REVIEW ARTICLE

Recent Therapeutic Approaches for the Management of Diabetes Mellitus

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ABSTRACT:

Background: Diabetes mellitus (DM) is a global epidemic with a prevalence anticipated to double in the next decade, placing a heavy burden on healthcare systems. While current treatments like metformin, secretagogues, thiazolidinediones, and insulin are useful, there is a pressing need for novel medications that not only achieve customized glycemic objectives but also address concurrent comorbidities and maximize safety. **Objective:** This review aims to focus specifically on the highly anticipated and recognized novel pharmacological approaches currently in the clinical pipeline for diabetes mellitus. It seeks to identify and evaluate these approaches based on growing incidental evidence and their potential to shift the treatment paradigm from management to cure. **Methods:** A narrative review of the current clinical pipeline was conducted, focusing on agents identified through global studies and growing incidental evidence. The approaches highlighted were selected based on their novel modes of action and significant recognition within the development landscape. **Main Outcome:** The primary outcomes of interest include the efficacy of novel approaches in maintaining optimum glucose levels, their mechanisms of action (e.g., improving insulin sensitivity, increasing insulin secretion, modulating the incretin axis, decreasing hepatic glucose synthesis), and their potential to address comorbidities and avoid complications. **Results:** The pharmacological pipeline for DM is rich with promising approaches. The approval of SGLT2 inhibitors like canagliflozin, dapagliflozin, and empagliflozin has laid the foundation for a new era in treatment. Current clinical developments are characterized by drugs utilizing new modes of action that go beyond traditional glycemic control, showing significant potential for improved efficacy and non-glycemic benefits. **Conclusion:** The development of novel DM medications is highly encouraging, raising the bar for future therapies. The evolving pipeline, with its emphasis on new mechanisms and evidence-based benefits, holds the promise of efficiently maintaining optimum glucose levels and potentially shifting the paradigm from chronic management towards a curative approach.

Key Words: Diabetes Mellitus, Glucose Level, Insulin Resistance, Management, Treatment, Trials.

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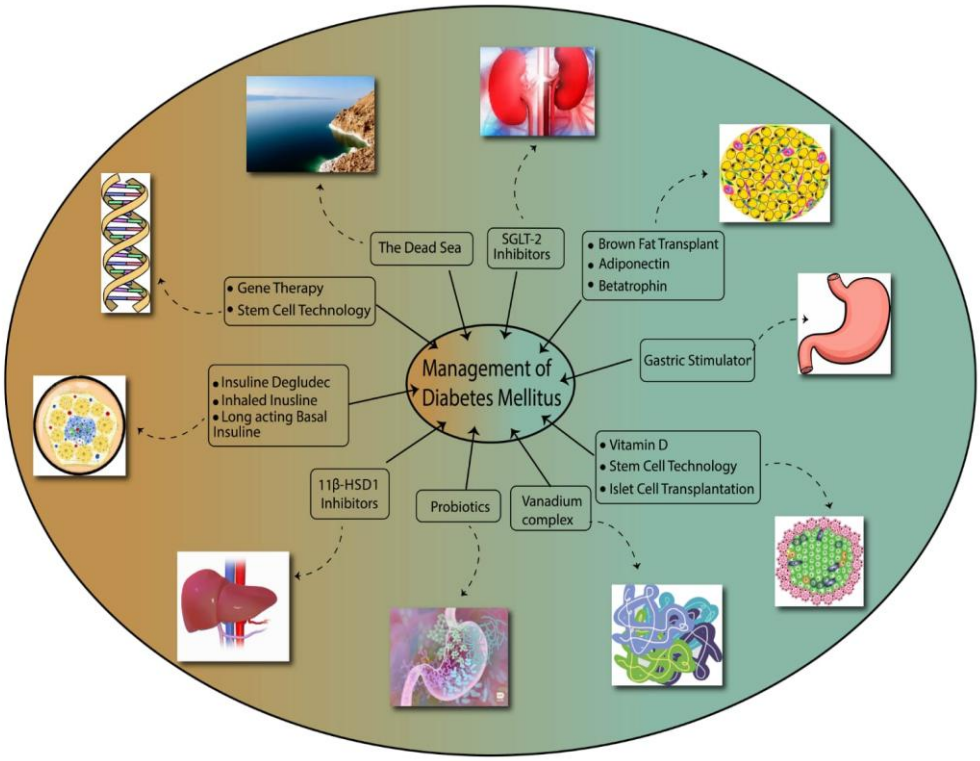
Graphical Abstract



