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A Fluid Approach to Type 2 Diabetes Management: Recent Advances in Medication Therapy from Tradition to Novelty

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Abstract

This review navigates the evolving landscape of Type 2 Diabetes (T2D) management by examining recent advancements in medication therapy, spanning from conventional approaches to groundbreaking innovations. Recognizing the dynamic nature of diabetes treatment, we delve into the traditional antidiabetic agents, such as metformin and sulfonylureas, and evaluate their sustained relevance in the context of contemporary therapeutic regimens.

The synthesis of established treatments with novel pharmacological interventions takes center stage as we explore the transformative impact of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose co-transporter-2 inhibitors (SGLT-2Is). These agents not only address glycemic control but also demonstrate cardiovascular and renal benefits, reshaping the paradigm of T2D management. Additionally, we investigate promising emerging therapies, including dual and triple combination therapies, personalized medicine approaches, and the potential role of oral hypoglycemic drugs in optimizing treatment strategies.

By embracing a fluid and integrative perspective, this review aims to provide healthcare professionals and researchers with a comprehensive understanding of the diverse pharmacotherapeutic options available, fostering informed decision-making and paving the way for enhanced personalized care in the dynamic landscape of T2D management.

Keyword: Incretin Mimics; Gliptin; Personalized Medicine

Highlights

Insulin resistance along with β cell dysfunction merge to generate type 2 diabetes mellitus (T2DM), a metabolic disorder.

The first-line treatments for the aforementioned illness include combination medication regimens and monotherapy.

An overview of current developments drugs centered on delivery techniques and traditional therapy modalities for type II diabetes are provided in this article.
Type 2 Diabetes is basically the disturbed metabolism of carbohydrate which further leads to other long term malfunction of nerves, nephrons and the retina.

Introduction

Type 2 diabetes mellitus is widely spreading all over the world as one of the unhealthy disorders among old to medium-aged individuals. The main underlying cause of this metabolic illness is an absence of releasing insulin caused by a gradual or marked failure of pancreatic Beta-Langerhans islet cells to make insulin. Other causes were peripheral tissues inability to absorb insulin. Diabetes and insulin resistance are strongly linked to BMI. Diabetes mellitus is most closely connected with obesity; for example, obese people have higher levels of proinflammatory markers, hormones, cytokines, non-steroidal oils, glycerol, and other substances that promote the development of insulin resistance. Weight growth and body mass are crucial in the onset and progression of either type 1 or type 2 diabetes. In obese people, the main causes are (I) insulin resistance and (II) Beta-cell malfunction. T2DM is a metabolic condition mostly brought on by decreased insulin sensitivity or production. They fall under the general headings of type 1 and type 2 disorders. Reduced insulin secretion from the pancreatic beta cells primarily causes Type 1, while Type 2 results from peripheral cells losing sensitivity to sufficient insulin secretion due to lost insulin receptor sensitivity. This leads to a decrease in insulin levels, causing a condition known as Type 2 diabetes mellitus. [1]

Which country is in the lead?

Bangladesh and Sri Lanka have sluggish rates of urbanization, while China, Pakistan, India, and Thailand have middle rates (30%). The main factors contributing to the rise in diabetes prevalence around the world are aging and urban population growth. Aging populations have been primarily blamed for the increased prevalence of diabetes[2]. Both China and India have a higher number of elderly and unhealthy individuals.

Urbanization and internal rural-to-urban migration have several negative effects, including decreased physical activity, a shift in diet toward high-energy foods, and significant increases in
body mass index (BMI) and upper body adiposity.[3]

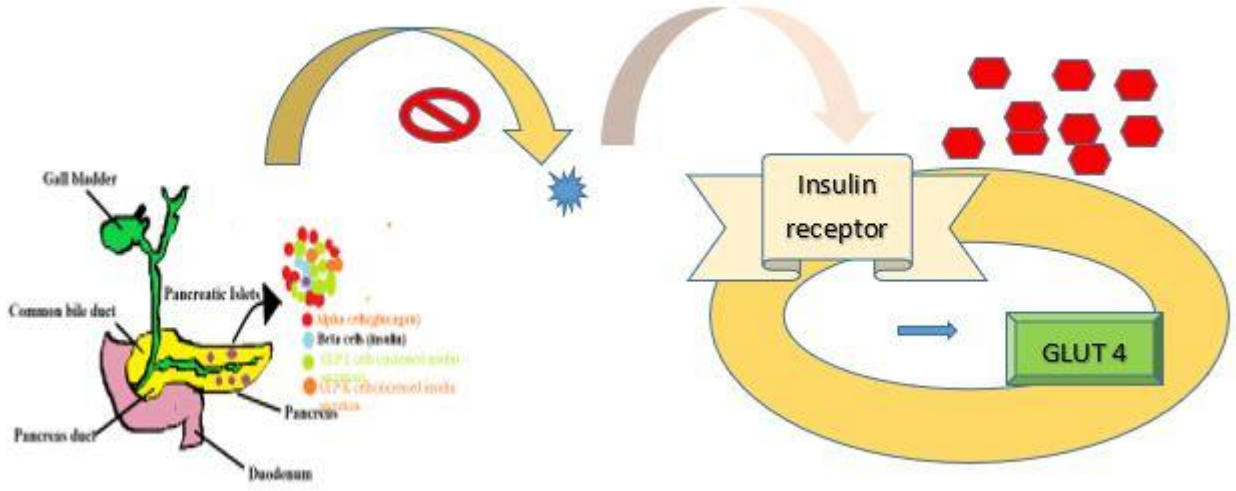

Fig.1: Type 1 diabetes mellitus: The mechanism demonstrates that the insulin receptor is unable to metabolize the concentrations of insulin due to its insufficient production. Consequently, the insulin is not absorbed by the receptors, which is the primary cause of type 1 diabetes.

