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REVIEW ARTICLE

Novel Drugs for Diabetes Mellitus: A Mini Review

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ABSTRACT
The most prevalent type of diabetes, type 2, is a chronic and progressive disease characterized by which the body does not produce or use insulin normally, causing elevated blood glucose (sugar) levels. Even though there are numerous drugs available to treat diabetes, many people fail to meet the suggested blood sugar objectives. Hormones involved in blood sugar regulation include glucose-dependent insulin tropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). The primary shortcomings which trigger diabetes of the type 2 variety to develop, and progress are impaired insulin secretion, increased hepatic glucose production, and decreased peripheral glucose consumption. However, the pathogenesis of this condition also involves brain insulin resistance/neurotransmitter dysfunction, increased adipocyte insulin resistance (increased lipolysis), diminished in cretin secretion/sensitivity, increased glucagon secretion, and enhanced renal glucose reabsorption. Although blood glucose levels are the primary focus of modern diabetes management, the aim of therapy should be to stall the course of the disease and eventual treatment failure. Early implementation of combination therapy employing many medications with various mechanisms of action is a necessary component of optimal care.
Keywords: *diabetes mellitus, insulin, drugs, therapy*

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INTRODUCTION

Diabetes is a complicated group of metabolic diseases, and the etiopathology of the disease determines its treatment and management (1). Diabetes is a condition that lasts a lifetime and is brought on by deficits in insulin secretion, action, or both. The importance of insulin as an anabolic hormone causes abnormalities in the metabolism of proteins, lipids, and carbohydrates(2).The primary causes of these metabolic abnormalities are decreased insulin levels to achieve the desired response and/or insulin resistance of target tissues, specifically skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes(2).

People with type 2 diabetes frequently experience no symptoms in the early stages of the disease. But people who have severe hyperglycemia, as is frequently the case in kids with complete insulin insufficiency, may also have polyuria, polydipsia, polyphagia, weight loss, and hazy eyesight. Ineffective diabetes care can lead to ketoacidosis or, less frequently, nonketotic hyperosmolar syndrome, both of which, if managed, can result in coma and death (2). Both macrovascular disorders like coronary heart disease, stroke, and peripheral artery disease as well as microvascular conditions like diabetic kidney disease, retinopathy, and peripheral neuropathy are associated with chronic hyperglycemia. People with type 2 diabetes mellitus frequently experience heart failure as an early sign of cardiovascular disease, which increases their chance of dying(3).

Although these conventional diabetes complications still cause a significant burden of disease, rates are reducing due to better diabetes management. As diabetics live longer, population-based studies suggest that vascular disease no longer causes most diabetes-related deaths (1), and that individuals with diabetes mellitus achieved significant improvements when recovering from acute myocardial infarction and that diabetes was not associated with worsening angina (4). As mentioned previously diabetes mellitus is classified by the American diabetes association into type 1 autoimmune diabetes which is

caused by elimination of pancreatic beta cells. In children and adolescents, 80-90% of cases are of the type 1 variety. at the same time type 2 diabetes is widespread in population of age 40-59(2) and in individuals with coexisting genetic predispositions or contemporaneous medication therapy such as corticosteroids as they are more susceptible to hyperglycemia (1). The rising prevalence of the increase in type 2 diabetes among younger population is primarily attributable to the change in their lifestyle in terms of becoming more sedentary life and less healthy nourishment which is the main cause of insulin resistance that led to type 2 diabetes, it also comes in another form which is gestational diabetes, this type of diabetes has an increased risk to maternal, neonatal, fetal outcome. other types of diabetes such as monogenic diabetes which is caused by a genetic defect in a single gene in pancreatic cells, which disrupts cell function or reduces the number of cells (2).

PATHOPHYSIOLOGICAL MECHANISMS OF DIABETES

Diabetes is defined by high blood sugar, in which insulin production does not match the body's demand for insulin. Therefore, we find that the pathophysiological mechanisms that explain the disappearance of beta cells are complex and heterogeneous for different types of diabetes. In addition to genetic and environmental factors, many studies have revealed the main role of epigenetics, gut microbiota, and intestinal permeability in the development of diabetes mellitus (3). Insulin resistance is characterized bythe inability of insulin to achieve a maximum response in its target organs; At the muscle level during glucose carrying, it results in a failure of glucose uptake in the muscles. At the liver level, there is an increase in glucose production in the liver, which is the cause of fasting hyperglycemia .There is also lipid insulin resistance.