1. Introduction

Diabetes mellitus (DM)has been turned into an epidemic imposing severe socio-economic crisis, especially to the developing countries around the globe.According to an estimate, about 415 million people are suffering fromDM,approximately1 in 11 of the world's adult population. Worryingly, 46% of diabetic people remain undiagnosed and the majorityof this population lives in middle and low-income countries and comprisesthe 40–59 age group[1]. Due to high blood sugar levels in DM, serious complications including vision loss, kidney impairment, peripheral nerve damage, infections, and heart diseases risk increase tremendously[2].Although there are several available therapeutic options for the treatment of type 1 and type 2 DM, limitations of their glycemic control, ease of administration, adverse effects profile, multiple drugs intake, and time-span of their relative control remain key issues for any kind of sustainable solution. There is a dire need for novel and evolving treatment strategies, necessary to maintain glycemic control due to the progressive nature of the disease.*In addition to medicine, researchers also emphasized that lifestyle changes e.g. exercise, weight loss, healthy food, and lifestyle choices can lead to better outcomes[3-5].* In the past 5 years,varieties of novel pharmacological interventions have been developed to treat people with diabetes. However,

the latest news about DM is encouraging because "New" is not necessary to be better, but these could be extra weapons in the deployment. Considerations of how diet and exercise can affect diabetes, new drugs, and improved monitoring devices are adding up to the positive outcomes for the patients. Due to improved medications and treatments available for the disease and theseveral complications that arise from it, the majority of type 2 DM patients are now living longer & healthier lives[6]. In recent months, the rate of U.S. Food and Drug Administration (FDA) approvals for the disease are rapid due to the response of the type 2 DM epidemics. Since January 2013, approximately nine newproducts have been approved for DM, that include inhaled insulin for both type 1 and 2 DM,and alogliptin a new drug, available in three different oral treatments[7].These are significant developments as the route of insulin administration has remained a counterproductive factor in fighting DM[8, 9]. Furthermore, the advancement in nanotechnology and stem cell technology is revolutionizing the available treatment optionsin DM management and medications[10, 11].Therapeutic options mostly heading toward palliation and control at present,butthey must be rationalized towards treatment and prevention. This is a big challenge if it can transcend economic compulsions and awaken to its true role in medicine. Hence, recent therapeutic approaches mainly focus on the development of newer drugs or techniques that are tolerable with enhanced efficacy with the ultimate goal of longevity with well-being in chronic diseases.Therefore, clinical trials addressing the recent treatment of DM have a remarkable potential influence on population well-being and related healthcare costs. In this review, we aim to summarize thelatest or current treatment options approved or in the clinical pipeline, with improved benefits refine risk predictions, and determine the optimal strategies for monitoring and adjusting basal glucose levels in DM.

2. Recent Therapeutic Approaches for Diabetes Mellitus Management

2.1. Sodium-Glucose Co-transporter 2 (SGLT-2) Inhibitors

The brush border of the proximal convoluted tubules contains SGLT-2 (transporter with a low affinity and great capacity), which is responsible for glucose reabsorption in the kidneys[12, 13]. In a hyperglycemic state, the kidneys may aggravate the problem by reabsorbing excess glucose, eventually leading to persistent hyperglycemia and the risk of micro and macrovascular complications[14]. By exerting a specific impact, SGLT-2 inhibitors cause kidneys to excrete glucose into the urine, which is independent of insulin release. Hence, these proposed mechanisms make a possible target to control hyperglycemia in patients with type 2 DM called sodium-glucose transporter 2[15]. These agents decrease A1C values from 0.5 to 1.5% and establish low occurrences of hypoglycemia with minimal side effects[16]. Canagliflozin by Janssen Pharmaceuticals is the first drug that was approved by the FDA that blocks the reabsorption of glucose and increases its excretion by kidneys[17, 18]. An improvement in fasting blood glucose levels and hemoglobin A1C in trials among 10,000 patients with canagliflozin secured FDA approval. In August 2014, another trademark was approved by the FDA, which is a fixed-dose tablet of canagliflozin and metformin for better diabetic control[19, 20].FDA approved another SGLT blocker,empagliflozin, in May 2014 and it hit the U.S. market with improved outcomes[21]. During Clinical trials of almost 4500 people with type 2 diabetes mellitus, empagliflozin

showed better hemoglobin A1C levels as compared to the placebo[22].Empagliflozin can also be used with pioglitazone[23], sulfonylureas[24], metformin[25], and insulin[26]. The FDA has asked BoehringerIngelheim, the manufacturer of empagliflozin, for its post-marketing surveillance studies to look at safe dosage levels and effectiveness in children and also the sensitivity outcomes studies in all the populations [27].With a reduction in body weight and HBA1c (glycated hemoglobin) levels, empagliflozin demonstrated promising effects in terms of glycemic management, glomerular filtration rate, and vascular efficiency. Hypoglycemia and DKA (diabetic ketoacidosis) are two major adverse effects, both of which raise the risk of kidney failure (Table 1). Mild symptoms of urinary tract infections and vaginal infections have also been reported, but these are uncommon[28].