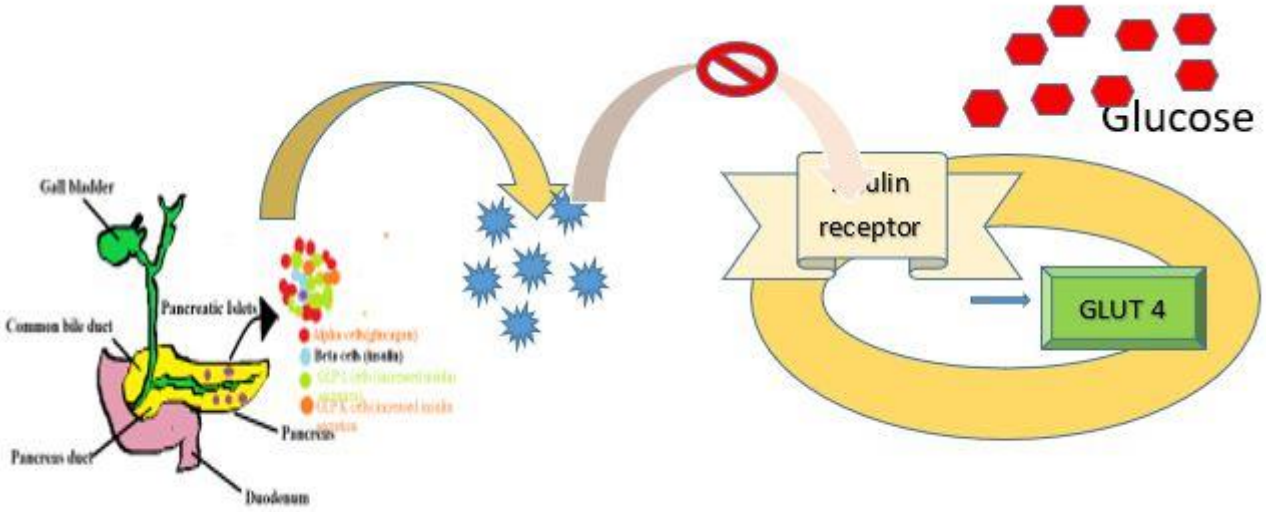

Fig. 2: Type 2 diabetes mellitus: The mechanism demonstrate that, despite sufficient insulin production, the insulin receptor is insensitive. As a result, insulin is produced in this type of diabetes but cannot be absorbed by the receptor, which is the primary cause of type 2 diabetes.

Presently, it is thought that type 2 diabetes is caused by at least eight basic mechanisms. The aforementioned symptoms include hyperglycemia-related defects in the kidneys, abnormal beta-cell insulin production, abnormal alpha-cell glucagon secretion, increased metabolism of lipids, increased hepatic glucose, abnormal incretin action, and abnormal neurotransmitter dysfunction [4]. As a major predictor of both cardiovascular and renal outcomes in people with type 2 diabetes, hypertension is closely associated with the development of albuminuria.[5]

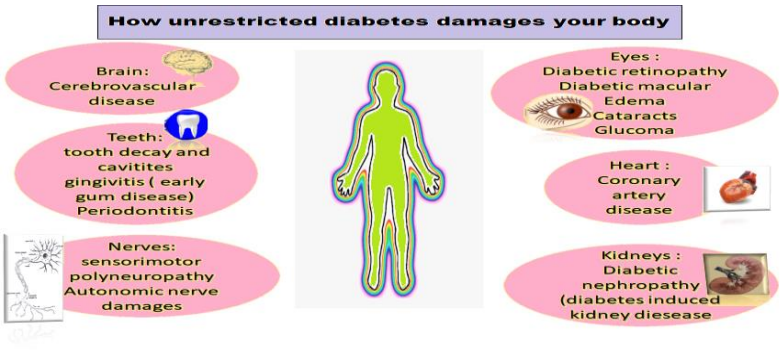

Fig. 3: Uncontrolled diabetes affects the body's different organs. Type 2 diabetes mellitus does not only affect a single organ of the body it causes long-term damage to neurons, the retina, and nephrons associated with other micro and macro cardiovascular risk**.**

Global Footprint of Type 2 Diabetes

Diabetes is the third largest cause of mortality in the United States, trailing cancers and heart related serious issues, making it one of the most significant and pervasive health crises of this century. Numerous new antidiabetes agents are discovered every year, but it is very burdensome to get rid of this lethal disease. Diabetes has a major effect on mortality and fatality. [6]

India and China are one of the most populated countries in the world out of which China beat India in the year 2023 in terms of the population.

It is now estimated that the number almost reached to 387 million people globally suffering from Diabetes. Due to changes in obesity rates and a decrease in or elimination of physical inactivity, numbers in emerging countries are considerably increasing. The prevalence of diabetes has exploded in the twenty-first century.