Relative insulin deficiency characterized by insufficient insulin secretion, given the level of glucose in the blood. This disorder, present from the onset of the disease, is progressive and inevitable and worsens with age and duration of diabetes, until it leads to the maximum insulin-necessary diabetes mellitus [4]. Several genes are implicated in the onset of diabetes, these genes having a role in pancreatic development or insulin synthesis [5].

Glucotoxicity: Hyperglycemia aggravates the deficit of pancreatic insulin secretion as well as insulin resistance, by raising the threshold of the "glucose sensor" of beta cells [6].

Lipotoxicity: Failure to slow down lipolysis due to insulinogenic and insulin resistance of adipocytes is responsible for an increase in free fatty acids. This increase in free fatty acids increases the "sensor threshold" of insulin secretion and aggravates the decrease in insulin secretion. It also increases insulin-stimulated glucose utilization [7]. Adipokines: Insulin resistance is partly linked to the secretion of adipokines by adipocytes such as tumor necrosis factor (TNF). Defined as a diminished response to the administration of exogenous insulin, insulin resistance is favored by android obesity, age, and sedentary lifestyle [7].

Diabetes is also accompanied by abnormalities as in the case of syndrome X (2005), characterized by android obesity associated with two of the following abnormalities: hypertriglyceridemia/ a decreased level of high-density lipoproteins (HDLc) / a hypertension/ fasting hyperglycemia or diabetes. The consequences of insulin resistance are an increased vascular risk due to diabetes and other abnormalities often associated: arterial hypertension (HTA), dyslipidemia, etc [8].

NOVEL THERAPY OF DIABETIC

The clinical data of 16 566 and 2746 patients treated with sodium glucose cotransporte-2 inhibitors (SGLT2i) and glucagon-like peptide 1 receptor agonists (GLP-1RA), independently, from January 1, 2016, to December 31, 2018, was examined in multicenter research in Taiwan. From the date of the medication record until the occurrence of new-onset atrial fibrillation (AF) or the conclusion of the ensuing period, patients were observed. They concluded that in patients with type 2 diabetes mellitus, SGLT2is had a decreased risk of newly developing AF compared to GLP-1RAs [9]. Another study analyzed a novel nano-carrier of hesperidin to achieve a sustained release of hesperidin and to investigate the effectiveness of the novel formulation as an antidiabetic drug in comparison to metformin in type 2 diabetes [10].

The US Food and Medication Administration has given the green light to 10 drug classes for the management of type 2 diabetes (T2DM). Drugs being developed for T2DM must demonstrate significant glycemic parameter reductions in addition to cardiovascular safety. Using contemporary T2DM therapies, the results of an increasing number of cardiovascular outcome trials have demonstrated a decreased risk of atherosclerotic cardiovascular disease, congestive heart failure, and chronic kidney disease. Guidelines now emphasize customized glycemic targets while also maximizing safety, non-glycemic benefits, and the avoidance of problems. They are also becoming more evidence-based and patient-centered. The expectations for novel T2DM medications have increased because they are now anticipated to accomplish

these goals and perhaps even address coexisting diseases. We are now closer than ever to realizing our shared objective of genuinely personalizing treatment for T2DM.(11)

One of the metabolic disorders characterized by hyperglycemia, diabetes frequently co-occurs with several complications. Hydrogen peroxide (H2O2), a biomarker of oxidative stress, is closely associated with the onset and progression of diabetes and its consequences. Sadly, no fluorescent probe has been described for imaging H2O2 in diabetic mice. Here, a brand-new NIR fluorescent probe called QX-B was created and developed to find H2O2. The fluorophore for the probe is the quinolinium-xanthene dye, and the response group is the borate ester. A significant NIR fluorescence signal at 772 nm is seen with the injection of H2O2. The probe exhibits exceptional selectivity to H2O2 over other compounds in addition to strong sensitivity with10-fold improvement, but it also shows remarkable H2O2 selectivity over other potential interference species. Meanwhile, the potential QX-B response mechanism to H2O2 was hypothesized and supported by experiments involving high-performance liquid chromatography (HPLC), mass spectrometry (MS), and density functional theory (DFT). Furthermore, QX-B has been successfully used to image exogenous and endogenous H2O2 in HeLa cells, HCT116 cells, 4T1 cells, and zebrafish due to its low cell cytotoxicity. More crucially, QX-B has been employed for the first time to monitor H2O2 in diabetic mice after being inspired by the performance of NIR fluorescence. For the diagnosis and management of diabetes and its consequences, this information is crucial.(12)

