International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

Novel Therapies for the Treatment of Diabetes Mellitus Type 2

Shubham Sunil Mane

Submitted: 12-01-2023 Accepted: 25-01-2023

ABSTRACT:
Diabetes mellitus type 2 is a chronic condition that affects millions of people worldwide. Despite the availability of several treatments, the management of this condition remains a challenge. New therapies that target specific pathways involved in the development of diabetes have the potential to improve patient outcomes. The goal of this review is to investigate novel therapies for the treatment of diabetes mellitus type 2. Diabetes mellitus type 2 is a chronic condition that affects millions of people worldwide. It is characterized by a lack of insulin production orinadequate use of insulin by the body, leading to high blood sugar levels and a range of complications, including heart disease, kidney disease, nerve damage, and eye problems, leading to high blood sugar levels and a range of complications. Novel therapies for type 2 diabetes may include focusing on reaching individualized glycaemic goals while optimizing safety, non-glycemic benefits, and the prevention of complications medications, medical devices, and lifestyle interventions that aim to improve insulin production and use, as well as to prevent or reduce complications. The review will involve a review of existing literature on novel therapies for type 2 diabetes, as well as the development of a research plan to assess the effectiveness and safety of these therapies. The results of the study will be used to inform the development of new treatments for type 2 diabetes. A comprehensive search of the literature using relevant keywords and databases, such as PubMed and MEDLINE has been done. This includes studies published in the last 5 years that evaluate the effectiveness and safety of novel therapies for type 2 diabetes. This will help us determine the reliability and validity of the evidence on novel therapies for type 2 diabetes.

History of diabetes mellitus type 2:

Diabetes mellitus type 2, also known as non-insulin dependent diabetes or adult-onset diabetes, is a chronic condition characterized by high levels of sugar (glucose) in the blood. The history of type 2 diabetes dates back to ancient civilizations, but it was not until the 19th and 20th centuries that the condition was fully understood and treatments were developed. The ancient Egyptians and Greeks were among the first to document the symptoms of type 2 diabetes, which they called "the disease of the urine." They observed that individuals with diabetes had excessive thirst, frequent urination, and sweet-tasting urine. In the 16th century, the physician Thomas Willis described diabetes as a "Mellitus," or honey, disease due to the sweet taste of the urine in individuals with the condition.

It wasn't until the 19th century that the role of the pancreas in diabetes was discovered. In 1889, a German physician named Oskar Minkowski and a French physiologist, Joseph von Mering conducted an experiment in which they removed the pancreas from a dog and observed that the animal developed diabetes. This led to the discovery that the pancreas produces a hormone called insulin, which regulates the level of sugar in the blood. In 1922, a Canadian physician named Frederick Banting and his assistant, Charles Best successfully isolated insulin from the pancreas of dogs and used it to treat individuals with diabetes. This marked a major milestone in the treatment of diabetes and resulted in the development of insulin therapy as a standard treatment for the condition.

Over the following decades, advances in the understanding and treatment of type 2 diabetes continued. In the 1950s, oral medications called sulfonylureas were developed to help control blood sugar levels in individuals with type 2 diabetes. In the 1980s, the first non-insulin injectable medications were introduced, including metformin, which helps the body use insulin more effectively. Today, type 2 diabetes is a common condition that affects millions of people around the world. It is typically diagnosed in adults, although it is increasingly being diagnosed in children and adolescents as well. The main risk factor for type 2 diabetes is obesity, and the condition is often associated with a sedentary lifestyle and poor diet. Treatment for type 2 diabetes typically involves a

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

combination of lifestyle changes, such as diet and exercise, and medication.

Traditional therapies in diabetes mellitus type 2

The traditional therapies for type 2 diabetes include lifestyle changes and medications to help control blood sugar levels. These therapies are designed to lower blood sugar levels, reduce the risk of complications, and improve overall quality of life.

Making healthy lifestyle changes, such as eating a balanced diet and engaging in regular physical activity, is an important part of the management of type 2 diabetes. A diet rich in fruits, vegetables, whole grains, and lean proteins can help to manage blood sugar levels and reduce the risk of complications. Exercise can also help to improve insulin sensitivity, lower blood sugar levels, and reduce the risk of complications.

Oral medications: There are several types of oral medications that can be used to treat type 2 diabetes, including sulfonylureas, meglitinides, thiazolidinediones, and biguanides. These medications work by increasing insulin production, improving insulin sensitivity, or both. Sulfonylureas, for example, stimulate the beta cells of the pancreas to produce more insulin. Meglitinides work in a similar way, but they have a faster onset of action and a shorter duration of effect. Thiazolidinediones improve insulin sensitivity by activating a protein called PPAR-gamma, which helps to regulate glucose metabolism. Biguanides, such as metformin, help to improve insulin sensitivity by inhibiting the production of glucose in the liver and increasing the uptake of glucose by cells.

Insulin therapy: In some cases, individuals with type 2 diabetes may require insulin therapy to control their blood sugar levels. Insulin can be administered through injections or an insulin pump. There are several types of insulin, including rapid-acting, short-acting, intermediate-acting, and long-acting. The type and dose of insulin used will depend on an individual's specific needs and circumstances.

