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A Comparative Review Of Drugs And Dosage Form Used In Diabetes Mellitus With Future Aspects

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ABSTRACT:

Regardless of age, diabetes is one of the most prevalent diseases that people deal with. There are several various types of diabetes medications available, but metformin is the most popular. This primary purpose of this article is to provide a comparison of various dosage forms used for treatment of diabetes. However, oral insulin therapy has a number of potential advantages and would be practical for patients. The study and development of oral insulin is a fascinating subject in the study of diabetes. We are making progress toward creating an insulin formulation that won't require injections before to meals, which will enhance the quality of life and mental health of more than nine million type 1 diabetics worldwide. Despite the fact that it is only currently available in injectable form, insulin is nevertheless crucial for the management of diabetes. The ultimate goal for improving simplicity of use and providing therapeutic benefits stemming from its direct distribution to the portal vein and liver is the development of an oral insulin.

KEYWORDS: Diabetes, pathophysiology, oral insulin, dosage forms.

INTRODUCTION:

Since 3,500 BC, diabetes has been acknowledged. It was well-known to the ancient Egyptians, as attested by the Ebers Papyrus. Aretaeus (130–200 CE), who adopted the term diabetes - which derives from the Greek word for siphon - 15 centuries later, correctly identified the warning signs and symptoms of diabetes. Aretaeus of Cappadocia is credited with creating the phrase "diabetes mellitus." It originated from the Greek verb "diabainein" which is made up of the prefix "dia"—which means "across, apart"—and the verb "bainein," which means "to walk, stand" [1]. Diabetes is a Greek term that meaning "to pass through," and mellitus is a Latin word that means "honey" (referring to sweetness) [2]. The most prevalent endocrine condition is diabetes mellitus (DM), which is sometimes known as "sugar"[9].

The clinical and financial costs of diabetes mellitus are enormous for society [3]. Diabetes is a chronic condition that develops when the body cannot properly use the insulin that the pancreas generates or when it does not create enough of it. Uncontrolled diabetes frequently results in hyper glycemia, or elevated blood sugar, which over time causes serious harm to a number of the body's systems, including the neurons and blood vessels. [4].

Diabetes is one of the primary causes of early illness and mortality worldwide due to its long-term effects. Diabetes affects 23.6 million Americans (7.8% of the population), and the prevalence of the disease seems to be rising [5].

Since the progression of the disease is linked to both macrovascular and microvascular damage, diabetes is regarded as an analogous vasculopathy (8)

TYPES OF DM

There are three primary forms of diabetes. They are gestational diabetes mellitus, type 2 diabetes, and type 1 diabetes (T1D). The autoimmune destruction to the -cells that causes T1D, also known as insulin-dependent diabetes mellitus (IDDM), causes the inhibition or stoppage of insulin production. Another name for T1D is "juvenile diabetes." Humans with T2D, also known as adult-onset diabetes or non-insulin-dependent diabetes mellitus (NIDDM), have low or no insulin levels, or they have insulin resistance. Glucose intolerance of varied degrees that manifests or is initially diagnosed during pregnancy and may or may not continue after birth is known as gestational diabetes mellitus.

Diabetes mellitus, either type 1 or type 2, is a dangerous and chronic disorder that is frequently characterized by abnormally raised blood glucose levels as a result of an inability to produce insulin or a decline in insulin sensitivity and function. [7]

PATHOPHYSIOLOGY

The body's ability to use insulin and the quantities of insulin present are factors in the pathophysiology of diabetes. In type 1 diabetes, there is no insulin at all, whereas in type 2 diabetes, the peripheral tissues are resistant to the actions of insulin. Normally, elevated blood glucose levels cause the pancreatic beta cells to release insulin. Glucose is constantly needed by the brain in order for proper activities to take place [10]. Populations are affected differently by type 1 and type 2 diabetes depending on their age, race, ethnicity, location, and socioeconomic level [11]. The earliest diabetes mellitus pathophysiology findings are inextricably tied to polyuria, believed to be its primary (and diagnostic) feature previously.[12]

MEDICATION FOR TYPE 2 DM

People with type 2 diabetes are more prone to suffer a variety of medical problems, such as damage to their eyes and nerves, as well as heart attacks and strokes. the severity of your diabetes, your age, and whether you have other health issues already will all influence the best sort of medication for you. [13]

Biguanides: Biguanides, of which metformin is the most frequently prescribed medication for obese and overweight patients, suppress hepatic glucose synthesis, improve insulin sensitivity, enhance glucose uptake by phosphorylating GLUT-enhancer factor, increase fatty acid oxidation, and reduce glucose absorption from the gastrointestinal tract.