Sr. No.	Treatment	Mode of Action	FDA Approval Stage	Advantages	Limitations
1.	Sodium Glucose Co-transporter 2 Inhibitors	Inhibit absorbance of excess glucose from kidneys	Phase 4 (Clinicaltrials.gov)	Inhibit re-absorption of glucose level of blood in proximal renal tubule to enhance hyperglycemia	Increase risk of kidney failure (Staplin et al., 2021)
2.	Inhaled Insulin	Fine insulin powder is inhaled, it enters in blood and produce immediate action	Phase 4 (Clinicaltrials.gov)	Rapid Action	Cough, Throat Pain, Irritation, Bronchospasm in COPD and Asthmatic Patients (Pettus et al., 2018)
3.	Basal Insulin	Delays the absorption of insulin from GIT and reduces clearance, result in prolonged duration of action	Phase 3 (Clinicaltrials.gov)	Mimic normal secretion patterns to regulate the glucose metabolism	Hypoglycemia, Weight Gain (Klonoff et al., 2019)

4.	11-β-HSD1 Inhibitors	Inhibit 11-β-Hydroxysteroid Dehydrogenase hence regulate insulin hemostasis	Phase 2 (Clinicaltrials.gov)	Improve insulin sensitivity and glucose tolerance	Nephrotoxicity (Almeida et al., 2021)
5.	Vitamin D	Facilitates the insulin secretion from pancreatic beta cells	Phase 4 (Clinicaltrials.gov)	Improve body's sensitivity to insulin and regulate blood glucose level	Autoimmunity and metabolic changes effect energy expenditure in body (Corrao et al., 2021)
6.	Stem Cell Technology	Transplantation of insulin producing islet cells isolated in vitro from a donor pancreas in diabetic patient	Phase 1 (Clinicaltrials.gov)	Stabilize glucose level without insulin	Immun-rejection (Triolo and Bellin, 2021)
7.	CRISPR Technology	CRISPR enables to edit the genetic material of an organism allow DNA sequences to be easily altered and modified the gene function	Preclinical Phase (Clinicaltrials.gov)	Directly target embryonic stem cells	Inaccurate on- or off-target editing (McCloskey et al., 2020)
8.	Betatrophin	Betatrophin has been found to stimulate production of the pancreatic [beta] cells that make insulin	Phase 2 (Clinicaltrials.gov)	Improves glucose tolerance and regulates lipids metabolism	Increased risk of cardiac and metabolic disorders [60]
9.	Adiponectin	Release Adiponectin from apM1 gene	Preclinical Phase (Clinicaltrials.gov)	Improve insulin sensitivity and	Change in genetic expression alter the release of protein

				glucose tolerance	(Yani and Yoshida, 2019)
10.	Islet Cell Transplantation	Beta cells are removed from donor's pancreas and transferred into a person with diabetes	Phase 1 (Clinicaltrials.gov)	Cells normally start to produce and release insulin	Organ and tissue rejection (Gamble et al., 2018)
11.	Brown Fat Transplant	Decrease body weight and white fat mass	Preclinical Phase (Clinicaltrials.gov)	Improve glucose sensitivity and glucose metabolism	Tissue rejection and immune response **[75, 76]**
12.	Vanadium Complex	Insulin receptors phosphorylated hence allowing glucose transport into the cell	Phase 2 (Clinicaltrials.gov)	Increase glucose uptake and lower blood glucose level	Tissue accumulation and Long-term toxicity may increase oxidative stress or pro-inflammatory reactions and renal problems [82]
13.	Gastric Stimulator	Stimulates afferent fibers of the vagal nerve to influence the cerebral satiation center, which is involved in registration of satiety and in insulin secretion and resistance	Phase 1 (Clinicaltrials.gov)	Improvement in glucose regulation with weight loss	Dysphagia, early satiety, constipation, abdominal pain (Wang et al., 2021)
14.	Gene Therapy	The targeted gene can be replaced in a host or the	Preclinical Phase (Clinicaltrials.gov)	Restore normal blood glucose level	Selection of suitable vector and transfection

		autoreactive T cells suppressed			efficiency needs to be explored [1]
15.	Probiotics	Enhance glucose metabolism	Randomized control Trials (Clinicaltrials.gov)	Regulate blood glucose level	Alteration in gut flora can lead to digestive issues, skin disorders, infections, and even mental health issues [92]
16.	Dead Sea Minerals	Mechanism not known	Not Available (Clinicaltrials.gov)	Decrease blood glucose level	Not known [98]
17.	Insulin Degludec	Formation of a subcutaneous depot that results in slow insulin release into the systemic circulation	Phase 3 (Clinicaltrials.gov)	Long duration of action and lower risk of hypoglycemia	Urticaria and hypoglycemia [100]