Other injectable medications: There are several non-insulin injectable medications that can be used to treat type 2 diabetes, including GLP-1 agonists and basal insulin analogues. GLP-1 agonists, such as exenatide and liraglutide, stimulate the production of insulin and slow the absorption of glucose from the intestines. They may be used in combination with oral medications or insulin. Basal insulin analogues, such as insulin glargine and insulin detemir, are long-acting insulins that are designed to provide a steady, low level of insulin throughout the day. They may be used in combination with rapid-acting insulins or as a standalone treatment.

Problems with traditional therapies

The main risk factor for type 2 diabetes is obesity, and the condition is often associated with a sedentary lifestyle and poor diet. The traditional therapies for type 2 diabetes include lifestyle changes and medications to help control blood sugar levels.

However, there are several potential problems with traditional therapies for type 2 diabetes. These problems include:

Ineffectiveness: Traditional therapies, such as diet and exercise, may not be effective in controlling blood sugar levels in all individuals with type 2 diabetes. In some cases, additional treatment may be needed, such as insulin therapy or other medications. For example, individuals who have had type 2 diabetes for a long time or who have severe insulin resistance may require insulin therapy to achieve adequate blood sugar control.

Side effects: Some traditional therapies, such as oral medications and insulin, can cause side effects. These side effects can be bothersome and may lead to nonadherence to treatment. For example, oral medications such as sulfonylureas and meglitinides can cause gastrointestinal side effects, such as nausea, diarrhoea, and bloating. They can also cause weight gain and increase the risk of low blood sugar (hypoglycemia). Insulin therapy can also cause side effects, such as weight gain and hypoglycemia, as well as injection site reactions. Non-insulin injectable medications, such as GLP-1 agonists and basal insulin analogues, can also cause side effects, including gastrointestinal issues, weight gain, and low blood sugar.

Long-term management: Type 2 diabetes is a chronic condition that requires ongoing management. This can be a burden for some individuals, who may struggle with maintaining a healthy diet and exercise routine or remembering to take medications on a regular basis. Some individuals may find it difficult to make the necessary lifestyle changes, especially if they have other responsibilities or lack support.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

Risk of complications: Despite the use of traditional therapies, some individuals with type 2 diabetes may still develop complications, such as heart disease, nerve damage, and eye problems. These complications can be serious and may result in disability or death. For example, high blood sugar levels over time can damage the blood vessels and nerves, leading to complications such as heart attack, stroke, and nerve damage. High blood sugar levels can also damage the small blood vessels in the eyes, leading to vision loss.

Drug-drug interactions: Medications can interact with each other and with certain foods or supplements, leading to reduced effectiveness or adverse reactions. For example, certain medications may be metabolized by the same liver enzymes, leading to competition for metabolism and reduced effectiveness of one or both drugs. It is important to disclose all medications, supplements, and herbal remedies to a healthcare provider to minimize the risk of drug-drug interactions.

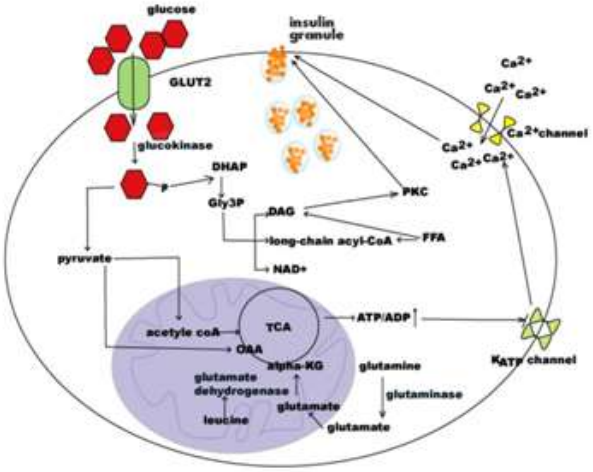
Inadequate duration of treatment: Some conditions may require long-term treatment with medications to achieve optimal results. For example, individuals with type 2 diabetes may need to take medications for an extended period of time to control their blood sugar levels and reduce the risk of complications. If treatment is stopped prematurely, the condition may worsen or relapse.

Drug resistance: Some individuals may develop resistance to medications over time, leading to treatment failure. For example, individuals with type 2 diabetes may develop resistance to oral medications that increase insulin production, such as sulfonylureas and meglitinides. This may be due to a decrease in insulin secretion by the beta cells or an increase in insulin resistance. In these cases, insulin therapy or other medications may be needed to achieve adequate blood sugar control.

Novel mechanisms of action

There are several glucose-lowering mechanisms that are being explored in the development of novel therapies for type 2 diabetes. These mechanisms include:

Stimulating insulin production: Some novel therapies are designed to stimulate the production of insulin by the beta cells of the pancreas.



These include both pancreas-selective and pancreas–liver dual-activating
glucokinase activators (GKAs) and G-protein-coupled receptor 40 (GPCR40)
agonists. For example, researchers are exploring the use of stem cell therapies to regenerate beta cells and restore insulin production.