Sulfonylureas: These are often well tolerated but involve a risk of hypo glycemia since they enhance endogenous insulin production. Compared to glipizide, glyburide is linked to greater rates of hypo glycemia.

Meglitinides: Although the binding location is different, the meglitinides Repaglinide and Nateglinide work on the ATP-dependent K-channel in pancreatic beta cells to stimulate the release of insulin from the beta cells in a manner similar to that of sulfonylurea.

Thiazolidinedione: Thiazolidinedione is a specific ligand for the transcription factor Peroxisome Proliferator-Activated Gamma and an insulin sensitizer. They are the first medications to treat the fundamental issue of insulin resistance in people with type 2 diabetes.

Alpha glucosidase inhibitors: Although they have not been widely used to treat type 2 DM patients, the alpha-glucosidase inhibitors acarbose, voglibose, and miglitol are probably safe and effective[14].

Table - 1 Brief history of medication for type 2 DM[15]

Year	Active Ingredient	Category of medications
before 1920s	no effective drugs	-
1921	first commercially available insulin in USA	Hormones
1946	Insulin	Neutral protamine Hagedorn-
1950	Tolbutamide	Sulfonylureas
1959	Metformin	Biguanides
1996	Troglitazone	Thiazolidinediones
1997	Repaglinide	Meglitinides
1995	Acarbose	α-Glucosidase Inhibitors
2005	Pramlintide	Amylin Agonists
2008	Colesevelam	Bile acid sequestrants
2009	Bromocriptine	Dopamine agonist
2013	Canagliflozin	Sodium GlucoseCo-Transporter 2 Inhibitors
2014	Dapagliflozin	Sodium Glucose Co-Transporter 2 Inhibitors
2016	Lixisenatide	Peptide

ADVANCED DRUGS FOR DM-2:

Numerous oral diabetes drugs, such as metformin, sulfonylurea, sodium-glucose co-transporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase inhibitors-4 (DPP4) inhibitors, glucagon-like peptide (GLP) analogues, etc., are available today to control diabetes.[16]

INJECTABLE AGENTS - TYPE-2:

RA-GLP1

Human GLP1 promotes insulin release and is produced in response to meal intake. GLP1, which is produced and released mostly by L-cells found in the distal ileum, and GIP, which is secreted by enteroendocrine K-cells in the proximal gut, are the two incretins that have been identified**.** Treatment with GLP1 in T2DM patients increased glucose-dependent insulin secretion, decreased glucagon secretion, slowed gastric emptying, improved satiety, and decreased food intake. GLP1 offers defence against myocardial ischemia as well.

By how long they last, RA-GLP1 are divided into short-acting and long-acting. Exenatide, taken twice daily, and lixisenatide are two examples of short-acting RA-GLP1. They both offer short-lived GLP1 receptor activation, but their effects on postprandial hyper glycemia, stomach emptying, and fasting glucose are more pronounced. Liraglutide, exenatide LAR's once-weekly formulation, albiglutide, and dulaglutide are examples of long-acting RA-GLP1; they continually activate the GLP1 receptor in contrast to short-acting effects on stomach emptying and postprandial hyper glycemia.[17]

INSULIN

Insulin is a polypeptide hormone that is primarily released by cells in the pancreatic islets of Langerhans [18]. Insulin is a quaternary macromolecule made of two polypeptide chains, an A chain (21 amino acid residues) and a B chain (30 amino acid residues), which are cross-linked by two disulphide linkages once the C-peptide is cleaved [19]. Through cellular glucose uptake facilitation, regulation of carbohydrate, lipid, and protein metabolism, and mitogenic actions that encourage cell division and development, it maintains appropriate blood glucose levels.[20]. The number of people who use insulin varies from country to country, although it is an essential part of managing diabetes mellitus (DM).[21]. Insulin is necessary for many individuals with advanced type 2 diabetes mellitus (T2DM) and for all T1DM patients in order to maintain blood glucose levels within the desired range. Insulin injections into the skin under the skin are the most popular method of administering insulin. Insulin can be administered subcutaneously using a variety of devices, including insulin pens, insulin pumps, and vials and syringes [22]. Insulin stores extra glucose for later use while allowing glucose to enter body cells where it is needed. It also performs other crucial tasks. Blood glucose (sugar) levels rise too high without insulin, which eventually causes injury to the body [23]. The main drawback of insulin therapy continues to be the danger of hypo glycaemia [24].

