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Review Article

Evolving Novel Drug Targets For Type 2 Diabetes: A Mechanistic Approach towards - Success, Challenges and Opportunities

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Abstract

The medications that are currently used to treat type 2 diabetes mellitus have significant drawbacks. Despite the development of new types of medications and targets, the global diabetic problem has not subsided. The search for fresh leads in routine trials continues to be significantly impacted by persistent unmet patient needs. The methods used to identify new drugs in this field have evolved along with market trends, which have led to a recent increase in the number of compounds. But worrying trends and brand-new difficulties are still present. Recently, a carcinogenic impurity known as N-nitrous dimethyl amine was discovered to be present in metformin, the most extensively used first-line medication for diabetes (NDMA). Purity and toxicity are thus significant obstacles to the discovery and development of new drugs. Newer pharmacological classes that target SGLT-2 also show both advancements and challenges. Glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors have the same effect in the past. Additionally, for therapeutic success, researchers must understand the significance of mechanistic features of novel molecules as well as atomic level exposure of both previously known and newly discovered protein targets, both of which aid in the identification of novel lead molecules with higher selectivity and specificity.

Keywords: Type 2 diabetes; Diabetes mellitus; Drug development; Drug discovery; Lead molecules; New targets

Introduction

Diabetes and its existence

The metabolic illness known as Diabetes Mellitus (DM), which is chronic and progressive, prevents the body from properly utilizing glucose [1]. Either the body's inadequate response to insulin or decreased insulin release by pancreatic beta-cells could be to blame. Blood glucose levels typically range from 80 mg/dl to 120 mg/dl which is maintained by insulin by aiding in the assimilation of glucose by the cells. Thus, a lack of insulin in the body causes hyperglycemia, which raises blood sugar levels and causes a number of metabolic and life-threatening problems, including, among others, cardiovascular, nephropathy, and neuropathic disorders [1]. Diabetes mellitus affects a sizable proportion of people worldwide (DM). According to studies, the global population of people aged 20 to 79 has 8.8% diabetics [2]. In accordance with a report from the International Diabetes Federation (IDF) [2] with a 30% obesity prevalence the world's most overweight population resides in the Federated States of Micronesia (Micronesia) [3]. Conversely, among the Western IDF regions, persons in North America and the Caribbean people between the ages of 20 and 79 having greatest frequency of diabetes (13%) [2]. The prevalence of diabetes is soaring in Mauritius (22%), followed by Sri Lanka (10.7%), and India (10.4%) in South Asian nations. Due to poor diets and sedentary lives, diabetes currently affects about 425 million people globally, and by the year 2045, that number is expected to rise to 629 million[4]. One theory holds that insufficient physical activity and a poor diet are the main contributors to serious diabetes in Micronesia and other adjacent islands. People in Micronesia eat an excessive amount of sugar to sustain themselves during periods of insufficient food availability. Even though there are more high-quality foods available now that they have recovered from such periods, sugar consumption has become a regular component of their everyday eating patterns. 73.1% of the population in Micronesia is overweight, and 32.1% of people there are diabetics, according to survey statistics [5]. Diabetes Mellitus poses a significant danger to both industrialized and developing nations. The 2017 National Diabetes Statistics Report estimates that around 30.3 million Americans have diabetes, and shockingly, about 23.8% of those individuals are undiagnosed [2]. Table 1 displays the IDF's most recent 2019 data. However, in nations like India, where 70% of people reside in rural areas. With inadequate health facilities, this underdeveloped health services system is the main factor leading to the incidence of diabetes. Widespread illiteracy and a lack of knowledge about better eating practices only help to make matters worse. These elements contribute to insufficient diabetes screening, the lack of preventative actions, and noncompliance with recommended diabetic management practices after diagnosis [6]. Obesity and T2DM may also be impacted

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Table 1: worldwide prevalence of diabetes by 2045.

2019 Rank	Territory/ Country	2019 (Millions)	Country/ Territory	2045 (Millions)
1	China	116.4	India	134.3
2	India	77	China	119.8
3	U. S. A	31	U. S	35.6
4	Pakistan	19.4	Mexico	21.8
5	Brazil	16.8	Brazil	20.3
6	Mexico	12.8	Egypt	16.7
7	Indonesia	10.7	Indonesia	16.7
8	Germany	9.5	Pakistan	16.1
9	Egypt	8.9	Bangladesh	13.7
10	Bangladesh	8.4	Turkey	11.2

by reduced physical activity and sedentary lifestyles. Consequently, it has been demonstrated that increasing physical activity can prevent the establishment of impaired glucose tolerance and aid to maintain the body's glucose homeostasis [7].