Recent Diabetes Medications

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are a relatively new class of medications that have been introduced for the treatment of type 2 diabetes mellitus (T2DM). They frequently strive for benefits that go beyond glucose management by steadily lowering blood pressure, body weight, and serum uric acid. They tend to lower hyperglycemia by increasing urine glucose excretion. [7]

The latest convincing developments in dual Relying on Glucose Tirazepatide, a glucagon-like peptide-1 (GLP-1) receptor agonist, and insulinotropic polypeptide (GIP) were developed based on preanalytical research in animals as models and clinical testing in humans, emphasizing its notable differences from other anti-diabetic medications. The suggestion is to enumerate any further treatment alternatives and methods that tirzepatide could provide. [8]

Although GIP and GLP-1 therapeutic drugs are available as oral hyperglycemic drugs which are used for the composition of Incretin. However, both can be quickly rendered inactive in vivo by dipeptidyl peptidase IV (DDP IV) [9].GLP-1, a polypeptide hormone released from the gut, quickens release the of insulin and suppression glucagon production was linked as a parent compound for novel treatments of diabetes, but was devalued (dipeptidyl peptidase-4) and eliminated (mainly by kidneys) too fast (half-life 1-2 min) to be useful as a therapeutic agent.GLP-1 receptor agonist has been used to treat patients with type 2 diabetes mellitus since 2007. [7].[10]

Table 1: The following table illustrates the means by which anti-diabetic medications work and the negative effects they have on the body

Medications designed to combat diabetes	The functioning mechanism	Deleterious effect
Biguanides	Both uptake and the amount of glucose released into the bloodstream by the liver and muscles are simultaneously decreased.	Dyspepsia and lactic acidosis.
DPP-4 is a dipeptidyl peptidase.	Increases the blood levels of the incretin-based imitators of GLP-1, which in turn suppresses the release of glucagon.	The risk of tumors and cancers is increased by DPP-4, which primarily suppresses neoplasm.[11] Potentially influencing cancer biology is CD26/DPP-4. DPP-4 has the potential to either repress or promote the growth of cancer.
Meglitinides with sulfonylureas	Boosts the pancreatic beta cell's power to generate insulin.	Cancer risk is associated with its long-term use.[12] Hypoglycemia
Thiazolidinediones	Regulate the insulin-related genes, which boost the mRNA production of insulin-dependent enzymes and improve insulin action in muscle.	Diseases of the heart and liver.
Alpha glucosidase inhibitor	The breakdown of carbohydrates(starch) is prevented which restricts the entry of glucose into the bloodstream.	Diarrhea and bloating

There are numerous medication classes currently available for Type II diabetes, some of which are listed below:

1. Dual-receptor agonist for calcitonin and amylin
2. Medications that block or inhibit the activity of SGLT2, or sodium-glucose co-transporter 2.
3. Glucosidase alpha modulator
4. Incretin mimics comprise Agonists for GLP-1 and DPP-IV stabilizers.[13]

Agonist of amylin

Duplex amylin and a hormone called calcitonin whose receptor agonists (DACRAs) are majorly released by the thyroid gland are useful for the medical management of T2DM through better responsiveness to insulin. They stand out for their innovative approach to treating T2DM. Additionally, it functions

similarly to other amylin agonists that are used in conjunction with other traditional T2DM treatments like metformin and GLP-1 analogs. Animal studies have demonstrated the metabolic success (beyond amylin) of duplex amylin calcitonin-like receptor agonists (DACRAs) on a range of classic amylin-related effects, such as body weight reduction and an improvement in postprandial glucose level regulation. By significantly enhancing glycemic status and HbA1c levels, which are primarily responsible for decreasing blood glucose levels, DACRAs produce favorable effects in animal models of T2DM.
[14]

Therapies based on Incretin

Incretin is discovered to be made up of GIP and GLP-1 medicines, however, there in vivo inactivation by DPP-IV inhibitor makes it less effective for treating T2DM. DPP-IV inhibitors, on the other hand, deplete DPP-IV without depleting GLP-1; as a result, they are the ideal new options in antidiabetic medical care based on this therapeutic target.