2.2. Inhaled Insulin

FDA approved Afrezza (human insulin) inhalation powder in 2014[29].Afrezza is an inhaled insulin that improves blood glucose levels in adults with diabetes when taken with meals. Afrezza was tested in patients with type 1 and type 2 DM for 24 weeks in a clinical trial[30].In patients with type 1 DMusing long-acting insulin, the efficacy of Afrezza to lower A1C decreases as compared to insulin aspart i.e., injectable fast-acting insulin in 2016[29]. In 1991, a 24 weeks study revealed that inhaled Afrezza human insulin did significantly lower A1C values as compared to a placebo control group when type 2 diabetes patients used oral anti-diabetic medications[31]. Afrezza may cause serious side effects when inhaled, such as bronchospasm in patients with chronic obstructive pulmonary disease or asthma. In 2007, Exubera was withdrawn from the U.S. market, (previously approved inhaled insulin), due to lack of sales. The outcome of Afrezza sales waits to be seen, although some experts expect that sales could reach $1.6 billion [32, 33].

2.3. Long-Acting Basal Insulin Analogue

Intype 2 DM patients, a long-acting basal insulin analogLY2605541is currently being evaluated in phase III studies[34]. The principal aim of insulin treatment in patients with type 1 and 2 DM is to replace the deficiency of endogenous secretion of insulinphysiologically and mimic the normal secretion patterns to efficiently regulate glucose

metabolism.The basal insulin analog LY2605541 contains insulin lispro modified with a 20kDa polyethylene glycol moiety having a large hydrodynamic size [35]. Thus, it delays the absorption of insulin from GIT and decreases clearance, causingan extended duration of action. The distribution pattern of this insulin to the tissues appears to change as the PEG molecular size increases. Hepatic sinusoidal endothelium may allow stronger LY2605541 transport into the liver than peripheral tissues (i.e., muscle and fat), perhaps delivering a unique hepatic action akin to normal physiology [36].PegLispro demonstrated good effects in phase 3 clinical trials, lowering A1C, glucose variability, nocturnal hypoglycemia, and weight gain. This medicine, however, was linked to abnormalities in liver enzymes and lipids, leading to its withdrawal [37]. Other developing insulins, such as combining insulin lispro with vesicles that impart hepato-selectivity, are currently being designed to resemble PegLispro without the negative effects.The additional clinical study will disclose whether a basal insulin analog with special liver-specific action results in therapeutic advantages.

2.4.11β-Hydroxysteroid Dehydrogenase Type 1 Inhibitors (11-β-HSD1)

Cortisone reductase, also known as 11-hydroxysteroid dehydrogenase, converts cortisone to cortisol. Insulin resistance and obesity may result from overexpression of this enzyme[38, 39]. 11-β-HSD1 has a functional role in metabolic disease and obesity in rodents, which proposes that hindering this target site in adipose tissues and liver may cause improved hepatic and peripheral insulin sensitivity, hence overall glucose level improves and probably declining the overall macrovascular hazard, suggested by preclinical evidence [40]. 11-HSD1 inhibitors were tested in diabetic patients in clinical trials and demonstrated improved glycemic control, blood pressure, and lipid profile, as well as rapid weight loss[41]. The extent of the therapeutic outcomes is small compared to other agents; hence, 11β-HSD1 inhibitors after development for the major therapeutic indications of type 2 DM have slowed down. In the past years, many 11beta-HSD1 inhibitors have been discovered, formulated, screened and synthesized. Administration of 11β-HSD1 selective inhibitors considerably reduces the progressionof disease in pre-clinical models and clinical trials of DM andanother metabolic syndrome *via*a significant reduction in intracellular concentrations of glucocorticoids[42]. Current programs are focused on further benefits for cognitive function and other cardiovascular diseases.

2.5.Role of Vitamin D in DM

Latest studies have found that vitamin D deficiencyresults in a decreasein insulin secretion andhyperglycemia.Vitamin D receptors are found in pancreatic beta cells and help to regulate the 1-hydroxylase enzyme[43, 44]. Vitamin D aids the release of insulin by pancreatic beta cells, hence regulating insulin secretion.So, vitamin D deficiency may be interrelated to impaired insulin secretion in type 2 DM[45].Parker et al. (2010) found that maintaining vitamin D serum levels in the normal range reduced the risk of developing DM by 55 percent[46].Both insulin sensitivity and secretion alsodepend upon the intracellular concentration of calcium and vitamin D has been found to regulate the calcium flux within the cells[47]. An inverse relationshipbetween the level of Vitamin D and the degree of glycemic

control has been reported in both observational and case-control studies [48].In patients with DM type 2, maintaining vitamin D levels in the normal range may help with glucose control and postpone or prevent the clinical development of disease in the elderly. [49, 50].According to a study by Zipitis et al., vitamin D supplementation reduced the risk of type 1 DM in children by 29%, when compared to those who did not get the supplements [51]. However, it is unclear whether type 1 diabetics' genetic make-up causes vitamin D insufficiency or whether vitamin D deficiency causes the risk of type 1 DM.

