirical benchmarks against which clinicians can compare their prescribing practices for patients who have DM and varying levels of comorbidity.

The current study had 2 goals: (1) to provide national estimates showing how the intensity of antidiabetic medication regimens for Medicare beneficiaries with DM varies by level of medical

spending (a proxy for overall disease burden); and (2) to identify potential predictive factors associated with the observed differences.

The final study sample comprised 1956 Medicare beneficiaries representing 23.1% of the MCBS sample after exclusions. We found a pronounced inverted U-shaped pattern in intensity of antidiabetic treatment. Compared with individuals in the group with the highest prevalence of antidiabetic use (decile 7), the unadjusted treatment odds ratios were 0.40 in decile 1 (95% CI, 0.26-0.60) and 0.54 in decile 10 (95% CI, 0.36-0.81). We found similar patterns in the complexity of drug regimens and numbers of antidiabetic prescriptions filled among users. Controlling for disease severity and other factors eliminated the inverted U-shaped pattern among higher cost beneficiaries but not for those in the lower spending deciles.

This national study found that high-cost Medicare beneficiaries with DM received substantially less intensive antidiabetic regimens compared with those incurring more modest medical expenditures in 2002. Longitudinal analysis is necessary to determine whether this finding indicates suboptimal therapy or has a more benign explanation. However, the magnitude of the association warrants the attention of clinicians who treat elderly and disabled diabetic patients with high disease burden. (Am J Geriatr Pharmacother. 2007 Sep)

CHAPTER THREE

METHODOLOGY

3.1 Type of study

It is a study attempted to establish the current prevalence and distribution of Diabetes Mellitus and to determine the status of diabetic awareness, treatment or prescription pattern and control in Bangladesh among different population.

3.2 Place of study

Treatment information were collected retrospectively from patient's diabetic books prescription and new patients initial form prescription of Bangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM) Shahbag, Dhaka.

3.3 Materials and Methods

Photographs of diabetic Books prescription and new patients initial form prescription of Bangladesh Institute of research & Rehabilitation in Diabetes, Endocrine and Metabolic Disorders (BIRDEM.) are taken using digital camera or mobile phone camera.

3.4 Sample size

The study was a descriptive study; in which 500 outcome patient's prescription with diabetes were taken.

3.5 Exclusion criteria

500 outcome diabetic patients was excluded for the study.

3.6 Study period

Study period was four months commencing, started from 15th June 2016 to 27th September 2016.

3.7 Data processing and analysis

After collection, each data were recorded in master sheet with the help of Microsoft Office 2010. It helps to check reaching values and inconsistency and were corrected immediately. The results was shown in the pie and column diagram.

Chapter Four

RESULT

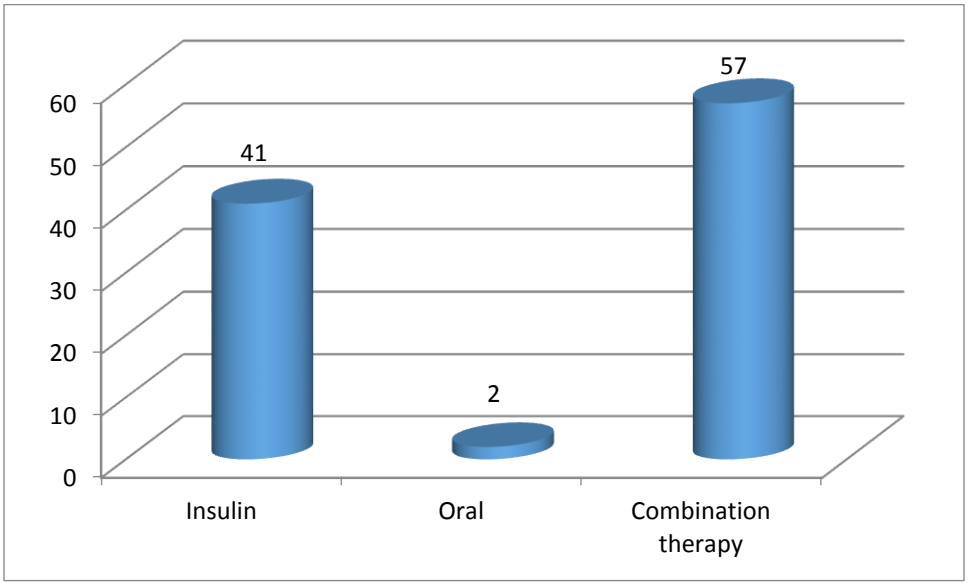

Fig 4.1: % distribution of insulin, oral and other drugs

The study had shown that, among 500 prescription, 41% Insulin, 2% oral and 57% other drugs were prescribed by the doctors or physicians.