Improving insulin sensitivity:

Other novel therapies are designed to improve insulin sensitivity, which is the ability of cells to respond to insulin and take up glucose from the bloodstream. For example, researchers are developing drugs that target different pathways involved in glucose metabolism, such as the AMP-activated protein kinase (AMPK) pathway, to improve insulin sensitivity. These include an antisense oligonucleotide inhibitor for protein tyrosine phosphatase 1B (PTP1B) mRNA, fibroblast growth factor 21 (FGF21) analogues, a diacylglycerol acetyl transferase 1 (DGAT1) inhibitor and an enterocytic microsomal triglyceride transfer protein (MTP) inhibitor.

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

Inhibiting the production of glucose: Other novel therapies are designed to inhibit the production of glucose in the liver. For example, researchers are exploring the use of SGLT2 inhibitors, which block the reabsorption of glucose by the kidneys, as a potential treatment for type 2 diabetes.

Drugs that utilize the incretin axis: The incretin axis refers to the pathways involved in the regulation of glucose metabolism by hormones known as incretins. Incretins are hormones produced by the gut that stimulate insulin secretion and reduce the production of glucose by the liver in response to food intake. There are two main incretins: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).

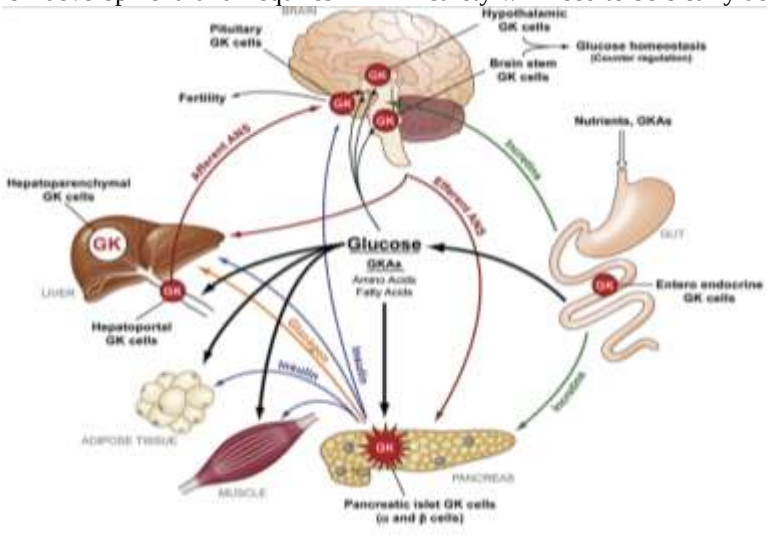
Drugs that directly target β-cells.

Beta cell regeneration therapies are designed to stimulate the proliferation or differentiation of beta cells, with the goal of restoring insulin production. Some approaches being explored include the use of stem cells, small molecules, and growth factors to stimulate beta cell proliferation or differentiation. Beta cell protectors are drugs that are designed to protect beta cells from damage, with the goal of preserving insulin production.

Some approaches being explored include the use of antioxidants and other agents that have anti-inflammatory or cytoprotective effects. Beta cell replacement therapies involve the transplantation of functional beta cells into individuals with type 2 diabetes, with the goal of restoring insulin production. This approach is still in the early stages of development and requires further research to determine its safety and efficacy.

Glucokinase activators.

GKAs are a novel therapy that directly targets β-cells, with at least 11 drugs under development (one in phase III, four in phase II and six in phase I clinical trials). Glucokinase, which facilitates the phosphorylation of glucose to glucose-6- phosphate, functions as the 'glucose sensor' of the body, maintaining plasma concentrations of glucose within a narrow range (4–6nM). The action of glucokinase is restricted to glucose-sensitive and glucose-responsive tissues such as the liver and pancreas. As such, the GKAs in development have been designed to target both liver and pancreas (dual) or to be more specific, targeting only one tissue (selective). Glucokinase activation in the liver stimulates hepatic glucose uptake and inhibits hepatic glycogenolysis, whereas glucokinase activation in the pancreatic β-cell stimulates insulin secretion. Dual GKAs can be further subdivided by their enzyme kinetics, which can render them more or less potent to stimulate insulin secretion, thereby underscoring the customizability of the molecules. Historically, GKAs have not thrived in development, limited by their lack of durability, risk of inducing hypoglycaemia, liver toxicity and ability to cause an increase in the plasma concentration of triglycerides27–30. Nevertheless, safety issues could be avoidable through careful patient selection and perhaps liver-selective GKAs might avoid the increased risk of hypoglycaemia; however, liver safety will need to be clearly demonstrated.



International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

G-protein-coupled receptor 40.

GPCR40 (also known as free fatty acid receptor 1; FFAR1) agonists have generated considerable interest as a novel mechanism for direct β-cell stimulation. Agonists of GPCR40 act in the β-cell to induce free fatty acid (FFA)-stimulated insulin secretion and two agents have advanced into phase II trials. These compounds act as cooperative, allosteric modulators of GPCR40 that rely on the ample circulating levels of FFAs to potentiate glucose-dependent insulin secretion. A previous GPCR40 agonist compound in development (fasiglifam, also called TAK 875) showed glucose-lowering properties in phase IIa clinical trials; however, considerable liver toxicity in phase III trials led to the termination of its development programme. Hence, continued vigilance towards safety will dominate the development of its successors as it is unclear how these new molecules differ from fasiglifam.