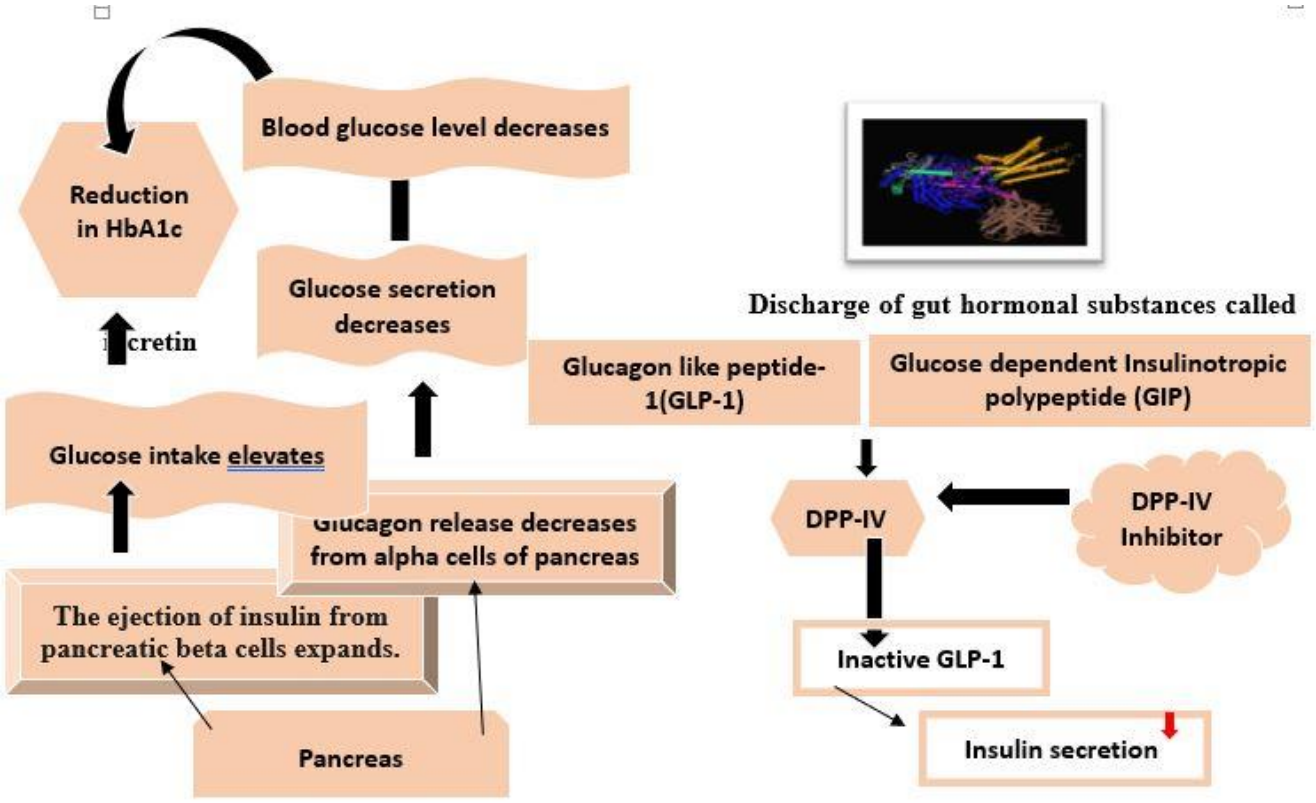

Fig. 4: Diagrammatic mechanism of incretin mimetic in reducing HbA1C and blood sugar: The pancreatic beta cells secrete insulin into the bloodstream, which raises the intake of glucose, while the pancreatic alpha cells secrete glucagon, which lowers the level of glucose. This results in a decline in blood glucose levels overall, which lowers the HbA1c ratio. Conversely, the gut hormone incretin causes a drop in the incretin mimics known as GLP-1 and GIP because the DPP-IV stabilizers cause DPP-IV to become active, which in turn inactivates GLP-1 and reduces insulin secretion.

Tragically, GIP, the first enteric insulin to be discovered, went unnoticed for a very long time due to its insufficient capacity to induce insulin release from pancreatic cells in individual with Type 2 diabetes mellitus.

Over ten years ago, the first GLP-1 receptor antagonist, exenatide, became available for use in pharmacies. Since then, the development of this class of incretin-based therapies has improved glycemic control and helped patients shed weight. After oral glucose-lowering medications failed (often before starting insulin therapy), they are now advised as the first injectable therapy. **[15]**

Drugs for treatment of T2DM

Microvascular, macro vascular (blindness), and cardiovascular (CVD) diseases are the three main effects of T2DM on global health. According to the methods by which they lower blood sugar, several medications are categorized, including Beta-
glucosidase inhibitors (AGIs), a hormone called insulin, sulfonylureas (SUs), meglitinides (glinides), an d thiazolidinediones (TZDs). On the other hand, some groups (like DPP4i) lack clinical evidence, while others (like hypoglycemia from SUs in elderly people) have both unknown benefits and potential risks. The clinical benefits of more recent drugs, like SGLT2 and GLP1, have been seen in people with T2DM.

Biguanide's mode of action: Metformin

In 2020, metformin as first-line therapy will have the highest percentage of incident users (up from 71.3% to 73.3%), indicating that it will primarily serve as a "blood sensitizer" to lower blood glucose levels.