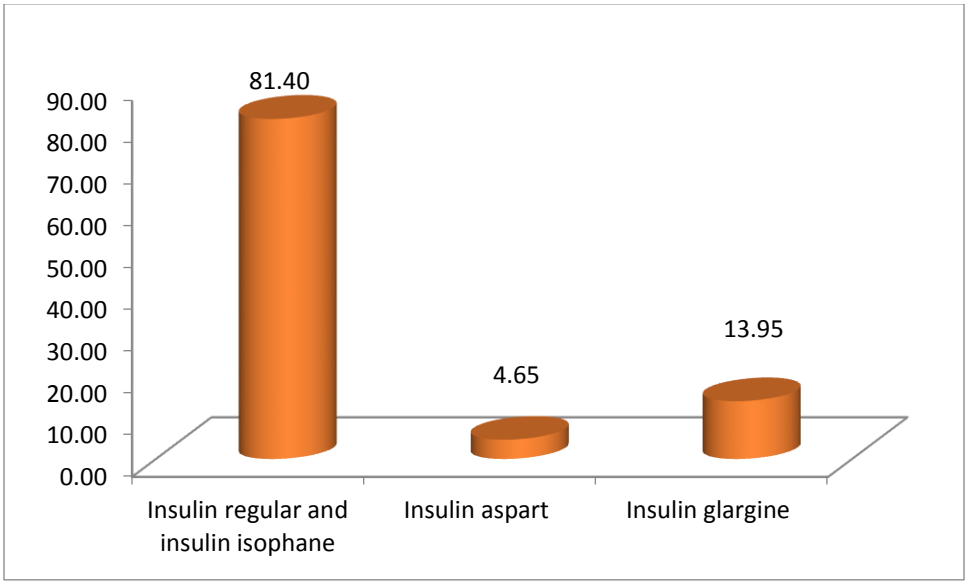

Fig 4.2: % distribution of insulin

After data processing and analysis we had found that, 41% insulin were prescribed in which 81.40 % Insulin Regular and Insulin Isophane, 13.95% Insulin Glargine, 4.65% Insulin Aspart were prescribed by the doctors or physicians.

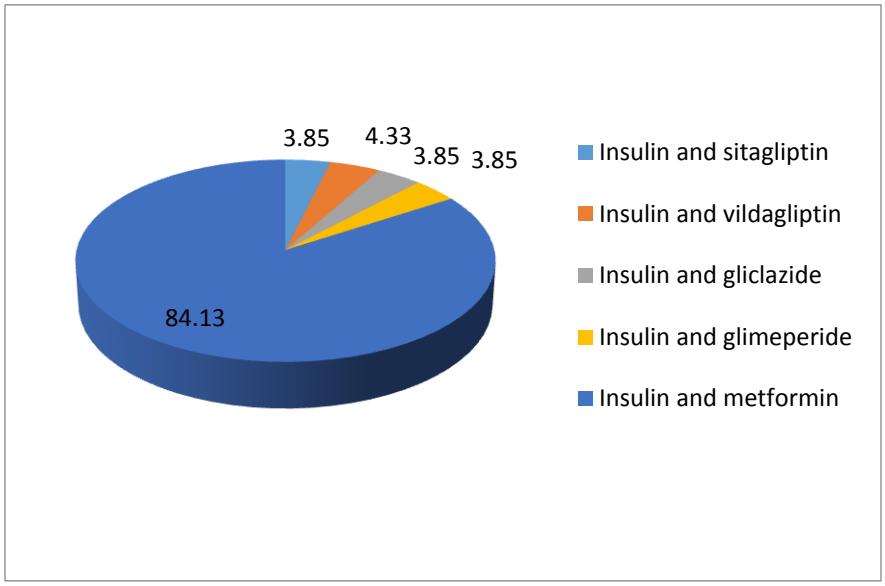

Fig 4.3: % of insulin combination therapy

Among 500 prescriptions, we got to know that, 84.13% insulin and metformin, 3.85% insulin and sitagliptin, 4.33% insulin and vildagliptin, 3.85% insulin and gliclazide & 3.85% insulin and glimepiride were prescribed by the doctors.