Newer Insulin Delivery Devices

Numerous advancements have been achieved to increase the simplicity and precision of administering insulin as well as to obtain tight glucose regulation. These include insulin pens, insulin syringes, insulin pumps, implantable pumps, and various insulin delivery method.[25]

Oral Insulin

The study and development of oral insulin is a fascinating subject in the study of diabetes [26]. The ultimate goal is still to create an oral insulin that is easier to use and offers therapeutic benefits due to its direct distribution to the liver and portal vein [27]. Researchers have been actively looking for a way to give insulin orally ever since this life-saving medication was originally created. The quest to discover an alternative to parenteral distribution has developed in line with the success of biologic medications. It has been difficult to get these very large, delicate biomolecules to withstand the severe conditions of the stomach and be absorbed into the bloodstream. However, researchers at Harvard Medical School and the Massachusetts Institute of Technology may have discovered a means to do it. A group led by Robert Langer, an expert in drug delivery, and gastroenterologist and bioengineer Carlo Giovanni Traverso created a hollow pill with its centre of mass close to a flattened end. With this shape, the flat surface of the pill faces the lining of the stomach when it is ingested. A small tension spring with a needle on top that is made of solid insulin is released when the flat end, which is made of sugar, dissolves in the stomach. Once inside the circulation, the needle dissolves after puncturing the outer membrane of the stomach.

The pill was found to deliver the same amount of insulin into the blood as a subcutaneous injection when tested on rats and pigs. Furthermore, the researchers confirmed that prodding the stomach lining does not appear to cause any harm, however further research is required to rule out any potential long-term health problems.

Notably, Rani Therapeutics has adopted a significantly different strategy. The pH of the environment promotes the production of carbon dioxide when this pill enters the small intestine, which inflates a tiny balloon and presses a needle filled with the medication through the intestinal mucosa. The company has carried out multiple research on animals and reported that during one human safety testing, no one saw the balloon inflating. It is currently organising clinical studies for the medication octreotide, which cures acromegaly.[28]