Compound	Mechanism of action	Trial phase	`Results	Ref. or clinical trial number
GKAs				
HMS5552 (dorzagliatin)	Dual GKA (pancreas and liver); GKA in pancreatic β-cells augments glucose-stimulated insulin secretion; GKA in liver	III	24 people with T2DM randomized to dorzagliatin 75mg QD or BID for 28 days; HbA1c – 1.22% with QD and-0.79% with BID	-
RO4389620 (piragliatin)		Ib	15 people with T2DM randomized to triple crossover of piragliatin 25mg, 100mg or placebo; glucose AUC during an OGTT at the 100mg dose was less than that observed at the 25mg dose, which was less than observed with placebo	-
PSN-821		I	No published data	NCT01386099
DS-7309		I	No published data	NCT01862939, NCT01956305
PB-201		I	210	NCT03973515
GPCR40 agonists				

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

MK 8666	GPR40 is highly expressed in pancreatic β-cells; its activation by fatty acids amplifies glucose-dependent insulin secretion	II	63 people with T2DM randomized to MK 8666 50mg QD, 150mg QD, 500mg QD for 14 days; dose dependent 31–54mg/dl decrease in fasting plasma glucose	-
JTT-851		II	No published data	NCT01699737

Potential for liver toxicity.

The liver toxicity associated with drugs that stimulate insulin secretion directly from β-cells is worth contemplating. Of note, both glucokinase and GPCR40 are expressed in the liver as well as in β-cells. In humans, naturally occurring mutations leading to hepatic glucokinase overexpression have been associated with increased de novo lipogenesis and subsequent hepatic steatosis. Furthermore, naturally occurring polymorphisms in the glucokinase regulatory protein have been associated with elevated plasma levels of triglyceride, FFAs and VLDL cholesterol in humans. By contrast, studies in animal models show that the liver toxicity seen with GPCR40 agonists seems to be mediated through disrupted bile acid homeostasis. Taking the liver toxicity data with GKAs and GPCR40 agonists together, it is clear that directly stimulating insulin secretion from the β-cell using drugs that also have actions in the liver could lead to untoward alterations in pathways of lipid metabolism.

Drugs that utilize the incretin axis.

The indirect stimulation of β-cells is achievable through drugs that affect the incretin axis. By definition, incretin hormones (for example, GLP1 and GIP) are hormones secreted by enteroendocrine cells in the gastrointestinal tract in response to the oral ingestion of nutrients. These hormones act to decrease the plasma concentrations of glucose by mediating delayed gastric emptying, augmenting insulin secretion and suppressing glucagon secretion. Of note, the glucose-lowering ability of drugs that act on the incretin axis is further amplified by the ability of incretins to induce weight loss.

Dual-acting or triple-acting incretin mimetics.

Importantly and unlike GKAs and GPCR40 agonists, insulin secretion invoked by incretin mimetics is glucose dependent; that is, the plasma concentrations of glucose must be elevated or rising for insulin secretion to be stimulated.

GLP1 receptor agonists have been used in T2DM care for the past 15 years to decrease plasma concentrations of glucose and body weight and, from 2016, to provide protection from cardiovascular disease. Expanded use of the incretin axis includes the development of molecules that act as both GLP1 receptor agonists and GIP receptor agonists and/or as glucagon receptor agonists. Such dual or triple agonist drugs aim to achieve even greater efficacy for glucose lowering, greater body weight loss and perhaps greater cardiovascular protection in patients with T2DM than provided by single agonists. In addition to their role in treating T2DM, dual acting or triple-acting agonists have the potential to attain independent indications for obesity, sleep apnoea, renal insufficiency, non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis in people with or without T2DM. Currently, drugs in clinical trials include one dual-acting GLP1–GIP receptor agonist in phase III, two dual-acting GLP1–glucagon receptor agonists in phase II and two triple-acting GLP1–GIP–glucagon receptor agonists in phase I trials. The clinical rationale for combining these dual-acting or triple-acting peptides is mainly to potentiate the weight loss effects as it is unlikely that the HbA1c reductions observed will be much greater than the 1.5% or even 2% that have already been achieved with compounds like semaglutide (approved) or tirzepatide (phase III), respectively. In addition, the stimulation rather than the supplementation of GLP1 and GIP is being tested using analogues of GPCR119; one drug is in phase I trials and another is in phase II47,48. The well-established ability of