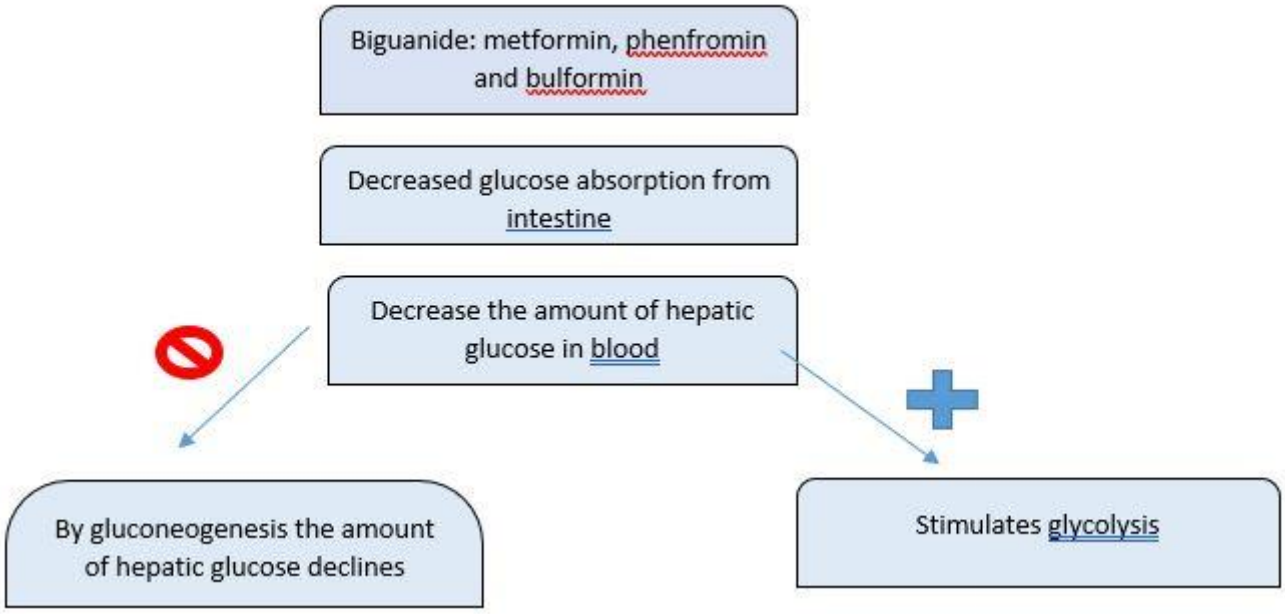

Fig 5: Biguanide's mode of action: Different types of biguanide such as metformin, phenformin, and bulformin cause a decrease in the raptness of glucose from the intestine and decrease the liver's glucose level which inhibit the gluconeogenesis and stimulate the glycolysis. Due to the risk of lactic acidosis, the latter two (phenformin and bulformin) were removed from clinical usage, but Metformin has a significantly lower risk and is, therefore, more widely used. [13]

Empagliflozin's SGLT2 inhibitor's mode of action

The primary function of SGLT2 is to reabsorb glucose from the glomerular filtrate and reintroduce it into the circulation. SGLT2 is inhibited by empagliflozin. The renal excretion of filtrated glucose is increased by empagliflozin, which also decreases the renal threshold by suppressing SGLT2.

Empagliflozin improves the excretion of glucose from the urine by significantly declining the renal tubular verge for glycosuria. Additionally, osmotic diuresis of glucose and natriuretic nature of sodium that is co-transported reduces blood pressure. [7] A methylene bridge connects the proximal and distal benzene rings of the SGLT2 protein's glucose ring. The proximal convoluted tubule (PCT) of nephrons consists of SGLT1 and SGLT2, both of which are crucial for the glomeruli to take in filtered glucose. [14]

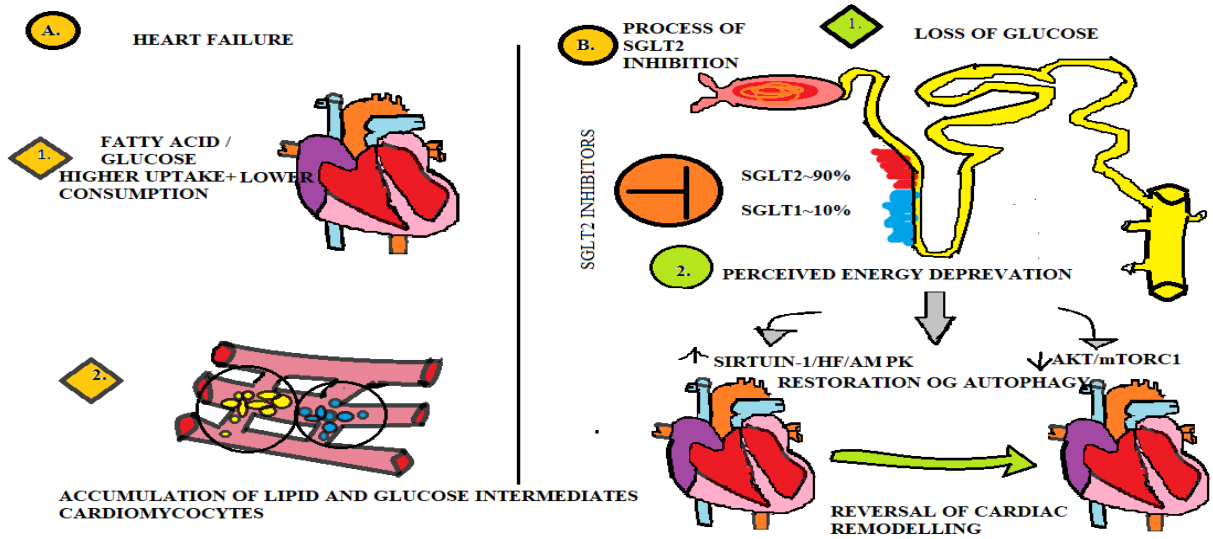

Fig. 6: Defective autophagy is the main cause of heart failure and SGLT2 inhibition plays a vital role in this. (A) Heart failure is a common condition caused by nutritional overabundance that promotes the growth of lipid and glucose intermediates in cardiomyocytes, impairing autophagy, apoptosis, oxidative stress, endoplasmic reticulum stress, and inflammation. (B) By disrupting the equilibrium between Sirt1 (which controls the UCP uncoupling protein 2 in pancreatic beta cells to influence the insulin production) and Hypoxia-inducible factor (HIF), which is crucial for maintaining oxygen homeostasis [16], SGLT2 inhibitors cause a situation of apparent nutritional imbalance. It acts as a transcription factor and controls the expression of numerous genes necessary for preserving homeostasis as oxygen concentrations fluctuate [17]. By controlling glucose absorption, anaerobic respiration in oxygen-depleted conditions, As the AMP-activated protein kinase (AMPK) signaling pathway is active in low-nutrient environments and inactive in high-nutrient environments, the mammalian/AKT Target of Rapamycin Complex 1 (Mtorc1) is activated in a reverse manner. HIF-1 further controls cellular responses to hypoxia. Because of this, restoring autophagy aids in undoing undesirable cardiac remodeling.