Diabetes Mellitus Classification

Earlier than its underlying systems were known, diabetes already existed. An Egyptian papyrus from 1550 BC made the first mention of diabetes, describing it as an uncommon illness characterized by rapid weight loss and frequent urination [8]. Apollonius of Memphis coined the word "diabetes" (which means "to syphon or pass through" in Greek), noting that people with diabetes frequently urinate. Galen, a Greek physician, surmised that it was a form of renal illness because glucosuria was the most noticeable symptom. Avicenna (980-1037), in "The Canon of Medicine", published a thorough description of diabetes mellitus in 1025[9]. Due to the disease's distinctive symptoms, a variety of tests were eventually established at the end of the 11th century, requiring an analysis of the urine sample of the patient, flavour, and savour. Evidently, the second word of diabetes, mellitus, from the flavour of a diabetic patient's urine is sweet (honey, in Latin) [10]. Matthew Dobson discovered towards the end of the 19th century, the sweet taste of diabetes patients' urine is caused by an excess of sugar in their urine. He also made a crucial distinction between insulin dependent and non-insulin dependent diabetes, the two main forms of diabetes that are today recognized. After giving a pancreatectomized dog islets of Langerhans, Macleod and Banting noticed a decrease in levels of blood sugar. For this ground-breaking innovation, they were given the Nobel Prize in 1923[11]. Eli Lilly was successful in securing the first commercial contract for the production of insulin. As the causes of diabetes began to be understood, various insulin formulations and other oral hypoglycemic medications gradually made their plan to get into the market during the late 20th century. Diabetes is currently divided into three main kinds, which are detailed below, in light of the lack of insulin and the resistance of cells to insulin. Diabetes mellitus 2019: WHO classification provides a thorough classification [12].

Type 1 diabetes mellitus

T1DM is also known as insulin-dependent diabetes mellitus is mostly brought on by the immune system of the body destroying pancreatic beta-cells. Patients with this kind of diabetes are seen in all patient age categories; however children are more likely to have it than adults [13].

Type 2 diabetes mellitus

T2DM is the most prevalent kind of diabetes .This is a complex, chronic disease. Since insulin is frequently utilized in the care of NIDDM, the name Non-insulin Dependent Diabetes Mellitus (NIDDM) is no longer in use. Although the precise process is yet unknown, Type 2 DM is thought to be brought on due to the steady emergence of resistant cells to insulin and -cell dysfunction. Obesity is a significant T2DM risk factor as it may increase the possibility of glucose intolerance. As a result, this will led to decrease in the amount of glucose that is absorbed by tissues like the heart or muscles while simultaneously increasing the glucose content that is made by organs like the liver [14]. Insulin secretion is increased by -cells in response to this. As a result, during early T2DM, hyperglycemia and hyperinsulinemia frequently coexist [15]. Later stages of the illness also result in decreased cell function. Therefore, essential therapies for T2DM include those that focus on cell function and reduce insulin resistance. Oxidative stress, ER stress, and autophagy are a few of the elements that affect how beta-cells function. Many of the targets that researchers developed over the years to prevent the formation or progression of diabetes in their patients became pharmacological objective.

Gestational Diabetes Mellitus (GDM)

GDM is a kind of pregnancy-related glucose intolerance. Around 2% to14% of pregnant women globally is affected by it [16]. After pregnancy; T2DM is more likely to occur in GDM moms. Their offspring are more likely to experience prenatal trauma, acquire obesity and diabetes later in life, and experience elevated rates of new-born trauma. Only a few cases of GDM necessitate medication, which can be controlled with exercise and diet.

Targets for Anti-diabetic Medications

Regular insulin delivery and dietary and lifestyle changes for those with T1DM are used to manage the condition [17]. The most effective remedy for T2DM proved elusive by virtue of the disease's complex pathophysiology. The most common kind of diabetes is T2DM. Substances that enhanced insulin's impact using target tissues and supported the recovery of -cell function have been the subject of numerous research. For individuals with T2DM, numerous targets have been identified during the past ten years as new oral medications [18] .Of these; starch blockers, insulin mimics and sensitizers, and insulin secretagogues are four main target kinds.

Secretagogues of insulin

Secretors of insulin function next to encouraging beta cells to generate extra insulin. A comparison of sulfonylureas and alternatives are available. Sulphonyl Ureas (SU) promotes the insulin production from the pancreas beta binding into cells to the sulphonyl urea receptors on these cells. In patients with T2DM, secretagogues have demonstrated high effectiveness in decreasing problems from glycated haemoglobin microvasculature [19]. Their primary flaw, though, is that they take a very long time to attach to the -cells, which causes the insulin release to take a very long period. Although they have a limited duration of action, non-sulfonylureas also cause -cells to produce

insulin. Five putative areas for insulin secretagogues -cell metabolism activation were suggested by Jean-Claude Henquin in 2004. These are: Increased KATP channel blockade, an increase in intracellular (Ca2+) concentration through channels other than KATP channels, the activation of various amplifying pathways in -cells, interactions with -receptors on cell membranes, and interactions with nuclear receptors on -cells are some of the mechanisms that contribute to this increase.