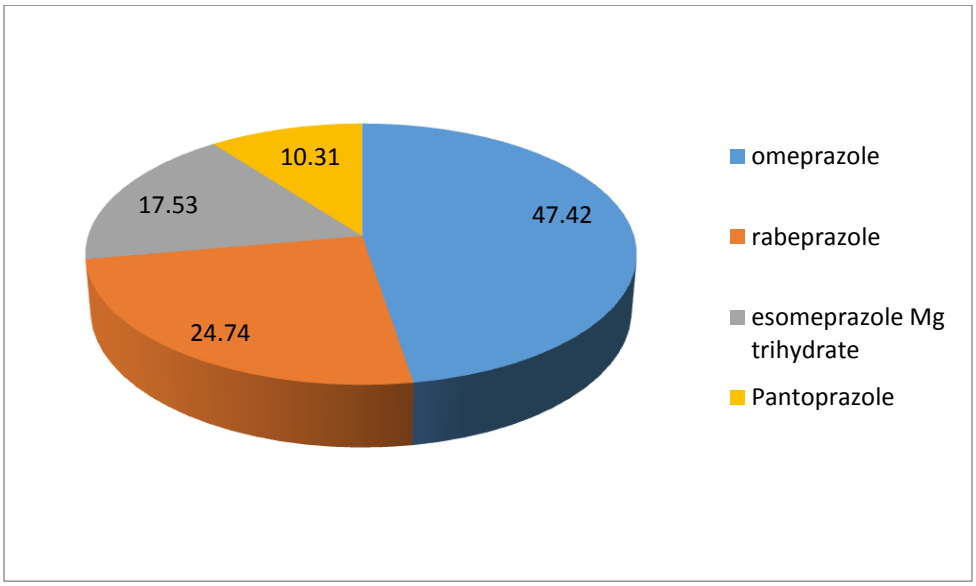

Fig 4.4: % of proton pump inhibitors (PPIs)

We got to know from the study that, 47.42% omeprazole, 24.74% rabeprazole, 17.53% esomeprazole Mg Trihydrate and 10.31% pantoprazole were prescribed by the doctors.

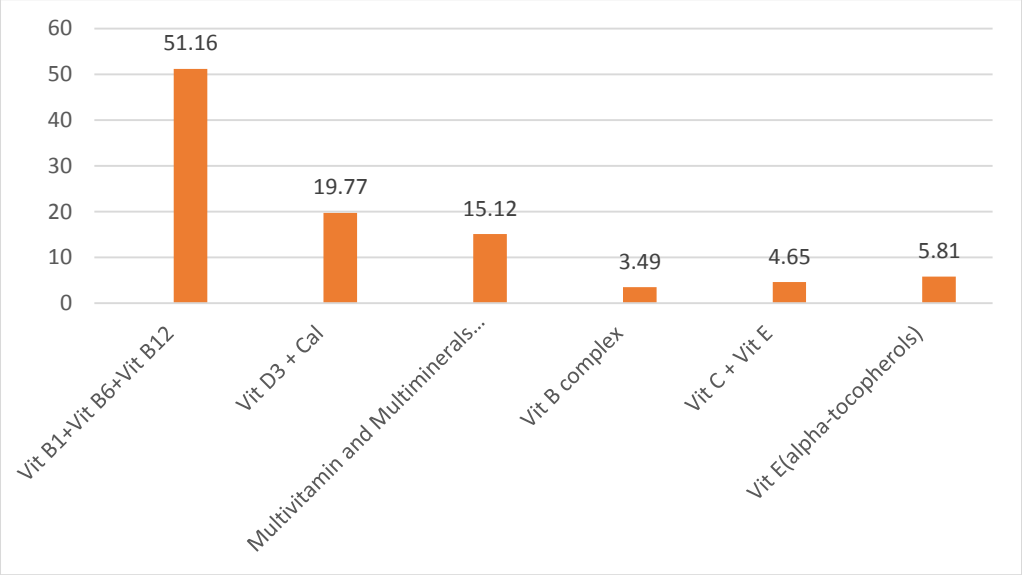

Fig 4.5: % of vitamin combination therapy

The study had shown that, 51.16% Vit B1+Vit B2+Vit B12,19.77% Vit D3+cal, 15.12% Multivitamin and Multiminerals A-Z Gold preparation,3.49% Vit B complex,4.65% Vit C+ Vit E and 5.81% Vit E (alpha-tocopherols) were prescribed by the doctors.