2.6. Stem Cell Technology

A new method is created in which stem cells derived pancreatic cells enclosed in capsules are placedunderneath the skin to restore insulin secretion is tested in diabetic diseased models (Stem Cell-Derived Beta Cells Under Skin Replace Insulin 2014). This method showed successful outcomes without producing probable complications. An artificial pancreas, consisting of beta cells cultivated on synthetic semi-permeable hollow fibers was created and tested in rats with alloxan-induced diabetes (Figure 1). These devices were implanted in the circulatory system as ex vivo arteriovenous shunts, which reduced plasma glucose levels from 533 to b/w 110-130 milligrams, boosted insulin concentration in plasma, and restored normal intravenous glucose tolerance testing [52]. Thus, in humans, if encapsulated islet cells prove to work efficiently, hoped that they produce the following benefits; prevent too high or too low sugar levels, reduce the need to take insulin by injections or insulin pumps,and also minimize the need for daily blood glucose tests[53]. For many months in diabetic patients, encapsulated islet cells technique would represent a cure therapeutic approach with minimal management. The researchers hoped that encapsulated islet cells would be effective for up to 2 years. Although stem cells have a high capacity for replication, immunological rejection of donor cells by the host immune system after transplantation is a major concern.

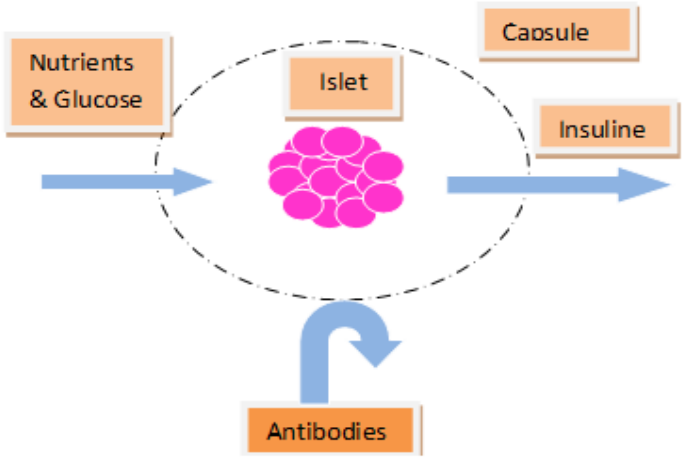


Fig 1 Schematic description of stem cell technology to encapsulate pancreatic cells to restore insulin secretion

2.7. Genome Editing and CRISPR Technology

Human-induced pluripotent stem cells (hiPSCs) have become a foremost focus of research [54].Various hiPSCs have been produced from patients of different diseases to understand the mechanisms of different diseases[55]. Genome editing (insertion, deletion or replacement) is one of the techniques of genetic engineering of DNA that was performed to recognize and understand the function of the gene of interest[56]. Genome editing tools e.g., the clustered regularly interspaced short palindromic repeat (CRISPR)/Cas9 system can be applied to hPSCs in the presence of a donor template to either create naturally occurring mutations or repair a mutation to generate isogenic controls in hPSCs.CRISPR/Cas9 is precisely easier to use and is more proficient at cutting target DNA [57]. The major advantage of this technique is that CRISPR/Cas9 system is economical and easily accessible in repositories such as Add gene leading to an exponential increase in genome engineering of cells to study disease biology. The genetically engineered hPSCs can easily be differentiated into the cell of interest that help in the study and understanding of the biology of the disease. Genome CRISPR editing using Cas9 technology may help in understanding the impact of specific genotypes.This technique can also be helpful for the regulation of the transcription process to enhance the functional maturation of stem cell-derived islets. These tools show promising impacts on tomorrow's translational diabetes research[58]. According to a study done by Maxwell et al., the gene-editing CRISPR system is used to correct a mutation in human-induced pluripotent stem cells (iPSCs) and subsequently transform them into beta cells. When these cells were implanted into experimental mice, they were able to manageDM in a long-term manner. When diabetic mice are given corrected beta cells, their blood glucose levels drop immediately, indicating that the condition has been reversed, and this effect lasts for six months[59]. This technology now allows for the use of gene therapy in conjunction with the patient's cells to cure diabetes mellitus through lab-grown beta cell transplantation.