Sensitizers and insulin mimickers

Typically obtained as dietary supplements, these substances aid in reducing blood glucose levels. They function similarly to insulin by turning on glucose transporters in the cells of the muscles and fat. Increasing the body's tissues' sensitivity to insulin is how insulin sensitizers function. It has also been demonstrated that the use of insulin sensitizers improves a number of detectable cardiac risk elements, including a higher chance of blood clotting, high C-reactive protein, lipid profiles, or blood pressure, undesirable lipoprotein (a) or serum fibrinogen and even aberrant cardiac muscle thickening [20].

Starch inhibitors

Alpha-glucosidase inhibitors, other significant class, work by delaying the absorption of carbohydrates. Acarbose and miglitol are the most widely used medicines [21]. Dipeptidyl Peptidase 4 (DPP-4) inhibitors are a different class that likewise affects the metabolism of carbohydrates. One hormone that is strongly expressed in adipose tissue and produced after a meal is consumed is Glucagon-Like Peptide-1 (GLP-1). It functions by postponing stomach emptying, boosting insulin production, and lowering glucagon production [22]. Sodium-glucose co-transporter type 2 (SGLT2) inhibitors are a different recently identified division. Recently approved medications in this category include dapagliflozin and canagliflozin. These substances work without the help of insulin by encouraging the kidneys to excrete glucose Figure 1A and B. Other benefits of these medications include a slight reduction in body weight and a minimal risk of hyperglycemia, etc [23]. The creation of novel compounds that are in various stages of clinical trials is a result of the continual hunt for the optimal anti-diabetic medication. Table 2 provides a list of various anti-diabetic medications going through phase-III clinical trials.

New Targets for the Treatment of Type 2 Diabetes

11β-.Hydroxysteroid Dehydrogenase

The enzyme 11-hydroxysteroid Dehydrogenase is responsible for turning inert cortisone into active cortisol. High levels of active glucocorticoid cortisol in the blood have been associated with several disorders including high blood pressure, diabetes, obesity, dyslipidemia, and diabetes, according to publications in the literature. The 11-HSD deletion higher insulin sensitivity was seen in transgenic mice and to be relatively high resistant to high fat-induced obesity, although investigations further revealed such animal models with over expressed 11-HSD were more susceptible to metabolic syndrome [24]. Consequently, 11-HSD is seen as a key therapeutic goal for T2DM.

Glutamine fructose-6-phosphate amidotransferase

Even as mentioned before, the majority of glucose that enters the cell is converted through glycolysis, and only a very little amount goes through the hexosamine pathway. Hexosamine's role in the biosynthesis of glucose intolerance and the production of growth factors is activated is well recognized. Enzyme, Glutamine Fructose-6-phosphate Amino Transferase (GFAT) plays a crucial part in the process due to its involvement in catalysing the first and rate-limiting step in the biosynthesis of hexosamine. Thus, it is regarded as a key treatment target for T2DM [25].

Protein tyrosine phosphates 1B

Protein tyrosine phosphatases, including Leukocyte Antigen-Related Tyrosine Phosphatase (LARTP) and Protein Tyrosine Phosphatase 1B (PTP1B), are crucial in controlling insulin signal transductions [26]. An essential stage in the transmission of the insulin signal is tyrosine phosphorylation in the insulin-receptor activation loop. Insulin signaling is negatively regulated by PTP1B, which dephosphorylates phosphor-tyrosine residues in insulin receptor kinase activation regions. The research also points to a link between PTP1B, insulin sensitivity, obesity, and type 2 diabetes. Leptin is negatively regulated by PTP1B as well signaling. Since leptin is largely involved in maintaining metabolic homeostasis, obesity causes a decrease in leptin sensitivity, which makes it difficult to feel satisfied despite having adequate energy reserves. PTP1B is crucial for the development of pancreatic beta cells. For instance, Fernandez-Ruiz et al. [27] discovered that PTP1B deletion mice produce more insulin in response to glucose and increased cell proliferation. These results strongly imply that PTP1B has a role in diabetes, which has sparked interest in PTP1B inhibitors and led to the discovery of a number of PTP1B inhibitors. Other sources have comprehensive account of the reported PTP1B inhibitors [28].

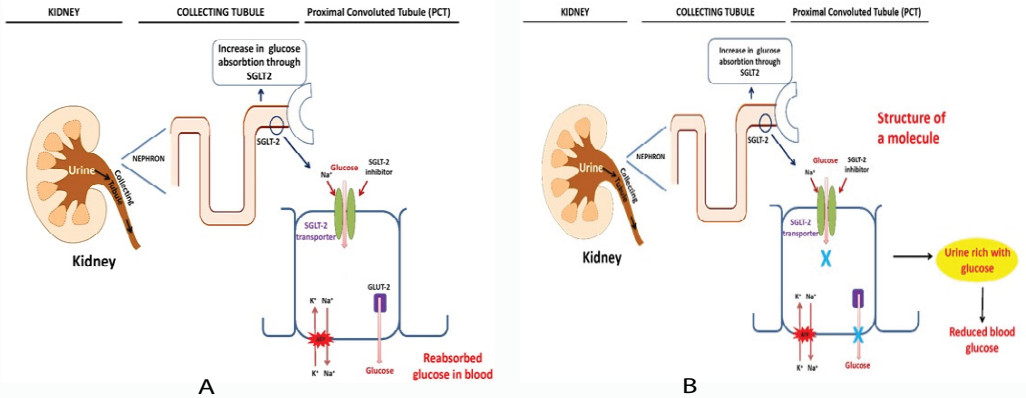

Figure 1: A) Sodium-glucose co-transporter type2 (SGL T2) inhibitor pathway. B) Sodium-glucose co-transporter type2 (SGL T2) inhibitor pathway.