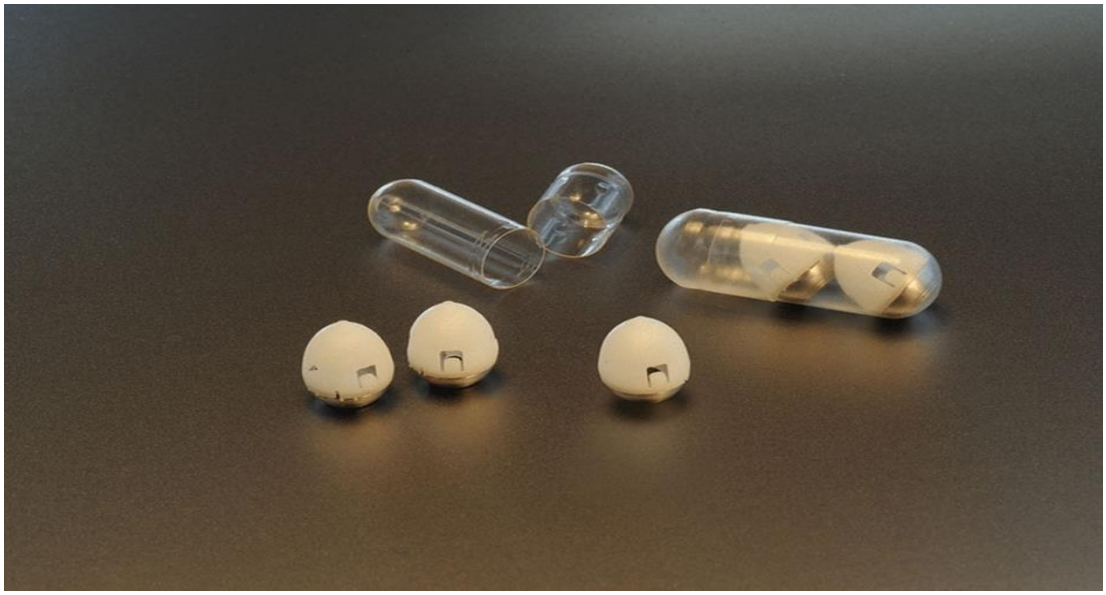

Figure 1:capsules of oral insulin

Advantages of Oral insulin

The most common way to administer insulin is subcutaneously, which is associated with painful injections, needle anxiety, lipodystrophy, noncompliance, and peripheral hyperinsulinemia [22]. Both doctors and patients are concerned about the complexity of insulin regimens, the possibility of hypo glycemia, the potential for weight gain, as well as the need for a needle stick when using insulin therapy. Due to the need to provide conventional insulin before to meals, insulin is seen to have a high index of incursion [26]. In the case of long-term therapy, the oral route of drug delivery is seen to be the most practical and to have high patient compliance. Oral insulin administration will assist to reduce the discomfort associated with injections, psychological hurdles related to several daily injections, such as needle phobia, and potential infections. Subcutaneous insulin therapy does not replicate the normal dynamics of endogenous insulin release, which results in failure to achieve release a lasting glycaemic control in patients. In addition, oral insulin is advantageous because it is delivered directly on the liver, its primary site of action, via the portal circulation, a mechanism very similar to endogenous insulin [29].

Obstacles of Oral insulin

Insulin delivered orally has the disadvantages of a slow onset of action and imprecise glycaemic control because oral delivery systems typically have a large number of excipients and suffer from dose dumping, release burst, variability in absorption, and bioavailability due to a number of confounding factors, including fasting and fed states, concurrent administration, and drug-drug interactions [30].

FUTURE ASPECTS IN TREATMENT OF DIABETES

CELL THERAPY

In cell therapy, the lost cells that create insulin, the hormone that regulates blood sugar, are replaced. Researchers have been striving to create therapies that replace the pancreatic cells with stem cells that have undergone transformation.

The US Diabetes Research Institute has created a miniature organ into which insulin-producing cells can be transplanted. Although the strategy is still in its early stages, it has been successful thus far. The development of this strategy to treat this condition has been undertaken by a Belgian company and other pharmaceuticals. The scientific community anticipates beginning clinical studies in the

upcoming years. Even while the technology is still a ways off from being commercialized and will be pricey, its advantages will make up for these drawbacks.

ATTACKING THE ORIGIN WITH IMMUNOTHERAPY

The insulin-producing beta cells in the pancreas are damaged by the body due to the autoimmune condition known as type 1 diabetes. Since type 1 diabetes is an autoimmune illness, immunotherapies are now being researched as a potential treatment for a variety of autoimmune diseases. This technology's goal is to stop the autoimmune procedure. A start up called Imcyse is working on an immunotherapy that involves injecting a chemical into the body to trigger the production of a new type of immune cell that specifically targets beta cell killer cells. [31]

DIETARY SUPPLEMENTS FOR THE MANAGEMENT OF DIABETES

A nutritional supplement made up of a combination of extracts from five plants has been created by the French biotech company Valbiotis. They released encouraging findings from a phase IIA research of their drug in July 2019 that aimed to compare its effectiveness to a placebo in pre-diabetic populations.

AUTOMATED PANCREAS REPLACEMEMNT THERAPY

The "artificial pancreas" — a completely automated system that can assess blood glucose levels and administer the proper quantity of insulin into the bloodstream, just like a functional pancreas would may offer a more immediate answer for those who have already lost their insulin-producing cells.

TARGETING THE MICROBIOME

In the last ten years, scientists have come to understand the significant impact that the microorganisms that live inside and on us have on our health. Numerous chronic diseases, including diabetes, have been related to the human microbiome, particularly the gut microbiome.

In 2017, University of Amsterdam researchers found that faecal transplants, which transfer a healthy person's microbiota to a person with diabetes's gut, can reduce insulin resistance in type 2 diabetics who are obese temporarily. Similar outcomes were shown in people who had just received a type 1 diabetes diagnosis in 2021.[31]

CONCLUSION

The most common and prevalent disease affecting both men and women is diabetes. The first-line treatment for diabetes is metformin. Metformin dosage dumping occurs in diabetic patients who take it often. Insulin is therefore the most important treatment for diabetic individuals. Although it is very helpful for diabetic patients, the biggest disadvantage is that when a patient takes the insulin, he or she develops a phobia and feels uneasy about taking the medication. The patient has pain and inflammation at the injection site. Therefore, oral administration of insulin is the more recent method, and people with diabetes can take the tablets without concern. Additionally, the advantages of oral insulin include less side effects and the prevention of hypo glycemia and weight gain.

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