NEW MEDICATION

The reason behind developing new medication to treat Diabetes Mellitus is that several limitations of the traditional drugs by are common, lack of efficacy due to improper dosage, decrease potency or changed effect by reason of metabolism or specificity to the target. (13) Moreover, potential hypoglycemic and weight gain, increase cardiovascular risk like thiazolidinedione. (14)The Goals of novel therapies are to assist patients in achieving their individualized glycemic target while maximizing safety, non-glycemic advantages, and the prevention of complication for patients who are at risk of specific complications. (14)

A novel class "Glimin" is a glucose-lowering agent that targets multiple diabetic pathophysiology, the first drug in this class is Imeglimin. Developed by Poxel in several Asian countries. (16) In June 2021 Imeglimin got its first approval use for the treatment of type 2 Diabetes Mellitus in Japan, related to extensive positive results in preclinical and clinical data from three pivotal clinical trials in phase III. (16)(17) The favorability related to safety, efficacy, and lack of severe hypoglycemia because of a unique mechanism of action it involves dual effect: both reverse pancreatic beta-cell dysfunction and enhance insulin action in liver and skeletal muscles, improvement key root cause of T2DM defective; cellular energy metabolism and protection from cell death. (17)

The triple combination tablet Empagliflozin/Linagliptin/Metformin extended release related to classes SGLT2i, DPP4i, and Biguanide. In January 2020 approved by the FDA for the treatment of type 2 Diabetes Mellitus in phase III. (18) The favorability related for the patient who needs lowering glucose concentration using multiple agents, according to the recommended treatment. Intensifications for T2DM, the studies that have been published show the safety and efficacy of these Combinations. These studies have proven bioequivalent to the corresponding free combination. (19)

Lyumjev was developed to reduce postprandial glycaemic peaks after eating. Lyumjev Is an ultra-rapid Lispro (Urli) formulation that is indicated to improve glycemic control in adults with both type 1 and type 2 diabetic patients, in 2020 approved by the FDA. (20)(21)

The two inactive ingredients are used to improve absorption at the site of injection. The First Ingredient Is Treprosinil used to induce vasodilation. The other ingredient, citrate, increases vascular permeability. These two ingredients permit Lispro to be absorbed rapidly, which leads to a faster onset and a shorter duration of action. In proportional terms, Urli is capable of have a six to seven-fold insulin exposure in the first 15 minutes in contrast to Lispro. (20)

THE EFFECT OF TREATMENT AFTER REPLACING NEW MEDICINES WITH OLD ONES

Sodium-glucose cotransporter 2 inhibitors (SGLT2i)

In 2021 study linking atrial fibrillation and diabetes with dapagliflozin from Sodium-glucose cotransporter 2 inhibitors (SGLT2i). It reported its effect on reducing and decreasing the incidence of atrial fibrillation and atrial flutter, and the effect was stable for heart patients or without, with no difference or effect due to gender or cumulative sugar A1c and the last history of attacks or the presence of atherosclerosis disease, history of ischemic stroke, body mass index.

On other hand known dapagliflozin beneficial to reduce hospitalization effects of dapagliflozin for kidney and heart failure, "dapagliflozin appears to lower the risk of AF/AFL events in a broad population of

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patients with type 2 diabetes mellitus, including those with and without coronary artery disease or heart failure at baseline". (22).

Dipeptidyl peptidase-4 (DPP-4)

Dipeptidyl peptidase-4 (DPP-4), One of the main clinical factors associated diabetic and severity of coronavirus disease 2019 (COVID-19) expressed in endocrine cells, endothelial cells and pneumocytes, a transmembrane glycoprotein and immune cells.This hypothesis was built based on the observation that MERS-CoV infection in type 2 diabetes (T2DM) could be associated with a DPP-4 dysregulated immune response.