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

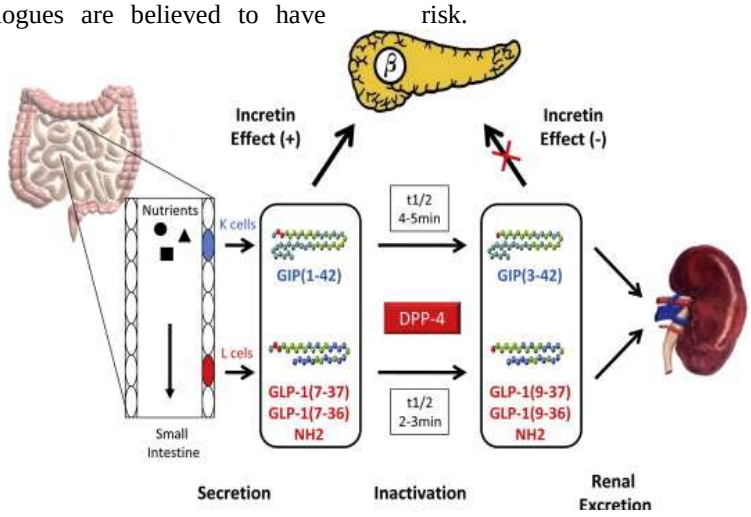
glucagon to stimulate hepatic glucose production makes it a counterintuitive choice as a treatment for T2DM. The rationale for integrating the pharmacology of GLP1 and glucagon relies upon the action of GLP1 to restrain the hyperglycaemic effect of glucagon while adding a centrally mediated anorectic action to synergize with the lipolytic and thermogenic capabilities of glucagon with the aim to substantially decrease body weight.

Oxyntomodulin analogues.

Oxyntomodulin, like GLP1 and glucagon, is a peptide product derived from the post-translational modification of preproglucagon. Oxyntomodulin analogues are designed to mimic the actions of oxyntomodulin and are being developed as an alternative to traditional therapies for type 2 diabetes, such as lifestyle changes and medications. The mechanism of action of oxyntomodulin analogues is not fully understood, but it is thought to involve several pathways that regulate glucose metabolism and energy balance. Oxyntomodulin is thought to act on receptors in the brain, pancreas, and gut to stimulate insulin secretion, reduce the production of glucose by the liver, and increase the feeling of fullness (satiety). It has been shown in vitro to be a natural chimera, binding and activating both GLP1 and glucagon receptors. The dual stimulation of GLP1 and glucagon receptors is currently being tested for T2DM using an analogue of oxyntomodulin (one drug in phase II trials). Similar to dual-acting GLP1–glucagon receptor agonists, oxyntomodulin exerts its glucoregulatory actions independent of but in addition to considerable weight loss. Oxyntomodulin analogues are believed to have similar effectsOxyntomodulin analogues may stimulate insulin secretion by the beta cells of the pancreas, which helps to lower blood sugar levels.Oxyntomodulin analogues may reduce the production of glucose by the liver, which helps to lower blood sugar levels.Oxyntomodulin analogues may improve insulin sensitivity, which is the ability of cells to respond to insulin and take up glucose from the bloodstream.

The therapeutic potential of the incretin axis.

The incretin axis refers to the pathways involved in the regulation of glucose metabolism by hormones known as incretins. Incretins are hormones produced by the gut that stimulate insulin secretion and reduce the production of glucose by the liver in response to food intake. There are two main incretins: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). The therapeutic potential of the incretin axis in the treatment of type 2 diabetes is significant, as it offers an alternative approach to traditional therapies such as lifestyle changes and medications. Incretin-based therapies are believed to have several potential advantages, Incretin-based therapies may improve insulin sensitivity, which is the ability of cells to respond to insulin and take up glucose from the bloodstream. Reduced risk of hypoglycemia Incretin-based therapies may have a lower risk of causing low blood sugar (hypoglycemia) compared to other glucose-lowering therapies, such as insulin and sulfonylureas. Incretin-based therapies may have weight loss effects, which may be beneficial in individuals with type 2 diabetes, as obesity is a risk.



International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

Compound	Mechanism of action	Trial phase	Results	Ref. or clinical trial number
Agonists for GLP1, GIP and/or glucagon				
AVE2268	GLP1–GIP–glucagon triple receptor agonist	I	No published data	NCT00361738
SAR425899	GLP1–glucagon dual receptor agonist	II	PK/PD established in 36 people with T2DM	-
MEDI0382	GLP1–glucagon dual receptor agonist	IIa	MEDI0382 lowered glucose AUC during a MTT versus placebo; PK/PD, safety, add-on established in phase I trial	NCT03745937, NCT02548585, NCT03444584, NCT03645421, NCT04515849
HM12460A	GLP1–GIP–glucagon triple receptor agonist	I	No published data	NCT01724814, NCT03332836
LY3298176 (tirzepatide)	GLP1–GIP dual receptor agonist	III	318 people with T2DM randomized to tirzepatide 1mg Q week, 5mg Q week, 10mg Q week, 15mg Q week, dulaglutide 1.5mg Q week or placebo for 26 weeks.	NCT03973515
GPCR119 agonist				
MBX-2982	GPR40 is highly expressed in pancreatic β-cells; its activation by fatty acids amplifies glucose-dependent insulin secretion	I	No published data	NCT01035879
Oxyntomodulin analogue				
OPK88003	This oxyntomodulin analogue has the potential actions of a GLP1–glucagon dual receptor agonist	II	No published data	NCT03406377

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

factor for the development of the disease. Improved beta cell functionIncretin-based therapies may improve beta cell function and insulin production, which may be impaired in individuals with type 2 diabetes. Several drugs that utilize the incretin axis are available for the treatment of type 2 diabetes, including GLP-1 agonists and DPP-4 inhibitors. However, incretin-based therapies are not without their drawbacks, and further research is needed to fully understand their potential and to develop safe and effective treatments. Furthermore, expanded use of the incretin axis for therapeutic purposes has provided unique insights into the complex interplay between diet, enteroendocrine cells and the microbiome in human health and disease53. Collectively, the knowledge to be gained from and the therapeutic potential of the incretin axis is vast.