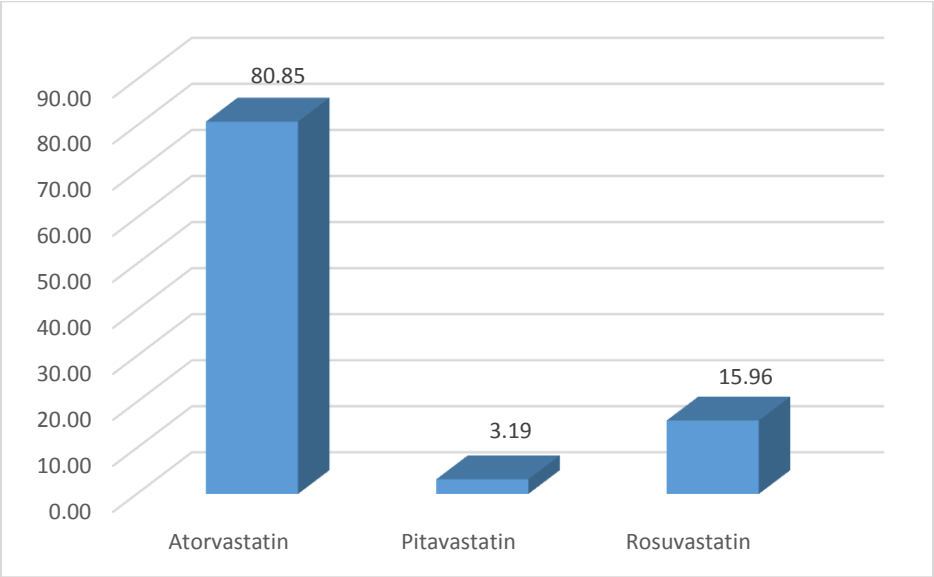

Fig 4.6: % of lipid lowering agents

From the study we got to know that, 18.8% lipid lowering agents were given in which 80.85% atorvastatin, 3.19% pitavastatin and 15.96% rosuvastatin were prescribed by the doctors.