Table 2: New anti-diabetic drugs in the drug discovery pipeline.

Name	Sponsor/Developer	Mechanism of action	Indication
Afrezza	MannKind	Ultra-rapid-acting mealtime insulin therapy	Adults with type 1 or type 2 diabetes
Albiglutide	GlaxoSmithKline	Glucagon-like peptide (GLP) 1 agonist	Once weekly for adults with type 2 diabetes
Aleglitazar	Roche	Dual peroxisome proliferator-activated receptor (PPAR) α/γ activation	Cardiovascular risk reduction in type 2 diabetes
Alogliptin, Alogliptin and pioglitazone, Alogliptin and metformin	Takeda Pharmaceuticals and Furiex Pharmaceuticals	DPP-4 inhibitor	Oral treatment of type 2 diabetes, individually and in two fixed-dose combinations
Atrasentan	AbbVie	Selective endothelin-A receptor antagonist	Oral once-daily treatment for diabetic nephropathy
Dulaglutide (LY2189265)	Eli Lilly	GLP-1 analog	Once weekly for type 2 diabetes
Empagliflozin (BI10773)	Boehringer Ingelheim and Eli Lilly	Sodium dependent glucose transporter 2 (SGLT2) inhibitor	Oral treatment for adults with type 2 diabetes
Ertugliflozin (MK-8835; PF-04971729)	Merck & Co., licensed from Pfizer	SGLT2 inhibitor	Type 2 diabetes
Fasiglifam (TAK-875)	Takeda	G-protein-coupled receptor (GPCR) 40 agonist	Type 2 diabetes
FIAsp (NN1218)	Novo Nordisk	Faster-acting formulation of insulin aspart.	Type 1 and 2 diabetes
Forxiga™ (dapagliflozin)	Bristol-Myers Squibb and AstraZeneca	SGLT2 inhibitor	Once-daily tablets for adults with type 2 diabetes
IDegLira (NN9068)	Novo Nordisk	Combination drug therapy	Type 2 diabetes
Invokana (canagliflozin)	Johnson & Johnson	SGLT2 inhibitor	Once-daily tablets for adults with type 2 diabetes
Ipragliflozin L-proline (ASP1941)	Astellas, MSD, and Kotobuki Pharmaceutical	SGLT2 inhibitor	Type 2 diabetes
Luseogliflozin hydrate (TS-071)	Taisho Pharmaceutical	SGLT2 inhibitor	Once-daily for type 2 diabetes
LixiLan (lixisenatide+ insulin glargine)	Sanofi; lixisenatide	Combination drug therapy	Type 2 diabetes
Lyxumia® (lixisenatide)	Sanofi; licensed from Zealand Pharma	GLP-1 agonist	Once-daily for type 2 diabetes
LY2605541 (basal insulin peglispro)	Eli Lilly	Basal insulin analog	Types 1 and 2 diabetes
LY2963016 (new insulin glargine product)	Eli Lilly and Boehringer Ingelheim	Basal insulin	Types 1 and 2 diabetes
Omarigliptin (MK-3102)	Merck & Co.	DPP-4 inhibitor	Once-weekly for adults with type 2 diabetes
Ryzodeg® (insulin degludec + insulin aspart)	Novo Nordisk	Soluble fixed combination of basal insulin with bolus insulin aspart	Once-daily for types 1 and 2 diabetes
Semaglutide (NN9535)	Novo Nordisk	GLP-1 analog	Once-weekly for type 2 diabetes
SYR-472 (trelagliptin succinate)	Takeda Pharmaceuticals and Furiex Pharmaceuticals	DPP-4 inhibitor	Once-weekly oral treatment for type 2 diabetes
Tresiba® (Insulin degludec)	Novo Nordisk	Once-daily basal insulin	Types 1 and 2 diabetes
U300	Sanofi	Insulin glargine	Type 1 and 2 diabetes

SLC16A11

The locus of a gene that is significantly correlated with type 2 diabetes was found through genome-based research by the Slim Initiative in Genomic Medicine for the Americas (SIGMA). These diabetes-related haplotypes impaired basigin interaction, which decreased SLC16A11 cell surface localization, and decreased SLC16A11 expression in the liver [29]. Modulation of fatty acid and lipid metabolism results from SLC16A11 disassemble in primary human hepatocytes. This distortion raises the levels of acylcarnitine, diacylglycerol, and triacylglycerol inside of cells, which causes blood triglyceride levels to rise and liver tissue to accumulate [30, 31] . Because triglyceride levels are linked to insulin resistance, SLC16A11 polymorphisms may make people more likely to develop diabetes *via* controlling lipid metabolism. But there are still a lot of unsolved issues. What are the specific substrates connected to the transit of mediators that target, T2DM is influence by the physiological and biochemical mechanisms, for instance.