Compound	Mechanism of action	Trial phase	Results	Ref. or clinical trial number
Antisense oligonucleotide inhibitor for PTP1B mRNA				
ISIS 113715 (IONIS-PTP-1BRx)	PTP1B has been shown to be a negative regulator of insulin and leptin signaling; the inhibition of PTP1B enhances insulin and leptin action	III	92 people with T2DM randomized to ISIS 113715 200mg SC Q week or placebo for 26 weeks; HbA1c –0.44% with ISIS 113715	
FGF21 analogue				
LY2405319	FGF21 has been shown to improve whole body insulin sensitivity, enhance insulin secretion while suppressing glucagon secretion, inhibit hepatic lipogenesis, and increase energy expenditure via the activation of brown adipose tissue	I	47 people with T2DM randomized to LY2405319 at 3mg, 10mg or 20mg QD for 28 days; LY2405319 lowered LDL-cholesterol, triglycerides, fasting insulin and body weight while increasing adiponectin but little effect on plasma concentrations of glucose was observed	
SRT2379		I	No published data	NCT01018628
SAR425899		I	No published data	NCT03414736 , NCT02973321 , NCT02411825
DGAT1 inhibitor				
PF-04620110	Inhibits the acetylation of diacylglycerol to triacylglycerol; the ectopic deposition of triacylglycerol has been linked to insulin resistance	I	PK/PD established in T2DM	NCT01298518
Enterocytic MTP inhibitor				
KD026 (SLx-4090)	Inhibits the production of apo B containing lipoproteins in the gut; by-products stimulate insulin signaling independent of the insulin	II	No published data	NCT02434744 , NCT00871936 ,

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

	receptor			NCT02434744
Novel PPAR agonists				
CS038 (chiglitazar)	Dual PPARα/γ agonist; intranuclear transcription factors that lower plasma levels of triglycerides and differentiate preadipocytes into mature adipocytes, respectively	III	No published data	NCT02173457, NCT02121717
T0903131 (formerly INT-131; besylate)	Partial PPARγ agonist; weak intranuclear transcription factor that differentiates pre-adipocytes into mature adipocytes	I	367 people with T2DM randomized to T0903131 0.5mg, 1mg, 2mg or 3mg QD versus placebo for 24 weeks; dose-dependent HbA1c −0.3% to −1.0% in T0903131	NCT00952445, NCT00631007
Other mechanisms				
DS-1150b	GLUT4 facilitative transporter stimulator; improves insulin signaling	I	No published data	NCT02004678
CAT-1004 (edasalonexent)	Anti-inflammatory	I	No published data	NCT01511900
MLR-1023 (tolimidone)	Selective allosteric activator of LYN kinase; improves insulin signaling	I	No published data	NCT03279263, NCT02317796
TC-6987	Nicotinic α7 receptor ligand; anti-inflammatory	II	No published data	NCT01293669
AZP-531 (livoletide)	Ghrelin analogue; inhibits food intake and induces weight loss	I	No published data	NCT02040012
TH-9507 (tesamorelin or Egrifta)	Ghrelin–GH receptor agonist; GH-releasing hormone analogue; decreases visceral adipose tissue accumulation	II	53 people with T2DM randomized to TH-9507 1mg or 2mg SC QD or placebo for 12 weeks; no difference in HbA1c was observed	NCT01264497
S707106	Unknown mechanism of action	II	No published data	NCT01154348, NCT01240759
Bimagrumab		II	No published data	NCT03005288

Drugs that improve insulin sensitivity

Perhaps the greatest need for new therapies in T2DM falls in the area of insulin sensitization and the approaches of the pharmaceutical industry to meeting this need could not be more diverse. Unfortunately, most of these approaches to date do not seem particularly promising for decreasing levels of glucose in patients with T2DM

Targeting FGF21.

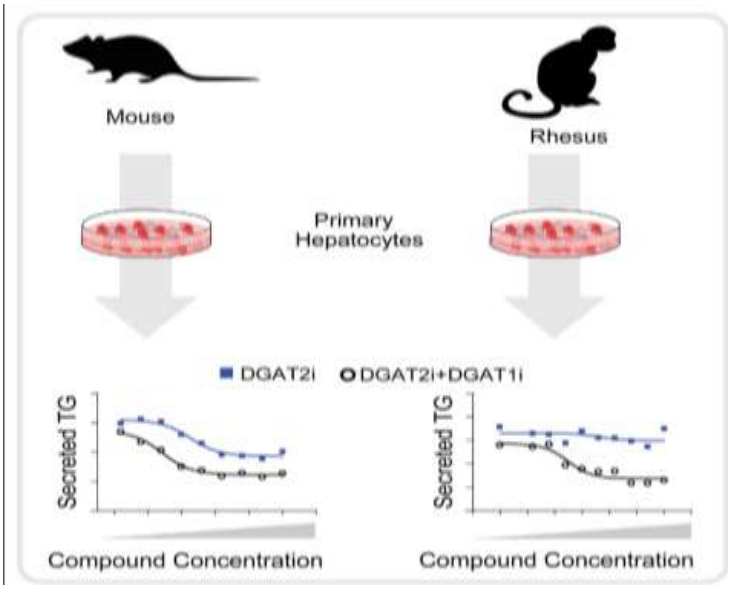
Considerable interest has been shown in FGF21, a hepatokine that activates the NADdependent protein deacetylase sirtuin (three drugs are currently in phase I trials). FGF21 is