2.8. Betatrophin

Betatrophin is a 22kDa hormone majorly present in the adipose tissues and liver which plays asignificant role to expand the mass of beta-cell, upholding pancreatic beta-cell proliferation, and improving the glucose tolerance in models of insulin resistance in mice[60, 61]. When the insulin receptor antagonist S961 was administered to mice during a study, it resulted in an increase in beta cell replication, which increased Betatrophin secretion in the liver. As a result, betatrophin emerged as a signaling molecule linked to beta cells that promotes a hepato-adipose-pancreatic cross-over in the face of insulin resistance.There is also a need for the identification of the betatrophin receptors to determine which would be the pathophysiological regulators of betatrophin to clarify the exact role of betatrophin in obesity and obesity-associated diseases such as type 2 DM and Dyslipidemia[62, 63].Identification ofthe betatrophin receptors and other possible co-factors will aid to elucidatethe liver and fat interactions withthe pancreas in the

regulation of β cell mass. Nonetheless, the identification of betatrophin as a hormone opens a new door toward possible diabetes therapy.

2.9.Adiponectin

Adiponectin is a recently discovered adipocytokine. It is a protein also known as gelatin binding protein 28[64]. It produces as a by-product of apM1 gene, comprising of 244 amino acids, which is precisely expressed in the human adipose cells by comprising [65]. Researchers aren't entirely sure what adiponectin's physiological role is, but research reveals that lowering apM1 gene expression in adipose tissue leads to lower adiponectin plasma levels, which have been linked to the etiology of type 2 DM and obesity [65, 66].Insulin resistance has been discovered in mice with adiponectin deficiency in their adipose tissue [67]. Adiponectin is a new adipose protein that has been studied for its therapeutic and pathological roles in human disease (diabetes type 2)[68].Especially, glucose tolerance and insulin sensitivity are directly proportional to the levels of serum adiponectin [69]. Subsequently, it could be hypothesized that adiponectin or drugs that animate adiponectin activity may perform a potential therapeutic role against ailment states associatedwith insulin resistance, type 2DM,and stoutness. Further research and tests are certainly required to justify the potential remedial uses of this therapeutic protein (adipocytokine) [70].

2.10. Islet Cell Transplantation

Islet cell transplantation is done by removing beta cells from the donor's pancreas and shifting it to a diabetic patient(recipient)[71]. Insulin is a major hormone ofβ-cells that are secreted by the pancreatic islets which regulate glucose levels in the blood. Approval fromFDA for clinical research studies on islet transplantation is essential and this procedure is performed in hospital custody only. After successful transplantation, the donor pancreatic islets start to produce β-cells that release insulin (Figure 2). It require two or more sessions of islets transplants, which are required by patients to fulfill their insulin need for proper anti-diabetic function. However, prolonged maintenance of insulin independence is hard to regulate properly. Due to this, most of the recipients require insulin again to keep their glucose at a safe level. During organ and tissue transplants, rejection of the donor cells by recipients is one of the greatest challenges (Table 1)[72].

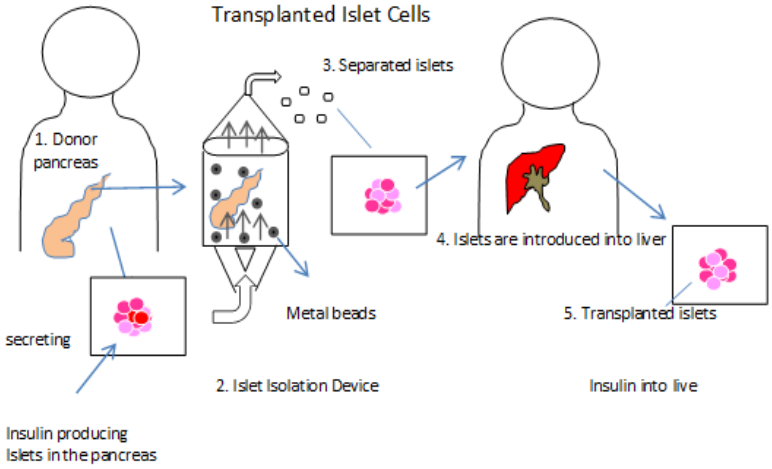


Figure 2. Transplantation Islet cell

2.11. Brown Fat Transplant

Adipose tissues are of two typesi.e., white adipose tissue and brown adipose[73]. Former tissue is sited under the skin, stores excess fat, and becomes distended resulting in increased body weight[74]. The latter one is derived from muscle cells and is thermogenic. In other words, it produces heat *via* energy consumption and is responsible for the optimal body temperature of warm-blooded animals. Body mass index and quantity of brown fat in the body are inversely proportional to each other; it means that lean people have more of this type of fat than obese persons do. On this basis, brown fat is considered "good fat". Brown fat transplanting in experimental animals has been shown to lower body weight, minimize white fat accumulation, improve insulin sensitivity, and improve glucose metabolism, according to researchers[75, 76]. A current study on human beings is going to be done to evaluate the similar outcomes of brown fat transplantation as in laboratory animals.