Nephroblastoma over expressed (CCN3/NOV)

The cysteine-rich protein CCN3 (also known as nephroblastoma over expressed) has growth-regulating properties. Numerous tissues of humans and bodily fluids, including the musculoskeletal system, kidneys, and cerebrospinal fluid, have been found to contain it [32]. In obese patients with hyperlipidemia, the average plasma levels of CCN3 are markedly raised and strongly correlated with hs-CRP, BMI, and fat mass [33]. Martinerie et al. showed that CCN3 impairment significantly reduced body weight in mice fed a conventional high-fat diet and increased glucose tolerance and insulin sensitivity [34]. Li et al. [35] also examined serum CCN3 levels in newly diagnosed T2DM (nT2DM) patients and contrasted them with those of healthy control subjects. In T2DM patients, it was shown that CCN3 levels were markedly increased. These findings indicate that CCN3 may play a role in obesity-related insulin resistance and can be a key target for a T2DM treatment [35].

FoxO1

The transcription factor for the forehead FoxO1 is a key modulator of insulin signalling in beta-cells and a crucial target of T2DM. In a high-fat diet model, it has been demonstrated that dominant-negative FoxO1 adipocytes increased both glucose and insulin tolerance. Additionally, Fox01 in the pancreas causes stress and apoptosis, which results in -cell malfunction. The two most prevalent post-translational modifications of FoxO1, which controls several gene activities, are acetylating and phosphorylation [36]. FoxO1 is mainly released from the nucleus through phosphorylation, where it is then destroyed

by ubiquitination. The ratio of protein acetylases to deacetylases determines the level of acetylating in FoxO1. In diabetic livers, even FoxO1 is activated by O-GlcNAcylation during oxidative stress-like conditions, which boosts the activation of numerous gluconeogenic and ROS detoxifying genes. [36] After immediately binding to FoxO1 to phosphorylate it and eventually destroy it out of the nucleus, PGC1-activation during fasting activates the series of gluconeogenesis genes.

FFA2/FFA3

FFAs, or free fatty acids, can function as signaling molecules. According to the length of their chains, FFAs are typically categorised into three subcategories: Short-Chain Fatty Acids (SCFAs), Medium-Chain Fatty Acids (MCFAs), and Long-Chain Fatty Acids (LCFAs). It is known that transmembrane receptors like FFA1, FFA2, and FFA3 are activated by FFAs with these different chain lengths. For instance, LCFAs trigger FFA1, which is highly expressed on pancreatic beta-cells. Additionally, the rise in insulin production triggered by glucose is significantly influenced by the activation of these receptors. Therefore, a number of FFA1 ligands have been discovered and evaluated due to its clear significance in glucose-stimulated insulin release. Although FFA2 and FFA3 receptors resemble FFA1 receptors and are activated by SCFAs, their function in insulin is complicated. Particularly in neutrophils, immunological cells, FFA2 receptors are highly expressed [37-39]. Additionally, research has revealed that isolated mouse islets and the murine pancreatic -cell line MIN6 express FFA2 [40, 41]. A diet high in fibre is associated with a lower incidence of diabetes and SCFAs, which provides indirect evidence for the involvement of FFA2 in diabetes. It is known that gut bacteria in the body create FFA2 ligands through the fermentation of dietary fibre [42]. FFA2 and FFA3 expression on human pancreatic -cells was demonstrated by Tang et al. [43]. It has been demonstrated that these receptors prevent the release of insulin by connecting to Gi-type G proteins. They also showed that genetically eliminating the FFA2 and FFA3 receptors from pancreatic beta-cells causes increased insulin secretion in HFD rats, whereas eliminating the receptors from intestinal cells had no effect on the animals' ability to tolerate glucose. This study showed that FFA2/FFA3 antagonists may help people with type 2 diabetes [43].

Epoxyeicosatrienoic acids (EETs)

The cytochrome p450 enzymes (monooxygenase/epoxygenase) in the vascular endothelium respond to various stimuli, such as the agonists Acetylcholine (ACH) or bradykinin, or shear stress, which activates phospholipase A2 to release arachidonic acid, to produce Epoxyeicosatrienoic acids (EETs) from arachidonic acid [10]. 20-hydroxyeicosatetraenoic acid (20-HETE) and EETs are produced by the cytochrome p450 enzyme. The Dihydroxyepoxytrienoic acids (DHETs) that the soluble epoxies hydrolases and Reactive Oxygen Species (ROS) induce quickly hydrolyze the EETs, converting them predominantly to glycerophospholipids [44].The research demonstrates that EETs exhibit anti-inflammatory, vasodilatory, and ant apoptotic effects, dramatically inhibited sEH, and increased EETs' levels in cells and circulation [45-47].