How a DPP-IV inhibitor works

Dipeptidyl peptidase-4 blockers (DPP-IV), a class of incretin-based medications, are advised for the second or third line of prevention for type 2 diabetes mellitus. Comparatively, the other glucose-declining drugs, they offer an encouraging drug tolerability and well-being portrait. Gliptins are a class of incretin-based drugs that function by boosting insulin production and suppressing glucagon secretion in a glucose-dependent way, which is generally a case of T2DM. Inhibitors of a dipeptidyl peptidase-IV (DPP-IV), sometimes known as "gliptins," are included under this class[15]. If a patient's intolerance to metformin is discovered, it is typically administered as the first line of treatment.

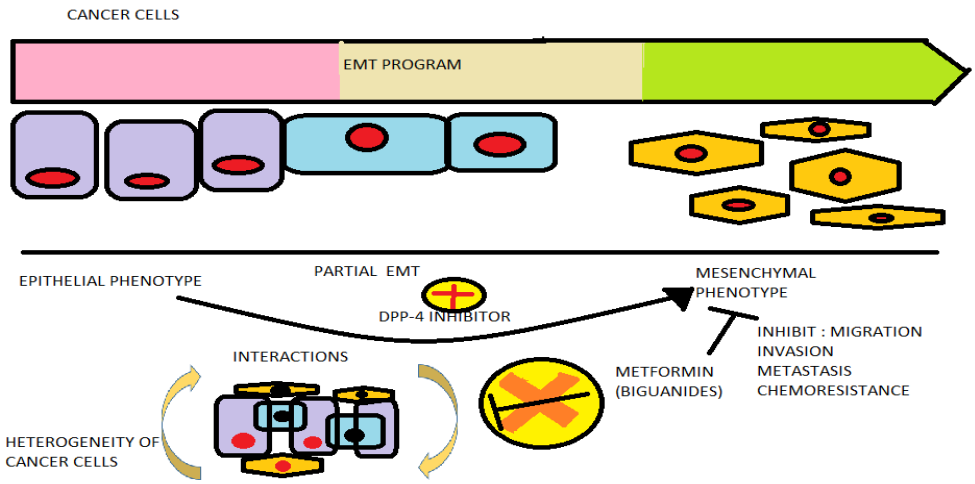

Fig 7: Metformin inhibits the progression of cancer caused by a DPP-4 inhibitor. Moreover, metformin inhibits a complicated developmental program known as the epithelial-mesenchymal transition (EMT) allows cancer cells to suppress the change from epithelial to mesenchymal features. EMT via. the mTOR pathway; consequently, the potential therapeutic approach of metformin's suppression of EMT trans-differentiation may prove beneficial in navigating the clinical response to chemotherapy in malignancies of the pancreas..[18]

Defeats for DPP-IV inhibitors

Alogliptin has the potential to reduce insulin resistance in adipose tissue as well as some atherogenic (to induce fatty acid deposition in arteries) lipids, as compared to other evaluated DPP-IV blockers. The ability of a DPP-IV inhibitor to reduce insulin resistance in adipose tissue is demonstrated for the first time in this work. Additionally, in people using alogliptin, adipose-IR is associated with non-LDL-C lipid characteristics rather than glycemic control. [16]

Even though all 14 classes of current medications for the prevention of type 2 diabetes mellitus are available, only 36% of individuals with the condition achieved glycemic control. New and developing therapies and their respective targets for T2DM have demonstrated this. seeking more modern and creative therapeutic solutions. Drugs that are simply focused on glycemic management should bear less of the burden than those that regulate the sleep-wake cycle and preserve the release of the DARK HORMONE melatonin. [17]

In addition to effectiveness and tolerability, other criteria for the success of a novel medicine include convenience of administration, practical dose frequency, favorability for weight control, and minimal risk of hypoglycemia.