2.12. The Use of Vanadium Complexes in DM

The development in metal-pharmaceuticals like rheumatoid arthritis medicine which contains Gold, auranofin and anticancer medicine which contains platinum and cisplatin has been renowned across the board[77, 78]. After assessments from various perspectives including regular science and bioinorganic science, vanadyl sulfate (VOSO(4)) and its structures with few sorts of ligands have been proposed as helpful for treating DM in trial diabetic animals[79, 80]. Protein tyrosine phosphatases are known to be inhibited by vanadium oxo-anions and complexes (PTPs). PTPs are inhibited keeping the insulin receptors phosphorylated and allows glucose to enter the cell. Vanadium edifices are interchangeable between V(IV) and V(V) under physiological settings, and V(V) can restrict PTPs. Furthermore, V(IV) can cause the elevation of glucose transporters to the plasma membrane, hence upregulating glucose uptake and lowering blood glucose levels. Because diabetes is a chronic condition, tissue buildup and long-term toxicity issues should be taken into account while administering metal-based drugs [81].In view of the mechanical assessment,

progressing headway with respect to the improvement of antidiabetic vanadyl structures, focusing on that the vanadyl molecule and its structures are suitable not simply in treating or quieting the two sorts of DM, yet, moreover in thwarting the start of the ailment [82].

2.13. Gastric Stimulator

MetaCure medical device DIAMOND isan implantable gastric stimulator attached to exterior stomach muscles with electrodes[83, 84]. Formerly, it was invented to treat obesity-related problems but later, its inventors found that it is also effective for glycemic control in the hundreds of people implanted with DIAMOND worldwide. Sometimes, it works more efficiently than many other anti-diabetic medications and synthetic insulin (metacure.com). It additionally assisted with improving diabetes-related conditions, for example, cholesterol and triglycerides levels and hypertension. In a minor invasive strategy, a little pacemaker-like gadget is embedded under the abdomen skin and connected by electrodes terminals to the stomach. The gadget naturally recognizes when eating starts and imparts delicate signals in the form of pulses to the stomach exterior muscles, for example, gastric contractility modulation signals or GCM. Subsequently, the DIAMOND plays physiological synchronism between food uptake and natural body hormone secretion and lowers postprandial glucose levels. Besides, GCM signals are responsible for the earlier satiation effect regarding sustained weight loss. Hence, DIAMOND therapy is completely reversible and safe for body physiology[85, 86].

2.14. Gene Therapy

During the 1970s,chains of experiments leading to cloning and expression of insulin in the cultured cells was a remarkable revolution in the field of medicine and hence in the treatment of DM,the application of gene therapy was proposed as a possible cure[87, 88]. For reducing the complications associated with the disease, the most important aspect is regulating the sugar levels. There are two methods of gene delivery in somatic gene therapy that involves the somatic cells of the body. The first oneis called ex-vivo gene therapy in whichtissues are removed from the body.*The in-vitro* method is used for the insertion of therapeutic genes and re-implanted back into the body. *In-vivo* therapy comprisesgene therapy vectors inserted directly into the patients by intra-bronchial, intravenous, and subcutaneous routes, or by local injection [1]. The purpose of ex-vivo therapy is to create cells that exhibit beta-cell characteristics, such as the ability to produce insulin. This technique can also be used to create beta cells for transplantation. Insulin gene therapy alternates beta-cell function by creating insulin secretory non beta-cells that are immune to autoimmune reactions, presenting a promising treatment option for type 1 diabetes.As a therapeutic strategy,*in-vivo* gene therapy is the technique of choice because it is simple, and the vector of the desired gene is directly inserted into the patient, but the development of safe (not toxic to host) and effective vectors remains as a challenging job for gene therapists. Currently, strategies for in-vivo therapy include the application of blood glucose-lowering genes, an enhancer of glucose utilization by skeletal muscles or liver, genetic transfer of glucose-lowering genes, which are non-insulin in

nature and an inhibitor of glucose production by the liver. For example, in the liverglucokinase (Gck) as a transgene is found to have a glucose-lowering effect. Probably it was that gene Gck that enhances glucose utilization by the body. For the treatment of diabetes genetic transfer of Gck is used as adjuvant therapy [89].