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

thought to be an insulin sensitizer through its ability to mitigate FFA-induced insulin resistance. Collectively, investigations have revealed FGF21 as a stimulator of fatty acid oxidation, particularly in the liver, that increases the production of ketone bodies and inhibits lipogenesis. Despite reports of circulating levels of FGF21 being higher in people with any combination of T2DM, NAFLD or obesity than in individuals without these conditions, people treated with FGF21 analogues show weight loss65. Nevertheless, a proof-of-concept study in people with T2DM treated with FGF21 analogues observed a decrease in the plasma levels of lipids but not in plasma concentrations of glucose.

Inhibitors of DGAT1 and MTP.

One inhibitor of DGAT1 is currently in phase I trials and one inhibitor of MTP is in phase II trials. The rationale for developing these agents lies in the assumption that altering lipid metabolism will favourably affect glucose metabolism. However, preclinical studies have yet to show that this scenario is the case and there might be reason to suspect that a glucose-lowering ability by these drugs will not be demonstrated after all. For example, the inhibition of DGAT1 might indeed decrease the tissue accumulation of triacylglycerol (aka triglyceride); however, it does so at the expense of an increased tissue accumulation of diacylglycerol, which is a far more inflammatory, insulin de-sensitizing lipid than triacylglycerol. Moreover, MTP acts in the liver and intestine to prevent the transfer of triglycerides to other apo-B containing lipoproteins, thereby reducing post-prandial hypertriglyceridaemia. Nevertheless, a link is lacking between decreasing plasma levels of triglycerides and insulin sensitization and/or decreases in plasma levels of glucose in humans.



Targeting the GH receptor.

Speculation exists as to whether the adverse effects of GH on glucose metabolism might be offset by its anabolic action as well as by its ability to stimulate the production of insulin-like growth factor 1 in the liver. The gastric-derived peptide, ghrelin, is an endogenous ligand for GH-releasing hormone receptor. GH receptor agonism can be achieved either directly using a GH–ghrelin receptor co-agonist (one drug in phase II trials) or indirectly using a pure ghrelin analogue (one drug in phase I trials). The potentiation of GH via ghrelin is unlikely to thrive in development as a treatment for T2DM owing to the inability of this mechanism to induce weight loss and blunting of glucose-stimulated insulin secretion. The anabolic action of GH might be better achieved with a more direct approach such as type II-B activin receptor modulation (one drug in phase II trials). Blockade of the type II-B activin receptor inhibits the actions of natural ligands that negatively regulate skeletal muscle growth, thereby leading to a preservation and even expansion of lean mass. Bimagrumab, a monoclonal antibody that inhibits the activin type II receptor, was shown in 2021 to increase lean mass, decrease fat mass and improve HbA1c in

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

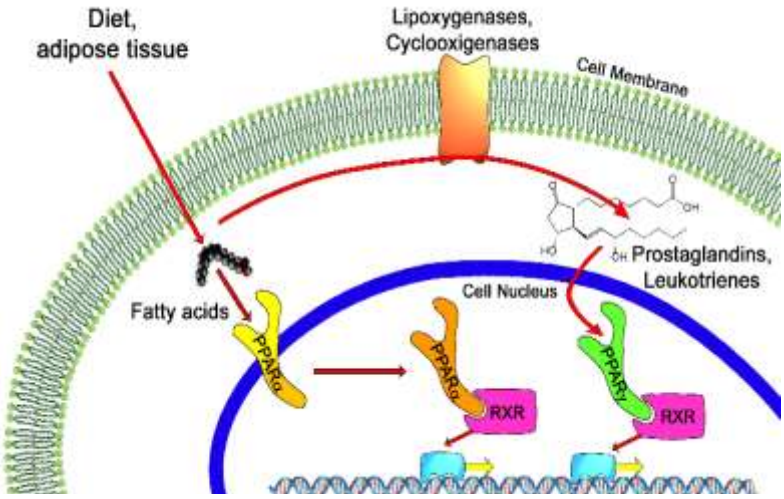
adults with T2DM. Although the precise mechanism of action remains largely unknown, it is clear that the anabolic action of bimagrumab is distinct from GH and harbours favourable effects on glucose metabolism.

Revisiting existing strategies.