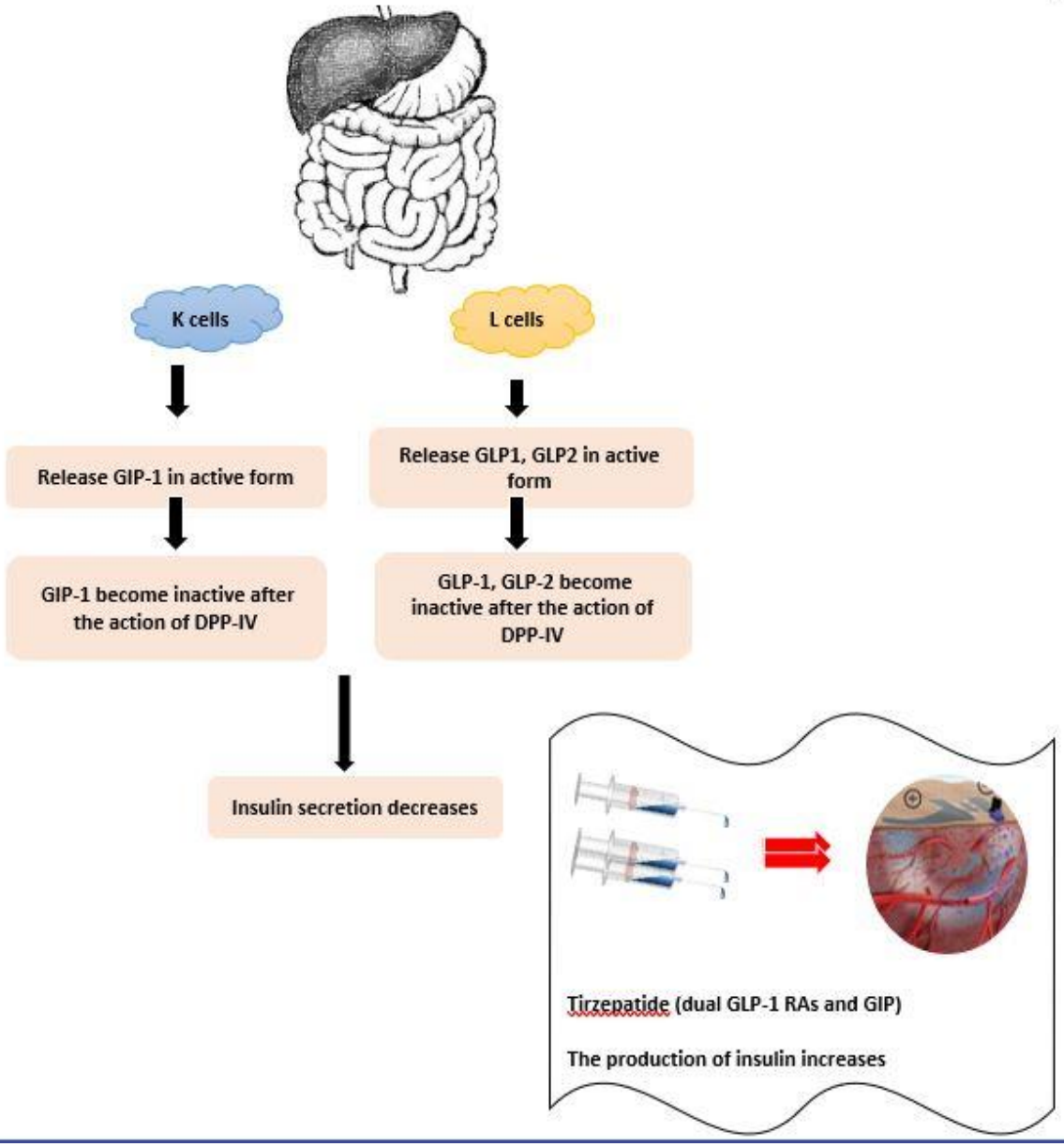

Fig. 8: Illustration of the DPP-IV inhibitors and tirzepatide's (dual GIP/GLP-1) a method of action, which involves raising blood levels of insulin secretion.

Table 2: Treatment of Diabetes mellitus with a monotherapy

Name of the drug	Pharmacological findings	Clinical results
1. Alpha glucosidase inhibitor	Voglibose, acarbose, and meglitinides are the three main antihyperglycemic medications used to lower postprandial blood glucose (PPBS) and suppress cytokine gene expression.	Voglibose was discovered to have higher control over PPBS with lower cardiovascular risks than other anti-diabetic medications. Its effectiveness was discovered in older individuals with renal or hepatic concerns where other anti-diabetic medications had failed to effectively treat diabetes.[19] Acarbose,

		voglibose, and miglitol, the three types of antidiabetic agents, were examined for their antihyperglycemic effects and propensity to cause cardiovascular problems linked to type 2 diabetes. [20].Voglibose prevented the synthesis of glucagon. It was successful in lowering HbA1c and cardiovascular issues as well. Voglibose has a much shorter drug reaction than acarbose and miglitol since it is administered at a modest dose. [21].
2. Analogs of amylin	The effectiveness of pramlintide, a new class of amylin analog, in lowering postprandial blood sugar and controlling weight in T2DM patients was examined.	Pramlintide slowed down the pace of stomach emptying, prevented glucagon from being released after eating, improved satiety, and slowed down the rate of food intake.[22] Pramlintide therapy is comparable to improvements in cardiovascular issues, oxidative stress markers, and patient satisfaction with their treatment. It is a peptide hormone called amylin analog. Amylin is also released alongside insulin from the pancreas' beta cells, which primarily work to promote stomach emptying. .[22]
3. SGLT2 blockers	The effects of Canagliflozin on hypoglycemia and management of other undesirable side effects linked with diabetes were evaluated.	In computation to an important fall in body mass, systolic(ventricular contraction and diastolic(ventricular dilation) blood pressure, and blood sugar levels, canagliflozin was found to be effectual.[22]Additionally, it lessened cardiovascular issues. connected to T2DM. HbA1c, FBS, and PPBS were among the major endpoint indicators that had decreased, according to the study. At the termination of the 168-day inquiry, auxiliary endpoint metrics, such as a loss of body weight indicated by decreased waist circumference and a decline in systolic and diastolic blood pressures showed a substantial reduction.[23]
3. GLP1 Analogs	Exenatide long-acting	Except for the triglyceride level, exenatide