An improvement in insulin sensitivity and subcutaneous fat. Fatty acid oxidation and obesity are increased by the rise in EET caused by CYP2J2. Although EETs have a naturally strong activity, such as vasodilatation, they can also reduce inflammation It is yet unknown how administration of EET or sEH inhibitors to obese mice affects mitochondrial function and Proliferator-activated Receptor Gamma Coactivator-1 (PGC-1), which are involved in adipogenesis [46,48-50].

Peroxisome proliferator-activated receptor gamma co-activator alpha (PGC-1α)

The human *PPARGC1A* gene produces the protein PGC-1. PGC-1 regulates the expression of insulin signalling, mitochondrial biogenesis, dynamics, and antioxidant genes, including uncoupling proteins, and so preserves energy balance and guards against mitochondrial dysfunction and metabolic diseases associated with adipocyte dysfunction [51]. The inflammatory response, which is frequently accompanied by metabolic problems, is made worse by PGC-1 dysregulation, which also affects cell homeostasis. Low levels of PGC-1 down regulate mitochondrial quality articulation during adipocyte dysfunction, causing irritation, oxidative pressure, and advancing atomic factor-B actuation [52].

Focusing on PGC-1 quality treatment may be an enticing remedial strategy for enhancing insulin affectability, metabolic movement, and vascular capacity in metabolic disorders because it increased fat tissue function and had a good impact on distant organs like the liver [53].

Peroxisome PROLIFERATOR-Activated Receptor g (PPARϒ)

PPAR is one of the most significant nuclear targets for TZDs. Although it is expressed in many different tissues and body cells in the body, it is expressed to a lesser level than in adipose tissues, which were once thought to be the positive regulator of adipogenesis. It has been shown that targeted PPAR deletion alters glucose homeostasis in a variety of cell targets, including adipose tissue, muscle, macrophages, and the brain, which in turn decreases the activity of TZDs. Adiponectin, a crucial insulin sensitising hormone, is widely known for being promoted and secreted by PPAR [36], are considered to offer viable avenues for treating different metabolic illnesses. Studies on its phosphorylation at S273 or sumoylation at Lys107, among others it is a well-known transcription factor that controls both the positive and negative activities of several genes. But a complete knowledge of PPAR's function and how it regulates insulin sensitivity remains difficult. It is still regarded as a crucial target despite its numerous side effects, which also include heart failure, weight gain, bladder cancer, plasma volume expansion, and others. It is quite interesting to investigate its downstream pathway and comprehend its mechanism. The significance of PPAR in mediating insulin sensitising activities has already been shown by epigenetic or post translational alterations to its structure [36]. The metabolic syndrome benefited from changes in PPAR that were caused by sirtuins.

Glucocorticoid receptor

Both endogenous and exogenous synthetic glucocorticoids have a specific impact on the action of insulin through the glucocorticoid receptor [54]. Both endogenous and exogenous synthetic glucocorticoids have a specific impact on the action of insulin through the glucocorticoid receptor [36]. The way that glucocorticoids exert their effects depends on whether they interact with other transcription factors to form a complex or whether they act directly on the promoter or enhancer regions of the genes. Numerous gluconeogenic genes, including Pck1 and G6pc, are impacted by homodimerization and direct binding, which are linked to insulin resistance [36], chronic stimulation of these receptors promotes proteolysis while inhibiting protein synthesis. In the end, this releases amino acids and serves as a substrate for the creation of glucose. Numerous studies demonstrate that GR activation decreases insulin-stimulated glucose uptake by influencing a wide range of downstream targets, despite the fact that the specific mechanism by which these receptors modulate insulin

resistance is still unknown.

Nuclear Factor (Erythroid-Derived 2)-Like 2 (*NRF2*)

In many diseases, *NRF2* is a crucial molecular node that provides cytoprotection. It is anticipated to be a key target in the development of new drugs due to its diverse involvement in numerous disorders. Concerning patients with Type 2 diabetes, a significant variation in the genotypic and allelic frequencies of four SNPs in the *NFE2L2* gene was discovered. Additionally, one study involved the inhibition of hepatic glucose 6 phosphatase via cAMP-CREB signaling, resulting in the activation of *NRF2* in obese diabetic db/db mice, demonstrating a lower blood glucose level [55]. Mice lacking in leptin demonstrated lower levels of white fat mass and decreased *NRF2* expression. This implies that *NRF2* is a crucial component of adipogenesis or other metabolic diseases. Although chronic glucose circumstances did not activate *NRF2*, it has been hypothesised that acute glucose doses can raise *NRF2* levels. In patients with prediabetes, expression is also down regulated [55]. The role of *NRF2*-mediated protection in diabetic retinal dysfunction is also well established. The apoptosis elicited by palmitate in the hepatocytes of obese patients is enhanced by *NRF2* knockdown.