To control the generation of glucose in the liver, researchers used a technique known as "protein targeting to glycogen" (PTG). PTG is a member of the glycogen targeting subunits of protein phosphatase-1, which are thought to regulate glycogen metabolism. Experiments in rats revealed that adenoviral-mediated PTG transfer promotes glycogen production in the liver while also lowering blood glucose levels [90], making it a possible therapeutic option for diabetes.Kojima et al reported that by delivering islets transcription factors, it is possible to induce the formation of β cells[91].Although it is currently difficult to regulate insulin production and control due to a lack of knowledge about insulin metabolism, it is becoming a viable method to promote cell neogenesis as a therapeutic tool for diabetes, since it may provide a remedy for type 1 diabetes autoimmunity.

2.15. Probiotic/Lactobacillus Pill

DM occurs when blood glucose level becomes too high because pancreatic beta cells do not produce any insulin (Type 1), or not enough insulin to help the entrance of glucose in the cells of the body, or insulin if produced does not work properly, known as insulin resistance [92]. Recent studies suggest, in both types of diabetes, manufactured probiotic pills could shift control of blood glucose levels away from the pancreas[93]. The diabetic rats were given a peptide hormone probiotic in the form of a tablet that the researchers tweaked over 90 days. The effects on blood glucose levels were then monitored, with the results compared to diabetic rats who did not get it[94]. Results were considerably exciting as the rats who received the probiotic pill had 30% lower blood glucose levels as compared to those that did not receive the pill. Further findings suggest that probiotic pills appeared to convert the rats' intestinal cells to act much like pancreatic cells [94].Another study showed thatconsumption of probiotics mightimprove glucose metabolism by a modest degree, with marked effects, either when the duration of the intervention is 8 weeks or more, or multiple species of probiotics are consumed. The effect of probiotics on glucose metabolism, especially in patients with diabetes mellitus type 2, as well as the mechanisms by which probiotics can affect glucose metabolism and health need further investigations [95].

2.16. Dead Sea

The mineral-rich dead sea has been well known asa treatment for skin, rheumatic and respiratory diseases [96, 97].The salty water of the dead sea helps to lower the glucose level in the blood and also improves the medical conditions of diabetic patients according to the research study of health sciences researchers at Ben Gurion University [98]. The study was performed with an initial group sample of 14 individuals having diabetes mellitus type 2 with the age group ranging from 18 to 65. The study was carried out in a pool filled with the water of the Dead Sea at 35°C temperature. Individuals showed a significant 13.5% drop in blood glucose levels with an average of 163 to 151 mg/dl immediately after a one-time dip of 20 minutes duration in the water of the Dead Sea. Blood glucose levels dropped to an average

of 141.4 mg/dlan hour after the dip in the Dead Seawater.Prof. ShaulSukenik from the Ben-Gurion University Research team said, "These are findings from an initial study from which it is difficult to conclude at this stage, Nevertheless, the results are promising." Hence, it's early to draw any conclusions regarding its use but further testing will determine dead sea dunk or dive could be prescribed as a way to reduce the dose of insulin needed [98].

2.17. Insulin Degludec

First-generation long-acting basal insulin analog, insulin glargine has improved insulin treatments in type 2 DM. Insulin glargine had a lower rate of nocturnal hypoglycemia episodes than neutral protamine hagedorn (NPH) insulins in diabetic patients, and both therapy groups had similar glycemic control and weight gain in previous trials. A novel ultra-long-acting insulin degludec is being tested as a basal insulin analog; its duration of action is up to 42 hours with a half-life of 25 hours[99].It has long-lasting effect due to the formation of soluble poly-hexamers at the injection site; its monomer is then progressively separated and absorbed in circulation, producingstable pharmacokinetic profiles under the steady-state condition. Insulin degludec's prolonged duration of action may allow for a reduction in the number of insulin treatments and dosage, encouraging patients to improve their insulin treatment. Second, insulin degludec's pharmacokinetic/pharmacodynamic (PK/PD) profiles are substantially less variable within patients, resulting in a lower risk of hypoglycemia. The reduced risk of severe hypoglycemia may reduce the likelihood of major side effects including mortality[100].

3. Conclusion

Clinical studieshave been conducted for the development of targeted therapies, butno therapeutic technique has beenentirely successful yet. New technologies have revolutionizedthe treatment options, and it is evident from the greater number of drugs in pipeline. In the present era, wide research studies haveled towards the discovery of multiple genes involved in cellular pathways that contribute to the disease development as well as the complete genomes sequencing has revolutionized the diabetes mellitus research. Globally increasing prevalence of diabetes is also creating a financial burden on the economy of the respective country. With the ongoing research, a right therapeutic approach for the treatment of diabetes is not unattainable.Our challenge is to keep doggedly moving the ball downfield as new insights are providing a way towards better treatment options.Undoubtedly, creative elucidations and continued partnership between regulatory agencies,industry and academia are required to further develop these new paradigms, with the joint ultimate goal of improving the health of patients with diabetes mellitus.

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Author statement

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