Remaining novel compounds in development for insulin sensitization for the purpose of decreasing blood concentrations of glucose in T2DM reminisce on existing themes. One approach seeks to upregulate insulin signalling in peripheral tissues by inhibiting dephosphorylation of the insulin receptor using an antisense oligonucleotide inhibitor for PTP1B mRNA (one drug in phase III trials). A second approach seeks to completely bypass glucose dependency by stimulating the translocation of the insulin-dependent glucose facilitative transporter (GLUT4) directly (one drug in phase I trials). A third strategy aims at the indirect potentiation of insulin action through the allosteric activation of LYN kinase (one drug in phase I trials). Activated LYN kinase can phosphorylate insulin receptor substrate 1 in insulin-responsive tissues, which in return phosphorylates LYN kinase, suggesting a regulatory feedback loop between LYN kinase and insulin receptor activation. Interestingly, the insulin secretagogue, glimepiride, harbours extra pancreatic action as an insulin sensitizer through the activation of LYN kinase; however, glimepiride is associated with hypoglycaemia. By contrast, hypoglycaemia has not been reported with the upregulation of insulin signalling in peripheral tissues by other compounds that specifically target LYN kinase currently in development.

PPAR agonists.

The pipeline also revisits PPAR agonists, striving to improve their efficacy and safety, either through dual PPARα–PPARγ agonism (one drug in phase III trials) or through partial dual PPARα–PPARγ agonism (one drug in phase I trials). PPARα agonists inhibit hepatic lipoprotein C-III expression and subsequent VLDL production, making them useful as single agents for decreasing plasma levels of triglyceride (for example, gemfibrozil and fenofibrate are approved for this indication). PPARγ agonists act as intranuclear transcription factors that improve insulin sensitivity by expanding subcutaneous adipose tissue depots and inducing the differentiation of pre-adipocytes into mature adipocytes (for example, rosiglitazone and pioglitazone). Contemporary clinical trials have eased historic concerns over the cardiovascular safety of some PPARγ single agonists.



However, thus far, none of the dual PPARα–PPARγ agonists has followed suit with numerous development programmes halted owing to renal and cardiovascular concerns (for example, aleglitazar, muraglitazar and tesaglitazar). Altogether, pharmaceuticals in development for T2DM mainly directly or indirectly exploit one of the original 'triumvirate' of defects, that is, impaired insulin secretion, reduced insulin sensitivity and increased hepatic glucose production, described in T2DM many years ago.

One agent in phase III clinical trials is imeglimin, a tetrahydrotriazine-containing oxidative phosphorylation blocker that might attend to the entire triumvirate: stimulating insulin secretion, improving insulin sensitivity and

International Journal of Pharmaceutical Research and Applications
Volume 8, Issue 1 Jan-Feb 2023, pp: 1206-1218 www.ijprajournal.com ISSN: 2249-7781

reducing hepatic glucose production through the enhancement of mitochondrial bioenergetics. However, the data remain highly controversial.

CONCLUSIONS

In conclusion, novel therapies for the treatment of diabetes mellitus type 2 have the potential to greatly improve the lives of people with this condition. These therapies include new medications that target specific pathways involved in the development of diabetes, as well as non-pharmacological approaches such as surgical interventions and the use of new technologies to monitor and manage blood sugar levels.

While more research is needed to fully understand the effectiveness and safety of these therapies, early results suggest that they may offer significant benefits for people with diabetes mellitus type 2. Further studies are needed to determine the best ways to incorporate these therapies into clinical practice and to improve patient outcomes. Overall, the development of novel therapies for diabetes mellitus type 2 represents an exciting and promising area of research that has the potential to revolutionize the way this condition is managed and treated.

REFERENCES

[1]. World Health Organization. Report of the Expert Committee on Diabetes. WHO https://apps.who.int/iris/handle/10665/41399.
[2]. Glycemic Targets: Standards of Medical Care in Diabetes-2020 - PubMed."
[3]. https://pubmed.ncbi.nlm.nih.gov/31862749/.
[4]. US National institute of Health Clinical Trials Database:https://clinicaltrials.gov/.
[5]. Dose-ranging study with the glucokinase activator AZD1656 in patients with type 2 diabetes mellitus on metformin
[6]. https://pubmed.ncbi.nlm.nih.gov/23464532/.
[7]. Effects of Intensive Glucose Lowering in Type 2 Diabetes. Hertzel Gerstein,
[8]. McMaster University,Michael E Miller, Robert P Byington, David C Goff.
[9]. **https://eportfolio.utm.my/user/badrul-fitri-bin-shaifull-naim/obesity-among-malaysian**
[10]. Chapter-19 Insulin, Oral Hypoglycaemic Drugs and Glucagon, Essentials of Medical Pharmacology, Tripathi KD, 6/e, 2008.
[11]. Chaper-30 The control of blood glucose and drug treatment of diabetes mellitus, RANG DALE'SPharmacology, H. P. RANG, M. DAIE, J. M. RITTER, R. J. FLOWER, G. HENDERSON, 7/e, 2011.
[12]. "Diabetes on the rise in Canada" 10 Jan. 2012, https://www.mountainviewoptometry.com/diabetes.
[13]. Native Oxyntomodulin Has Significant Glucoregulatory Effects Independent of Weight Loss in Obese Humans With and Without Type 2 Diabetes.
[14]. https://pubmed.ncbi.nlm.nih.gov/29545266/