Neprilysin

Neprilysin is a zinc-dependent metalloprotease that cleaves peptides (GLP-1(7-36) amide, GLP-1(9-36) amide from GLP-1(28-36) amide, and GLP-1(32-36) amide) and activates a number of peptide hormones, including glucagon, substance P, enkephalins, neurotensin, oxytocin, and bradykinin [56]. The primary circulation form of GLP-1 in plasma, GLP-1 (9-36) amide, was once believed to be the c-terminal metabolite that results from the enzymatic cleavage of incretin hormone GLP-1 (7-36) amide by dipeptidyl peptidase-IV. Mitochondrial activity prevents INS-1 -cell death by inhibiting membrane depolarization and caspase activation. The delivery of GLP-1 (28-36) amide, which promotes -cell mass and proliferation by activating the cAMP/PKA signalling cascade and phosphorylation the Wnt/-catenin signalling, further demonstrates the impact of these metabolites on diabetes. In addition to GLP-1R, these additional metabolites were thought to have an insulinomimetic activity that adds to the pleiotropic effects of GLP1. By modifying energy balance, it has been discovered that direct administration of these metabolites exerts antioxidant, anti-apoptotic, and proliferative effects on pancreatic -cells. These metabolites are said to maintain the pathway.

Drugs Targeting Molecular Pathways Implicated in Diabetes and CVD

When creating novel treatments, it's important to remember that T2DM is multifactorial, and that the earliest feasible start to therapy is crucial. T2DM is frequently connected, in addition, to an elevated risk of CVD. According to current FDA regulations, all innovative diabetic therapies must have cardiovascular impact profiles that are neutral or at least protective. Therefore, sub-atomic pathway targets that may be related to both diabetes and cardiovascular disease are of special interest. Focusing on 11-hydroxysteroid dehydrogenase type 1 (11-HSD1), GPR119, TGR5, sirtuin 1 (SIRT1), the sodium-glucose co-carrier 2 (SGLT2), and GPR40 is one of these techniques. The rationale for each of these is briefly described below (Table 3).

When considered collectively, these clinical results provide strong support for the notion that a variety of inhibitors, activators, agonists, and antagonists have potential as novel therapeutics for T2DM and related metabolic disorders.

Challenges and Opportunities

The fact that, despite the positive effects of current glucose-lowering medications, morbidity and mortality remain significant in T2DM patients emphasizes the need for the development of pharmacotherapeutics with a special focus on the numerous metabolic irregularities and different pathways associated with morbidity. The biggest challenge in treating type 2 diabetes is probably preventing the long-term side effects of any therapeutic strategy, like CVD and nonalcoholic greasy liver disease (NAFLD/NASH). Hyperglycemia levels have been linked to a higher risk of micro- and macro vascular consequences in T2DM, including fatal CVD events. According to research on individuals with long-standing T2DM, intensive glucose management in such patients does not appear to have any benefits and may even raise the risk of CVD events. In any case, the latest Accord and advance patient research. Studies on adults with long-term T2DM have shown that intensive glucose management in such patients does not appear to have any benefits and may even increase the risk of CVD events. In this way, other independent risk factors could exist and combine to increase the risk of CVD in these patients. On the other hand, these discoveries may essentially mirror the drawbacks of current diabetic therapies due to unexpected effects that act against the potential advantages of glucose lowering medications. Further research is required on the identification of SGLT2 inhibitors that seem to have little drawbacks the most frequent adverse events in females throughout Phase-III clinical investigations were vulvovaginal candidiasis and mycotic infections. Due to the fact that glucose discharged in the urine also causes an increase in water and saline excretion, osmotic diuresis is conceivable. This condition might lead to hyperkalemia, renal failure, acidosis, or ketoacidosis. The typical SGLT2 inhibitor is expensive and difficult to use for long periods oftime.[http://www.rheumatologynetwork.com/sglt2/sglt2-inhibitors-pros-cons-comparisons-and considerations]. Resveratrol is thought to be the most thoroughly characterized substance in the field of the hunt for novel therapeutic compounds that can activate sirtuins. However, it doesn't immediately activate SIRT1. SRT1720 and SRT2104, which are active, have been synthesized into many molecules with comparable structures. Unexpectedly, they activate some fluorophore tags despite the fact that they still require some substrate. If natural sirtuin is comparable to the fluorophore substrate, they immediately activate SIRT1 (Figure 2) [73].

Summary

In the past thirty years, there has been upheaval in the improvement of diabetes therapy, particularly in the use of basic insulin for glycemic control. This beneficial activity aims to advance a wide range of possible medicines and gain a better knowledge of the hidden systems underlying disease pathology. Sadly, sedentary habits and disparate nutritional tastes are to blame for the current obesity epidemic. Along these lines, there is a growing need to advance the methods used to treat diabetes and prediabetes. Despite obviously improved therapeutic choices, the International Diabetes Federation notes that many diabetic patients are either unable or unwilling to adhere to current clinical care recommendations.