	release (LAR) given once a week to T2DM patients was studied as an addition to the standard metformin dose for eight months.	upgrade the Fragment based screening (FBS), HbA1c ratio, body mass index(BMI), and lipid panel. Therefore, exenatide LAR given once a week together with metformin may have cardio protective effects in T2DM patients. [24] The cardiovascular risk markers HbA1c, body weight, diastolic blood pressure, total cholesterol, low-density lipoprotein cholesterol (LDL), and high-density lipoprotein cholesterol (HDL) all showed a significant improvement. After seven years of Exenatide therapy, glycemic management and the related cardiovascular risk factors demonstrated a persistent improvement. [25]
	In T2DM patients receiving metformin and sulfonylureas as part of dual therapy, lixisenatide was evaluated for effectiveness and safety.	Once daily administration of 20mcg of lixisenatide was observed to significantly lower FBS and PPBS as well as body weight in treated patients compared to placebo recipients. The frequency of unwanted side effects and hypoglycemic episodes decreased as in contrast to Exenatide (10mcg twice daily).
5. Dipeptidyl Peptidase - IV inhibitors	Anagliptin, a new DPP–IV inhibitor was investigated by Liquid chromatography – High resolution mass spectrometry (LC–HRMS) method for its effect on serum levels of glucagon and GLP, which maintain glucose homeostasis.	The group treated with anagliptin showed an increase in plasma GLP – 1 and GIP levels after the test meal resulting in a reduction in glucose by an increase in insulin secretion. In both groups, gastric emptying delay was not observed.
	Individuals with T2DM and end-stage renal disease have teneligliptin in both safety and effectiveness evaluations.	Teneligliptin monotherapy significantly improved glycemic control in individuals with T2DM on hemodialysis. Teneligliptin reduced glycated albumin, HbA1c, and fasting blood glucose levels without severe precipitation of hypoglycemia. The HbA1c depletion ratio was in range of 0.8 - 0.9%

		after the execution of 84 days.

Table 3: Treatment of type 2 diabetes with dual therapy and medication to combat diabetes.

The name of the medication combo	Clinical Results after Pharmacological Studies	The side effects of following drugs
Vildagliptin	The investigation of dual therapy of vildagliptin resulted in a eminent depletion in the HbA1c proportion.	Overall gastrointestinal problems were substantially more prevalent in the vildagliptin group. [26]
Sulfonylureas, acarbose, thiazolidinedione, and glinides, together with metformin	Following an evaluation of four metformin-based dual treatments, it was determined that the combination of metformin and thiazolidinedione was both the most efficient and the least risky for cardiovascular disorders.	Cancer and type 2 diabetes may have a connection, and dietary anti-diabetic medications, such as metformin and sulfonylurea, may be a factor.[10] Through both direct and indirect mechanisms (lowering hyperinsulinemia and glycemic levels), metformin may be linked to carcinogenesis. Additionally, certain malignancies, such as colon and breast cancers, are thought to be at risk due to high glucose levels. [27]
Oral antihyperglycemic medication, metformin, sulfonylurea, and basal insulin		The effectiveness of decreasing blood sugar, while sorting out a class of antihyperglycemic medicament for a combination treatment, consideration is given to the risk of hypoglycemia, body weight increase, and related cardiovascular benefits.[28]
Metformin with Sulfonylurea/ antihyperglycemic agent		Severe renal or hepatic failure as a subsequent outcome.
Gliclazide and Metformin and/or Acarbose		It's unlikely that gliclazide and acarbose-induced alterations in body composition are the result of uncomplicated adiposity, and they may not have any adverse consequences on the cardio metabolic risk outline. [29]. Being overweight is a typical side effect of antihyperglycemic

		medications for individuals with type 2 diabetes mellitus.

The Therapeutic gap for Type 2 Diabetes

There are numerous therapy options available to treat T2DM. As time goes on, the number of FDA-approved drugs has practically crossed 60. Additionally, there are currently clinical trials evaluating almost 100 additional anti-diabetic drugs. Metformin, SGLT2 inhibitors, and DPP-4 inhibitors are only a few of the medication combinations that are available in addition to the standard therapies of insulin therapy and metformin. These combinations have seen significant growth in popularity over the past few decades. Additionally, there are a variety of captivating alternatives available in ongoing trials, like efpeglenatide, tirzepatide, and lobeglitazone (derivative of thiazolidinedione which also act as insulin sensitizer). The pharmaceutical industry has widely approved modern drugs such as SGLT2 inhibitors, DPP-4 blockers, and glucagon-like peptide-1 (GLP-1) receptor agonists, and more reasonably priced alternatives are on the horizon.. There are over-the-counter medicine alternatives available in poor economies. The urge to develop more individualized and accessible treatments are also increasing due to T2DM's increased prevalence. . [30]

Conclusion:

Plethora of medications are currently available to treat type 2 diabetes mellitus. As new treatments and drug combinations are developed continuously to treat T2DM, the burden of drug dosages has increased with little to no improvement in the human body's long-term health. Additionally, ketosis (the buildup of ketone bodies) is a major side effect of these treatments. However, the medications have numerous micro and macro vascular side effects, including issues with the heart, kidneys, and neuron-associated disease. Diabetic nephropathy, one of the deadly diseases that affects the kidneys, is becoming widespread and difficult to cure. This is a significant downside of every medicine now on the market for the treatment of diabetic mellitus. Therefore, researchers need to consider moving the focus away from oral anti-hyperglycemic medications, which typically lower blood glucose levels, rather toward biological circadian rhythms, which regulate sleep and waking cycles. Instead of increasing doses of oral hyper/hypoglycemic medicines prescribed, which come with deadly long- and short-term effects on the body, the focus must be moved to the prompt management of diabetes which targets the sleep and wake cycle of humans.

Conflict of Interest: The authors declare that there are no conflicts of interest regarding the publication of this paper.

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