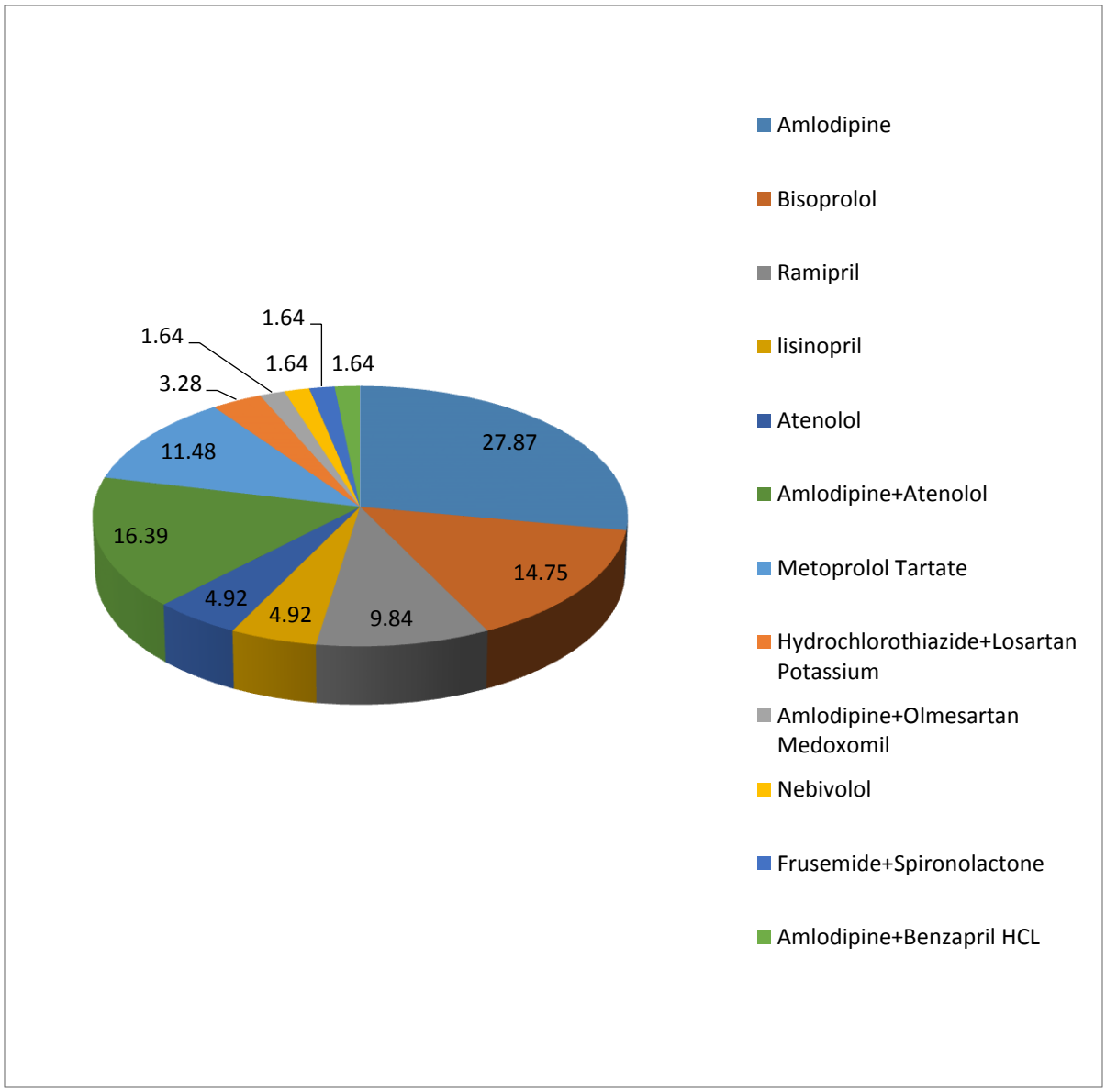

Fig 4.7: % of anti-hypertensive drugs

The study had shown that 27.87% Amlodipine, 14.75% Bisoprolol, 9.84% Ramipril, 4.92% Lisinopril, 4.92% Atenolol, 16.39% Amlodipine and Atenolol combination, 11.48% Metoprolol Tartate, 3.28% hydrochlorothiazide and losartan potassium combination, 1.64% Amlodipine and OlmesartanMedoxomil, 1.64% Nebivolol, 1.64% Frusemide and spironolactone combination, 1.64% Amlodipine and benzapril HCL were prescribed by the doctor.

Chapter Five

Discussion and Conclusion

Discussion

The sample was collected from the BIRDEM hospital Shahabag, Dhaka from 15th June to 27th September, 2016. The study was a descriptive study; in which 500 prescription with diabetes were taken. Treatment information were collected retrospectively from patients diabetic books prescription and new patients initial form prescription of BIRDEM.

In this study, it was found that, 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 dermadromes.*(*WHO,2013)

This outcome of the study showed that, 41% insulin, 2% oral and 57% combination therapy were prescribed (**Fig 4.1**) by the doctors. Among 41% insulin, 81.40% insulin regular and insulin isophane, 4.65% insulin aspart and 13.95% insulin glargine were prescribed (**Fig 4.2**). In **Fig 4.3** showed that insulin combination therapy in which 84.13% insulin and metformin, 3.85% insulin and sitagliptin, 4.33% insulin and vildagliptin, 3.85% insulin gliclazide, 3.85% insulin and glimepiride were prescribed. In **Fig 4.4** had shown that, 47.42% omeprazole, 24.74% rabeprazole, 17.53% esomeprazole Mg Trihydrate and 10.31% pantoprazole were prescribed by the doctors. In **Fig 4.5** had shown vitamin combination therapy in which 51.16% Vit B1+Vit B2+Vit B12, 19.77% Vit D3+cal, 15.12% Multivitamin and Multiminerals A-Z Gold preparation, 3.49% Vit B complex, 4.65% Vit C+ Vit E and 5.81% Vit E (alpha-tocopherols) were prescribed by the doctors. In **Fig 4.6** had shown that 18.8% lipid lowering agents were given in which 80.85% atorvastatin, 3.19% pitavastatin and 15.96% rosuvastatin were prescribed by the doctors. In **Fig 4.7** had shown that 27.87% Amlodipine, 14.75% Bisoprolol, 9.84% Ramipril, 4.92% Lisinopril, 4.92% Atenolol, 16.39% Amlodipine and Atenolol combination, 11.48% Metoprolol Tartate, 3.28% hydrochlorothiazide and losartan potassium combination,

1.64% Amlodipine and Olmesartan Medoxomil, 1.64% Nebivolol, 1.64% Frusemide and spironolactone combination, 1.64% Amlodipine and benzapril HCL were prescribed by the doctor.

Conclusion

Insulin, metformin and other supportive drugs are prescribed commonly for the treatment of diabetes. This research revealed that insulin alone or in combination with metformin or alone metformin or in combination with other drugs or PPIs, Vitamin and its combination with drugs, anti-hypertensive drugs, lipid lowering agents and other types of drugs which were prescribed for the treatment of patient suffering from diabetes. Among the metformin, insulin, PPIs, vitamin, antihypertensive drugs, the mostly prescribed were insulin and metformin in diabetic hospital of Bangladesh for the treatment of diabetes.

In terms of updating the new antidiabetic drug list comprehensively according to the patients need for the treatment of diabetes, further follow up is required for the exclusion of the evidence based effective drugs. Concerted efforts are needed to motivate and updating the new antidiabetic drugs compare with previous antidiabetic drugs. Therefore, it will bring a radical change in treatment of diabetic patients. In conclusion, multicenter research with a large sample is still needed to consolidate the observation of this study.

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