Large clinical trials including Accord, Advance, and Vadt, where better HbA1c level controlled to reductions in significant micro vascular diabetic complications, but where rates of macro vascular infection and mortality remained largely unchanged, are evaluating HbA1c-reducing medications. Therefore, it is generally understood that potential therapy strategies should target clinical outcomes in line

Table 3: List of new anti-diabetic drugs targeting molecular pathways implicated in diabetes and CVD.

Targets	Mechanism of action	Leads	References
11β-HSD1(hydroxysteroid dehydrogenase)	Blocking cortisol	INCB13739, MK-0916, BI 135585	[57,58]
G protein-coupled receptor (GPR119)	increases cAMP signaling	APD5979, MBX-2982	
TGR5	cAMP accumulation and enhanced GLP-1 secretion (intestine), anti-inflammatory effect (liver),	INT-777	[59]
SIRT1	Improve insulin sensitivity, increase glucose homeostasis, increase mitochondrial capacity	SRT2104, resveratrol	[60]
SGLT-2	Increase kidney dependent glucose homeostasis	dapagliflozin, canagliflozin, sergliflozin, remogliflozin, ipragliflozin, and empagliflozin etc)	[61]
GPR40	Increase incretin secretion, improved glucose tolerance	Modulators	[62]
PPAR-γ	Improved serum lipid profile, glucose homeostasis, insulin sensitivity, reducing inflammation and weight gain	Piolitazone, aleglitazar, glitazones, GFT505	
Tyrosine Kinase	Reduced Beta cell apoptosis, Enhanced insulin secretion, increased beta cell survival, reduced insulin resistance,	Imatinib, Sunitinib, Dasatinib, Sorafenib, Erlotinib	[63]
PPLR	Improved JAK2/STAT5 pathway for glucose uptake	Bromocriptine	
Insulin degrading enzyme (IDE)	thiol zinc-metalloendopeptidase that cleaves small proteins of diverse sequence	BDM44768, 6bK, NTE-1	[64]
FATP5	Enhance the uptake of long chain and very long chain fatty acids into the cells	Chenodiol and Ursodiol	[65]
Sestrin	Enhances Hepatic Insulin Sensitivity	Enhances Hepatic Insulin Sensitivity	[66]
Statin	For diabetic dyslipidemia		
Adiponectin	Decreased adiponectin levels are thought to play	AdipoRon is a novel orally-active small molecule that serves as a potent selective agonist of the AdipoR1 and AdipoR2 adiponectin receptors	[67,68]
Glut4	Triggering the canonical PI3K–AKT pathway is essential and ample to activate exocytosis of GLUT4 storage vesicles to the plasma membrane	Staurosporine is used to promote GSVs translocation and glucose uptake through the AMPK pathway.	[69,70]
PGC-1α	Reduction in PGC-1a triggers insulin resistance and ultimately causes diabetes	Still waiting to synthesize agonist	[71,72]

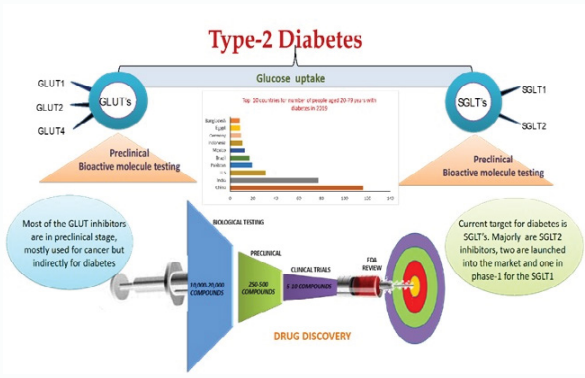

Figure 2: Timeline of T2DM Drug Development.

with a multifaceted understanding of T2DM.

To comprehend the multifactorial nature of T2DM, a wide range of approaches are being used. The ClinicalTrials.gov website lists more than 1,000 ongoing Type 2 diabetes trials in different countries. These studies cover a wide range of topics, such as liver illnesses and cardiovascular involvement. Generally speaking, the development of novel therapeutic strategies for T2DM and disorders connected to diabetes has enormous potential for the years to come.

Concluding Remarks and Future Perspectives

The T2DM drugs that are now on the market have substantial drawbacks and adverse effects. These glaring flaws jeopardize their effectiveness for a variety of clinical objectives. In order to find new therapeutic targets or pharmacological combinations, research is ongoing.

Future therapeutic and pharmaceutical advancements must adopt a comprehensive approach with a special emphasis on the following elements: (1) they should target mechanisms to achieve effective glycemic control with a safe weight loss profile; and (2) they should slow the progression of diabetes-related micro-vascular and cardiac complications.

The effects of bariatric surgery have been astounding for many patients; however, reports of significant rebound after six months have also been documented. Focusing on the factors that might be involved in those early phases of improvement is essential for the scientific community if it wants to advance T2DM research. In order to achieve these objectives, a number of institutions have already started enrolling cohorts of obese diabetic and non-diabetic people in a gastric banding project. Blood and tissue samples will be taken from these patients (as well as a corresponding control arm) both during the surgical procedure and longitudinally throughout the course of a five-year follow-up.

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