Experiments have been conducted that include the safety of using diabetes medicines for patients with corona, was the target to know more about effect anti diabetes drug specific with drug dipeptidyl peptidase-4 (DPP-4) inhibitors when patient have (COVID-19) coronavirus .The study proof "can use DPP-4 inhibitors it's consider the safety of during the COVID-19 pandemic for diabetes management and they can be continued use ". (22)

Glucagon-like peptide 1 (GLP-1)

In other effects of peptidyl Peptidase 4 Inhibitors in patient Diabetes Mellitus on Renal Function which have impaction improve renal outcomes in patients glucagon-like peptide 1 (GLP-1) receptor agonists can with type 2 diabetes mellitus.Results this study have effect to lower risk of eGFR decline when use of DPP-4 inhibitors, in patients with type 2 DM., alone or in combination with other glucose-lowering agents for glycemic control. (23)

Semaglutide, a glucagon like peptide-1 (GLP-1) receptor agonist, have effects as anti-obesity purpose .use treatment option for better glycemic control in type 2as second line available as monotherapy. in patients with renal or hepatic disorders demanding no dose modification. done modification enhanced albumin binding and reduced renal clearance in adults and elderly has been proved to be safe.

Another effect on established that it can reduce various (CV) Cardiovascular by negatively regulating has been reported multiple inflammatory pathways reduce atherosclerosis after taking Semaglutide is both subcutaneous as well as oral dosage form (first approved oral GLP-1 receptor agonist). It has been approved as a diabetes and currently under scrutiny for but still have some side effects mild effect like constipation, diarrhea, vomiting, nausea, and dyspepsia other side effect have infrequent rise pancreatic enzyme (amylase and lipase) levels nasopharyngitis, headache, infections in urinary tract, upper respiratory tract. no risk of hypoglycemia in monotherapy but suffers from gastrointestinal adverse effects. (23)In two studies more than the result diabetes in patients using semaglutide/liraglutide and other meta-analysis indicates which appeared GLP-1RAs associated with a appeared reduction in albuminuria also semaglutide/liraglutide have protective effect in patients chronic kidney disease . (24)(25)

SODIUM-GLUCOSE COTRANSPORTER 2 INHIBITORS (SGLT2I) A CASE REPORT

In the most recent 2021 monitoring of a case issued about the effect of SGLT2, it was proven that it can lower the level of sugar in the blood without any side effects. The case was for a 74-year-old woman have uncontrolled hyperglycemia after taking new oral drug alpelisib(PI3K inhibitor) which an indication for the treatment of some advanced or metastatic breast cancers. After takingnormal anti-diabetic drugs such as metformin and vildagliptin, combined with intravenous insulin infusion of more than 250 units/day" do not have any improve, in this report proof to manage severe hyperglycemia when use of a sodium-glucose cotransporter 2 (SGLT2) inhibitor without significant side-effects. need more Longer-term and larger studies for confirm the effect useful SGLT2 inhibitors as good as remove side effect for anti-cancer efficacy. But in this report view improve it successful to manage severe hyperglycemia are use of dapagliflozin (an SGLT2 inhibitor). (25)

CONCLUSION

Diabetes is a complex set of metabolic illnesses, through a several novel medication and therapy, a complete and successful cure of DM remain untouched. Considered a novel therapy depending on patient condition and accompanying health offer, the SGLT2is and GLP-1RAs among T2DM patients they lower chance of new-beginning AF, sustained release of hesperidin showed antidiabetic, antihyperlipidemic, antioxidant, and anti-inflammatory properties, Imeglimin related to a novel class "Glimin" have unique mechanism of action it involves dual effect, Lyumjev was developed to reduce postprandial glycemic peaks after eating ,The Goals of novel therapies are to assist patients in achieving their individualized glycemic target while maximizing safety, non-glycemic advantages, and the prevention of complication for patients who are at risk of specific complications.

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AUTHOR CONTRIBUTION

All authors contributed equally as a first author in the conception, idea, writing and revising the manuscript.

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