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REVIEW

Diabetes Research and Metabolism

Diagnosis and Therapeutic Management of Diabetes during the COVID-19 Pandemic: A Comprehensive Update

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Abstract

This review is intended to outline the risk and association of Coronavirus (SARS-CoV-2) with diabetes mellitus (DM). It summarizes the recent developments in diagnosis and therapies for diabetic patients to overcome the complications and fatality due to COVID 19 infection. DM becomes more perilous to the society in this pandemic situation due to its serious comorbidities. It is important to transpire the knowledge of new developments in the diagnosis and management of DM for overseeing and handling the infection effectively. The possibilities of withholding the complications and manage the progression like using insulin secretagogues, glucose inhibitory drugs, insulin therapeutics, regenerative medicines and devices with artificial intelligence are discussed here with highlighted information of recent developments on each category. Various genes contributing in the progression of DM were also extracted from literature and discussed. Understanding these important insights would helpful for reducing the susceptibility of COVID 19 infection in DM patients.

Keywords: *diabetes mellitus; risk-factors; complications; diagnosis; therapeutic strategies*

Introduction

Diabetes Mellitus (DM) is a progressive metabolic disorder attributed to frailty and health impairment worldwide. It causes glucose accumulation in blood plasma, rather than utilized by cells and eventually leads to hyperglycemia. The incidence of DM is steadily progressing for decades and which has been driven by numerous risk factors. It typically occurs due to the defective insulin secretion and action [1]. According to the International Diabetes Federation (IDF 2019) report, it is estimated that around 463 million adults of world populations have DM and the prevalence would possibly rise to 700 million in 2045 (https://diabetesatlas.org/data/en/world). The deaths attributable to DM in 20 to 79 years old adult population were estimated as 4.2 million in 2019. Figure 1 displays the countries with high population of DM in 2019. China, India and USA are having extremely highest incidence of DM among other countries (Figure 1). COVID-19 (SARS CoV-2) is a highly contagious, β type coronavirus belongs to the order of nidovirales. The infection was identified at the end of year 2019 from Wuhan, Hubei province of China, and their incidence was drastically increased among the world population. As of November 29, 2020, more than 61.86 million positive cases and 14.48 lakh deaths have been confirmed globally (WHO: https://www.covid19.who.int). This is considered as more serious infection than SARS (Severe Acute Respiratory Syndrome CoV) and MERS (Middle East Respiratory Syndrome) coronaviruses due to its highest reproductive number (R0: 3) and fatality rate [2]. However, this infection has moderate serial interval (5 to 6 days) in terms of transmission. Which is much greater than other viral infections like influenza A (H1N1) [3]. Recent studies identified that people with a weak immune system, chronic respiratory or cardiovascular diseases and diabetes are more susceptible to develop serious complications during the infection [4]. Since there are no exclusive therapies available for the treatment of COVID-19, DM patients have to be under intense care with regular monitoring of insulin and glucose status. Though the therapeutic ways to abolish the disease are evolving every day, we are still

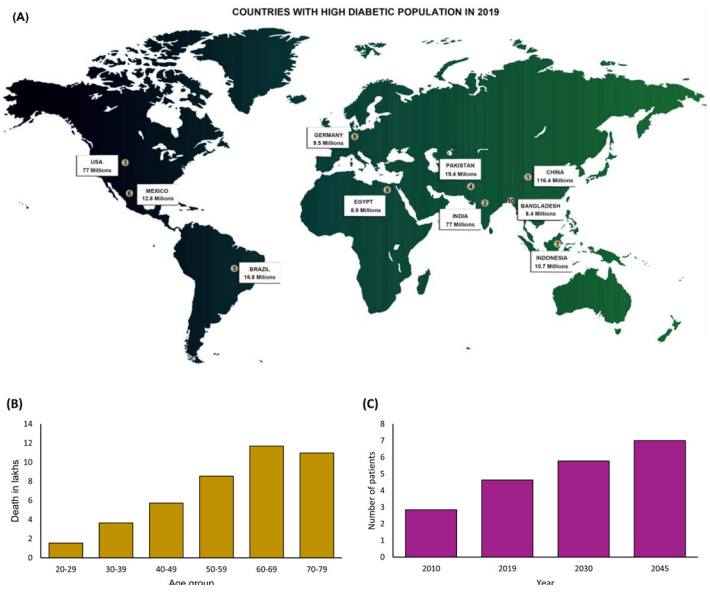

Figure 1. *(A) Countries with largest diabetic population in 2019 (European diabetes expo 2020); (B) Death attributable to DM by age groups (20-79 years) in 2019; (C) Estimation of DM incidence from 2010 to 2045 years (IDF report 2019)*

far from attaining complete recovery from DM [5]. One of the plausible reasons behind this would be a lack of acquaintance with contemporary and emerging management options for prevention and rehabilitation. In this review, we discussed a detailed critique of the prognosis of diabetes, current perception about the disease complications and their treatment strategies for the effective management of the COVID-19 infection..

Risk factors and complications

Based on the mechanism of incidence, DM mainly categorized as, type 1 (a & b), type 2, gestational and monogenic diabetes. Overall pathophysiology behind the development of type 1 and type 2 diabetes was depicted in the figure (Figure 1). Risk factors associated with type 1 diabetes are yet under investigation, though the genetic makeup, environmental factors, viral infections, pancreatic diseases would possibly trigger this condition [6]. The incidence of type 2 diabetes mostly associated with obesity, family history, unhealthy diet, sedentary lifestyle/ physical inactivity, age, high blood pressure, ethnicity, impaired glucose tolerance, abnormal levels of cholesterol/ triglycerides and certain medications like corticosteroids [7]. Those risk factors cause insulin resistance in hepatocytes, skeletal muscles, adipose tissues and other body cells. Despite that the epithelial cells do not require insulin to uptake glucose, it accumulates glucose inside the cytoplasm, and promote free radical generation, glycation of inner membrane proteins and lipids (advanced glycation end products). There are some secondary risk factors such as sustained systemic inflammation, which contribute in the elevation of plasma glucose levels by suppressing CYP7A1 and activating Rho-associated protein kinase in hepatocytes [8].

A variety of protracted micro and macrovascular health complications like vision problem, kidney disease, nerve damage, stroke, coronary heart disease, peripheral vascular diseases (atherosclerosis) and some transient health problems are the communal complications of DM [9]. Over the period of disease progression kidney lose its stability to function and raise the risk of diabetic nephropathy. The common reasons for diabetic nephropathy include genetic predisposition, poor glycemic control, inflammatory mediators, hypertension, etc. In certain cases, it could lead to severe complications like end stage renal failure (ESRF) and glomerular sclerosis [10,11]. Nerves are also being one of the major susceptible sites for DM patients. The nerve damages lead to peripheral nerve dysfunction, which affects various nerve cell types like sensory, motor and autonomic cells [12]. Based on the site, and type of the cell which were affected, it is categorized as diabetic peripheral neuropathy (DPN), sensorimotor polyneuropathy and cardiovascular autonomic neuropathy (CAN) [13]. Chronic diabetic patients may experience diabetic retinopathy, it affects eyes by damaging blood vessels in the retina, which might predispose severe impairment and vision loss. In progressive state, it causes serious consequences like abnormal tissue growth and block of blood vessels in the eyes (neovascularization). Fluorescein angiography and optical coherence tomography are available radiological diagnostic methods for diabetic retinopathy. It could be managed using regular anti-VEGF drugs and minor surgeries [14,15].

SARS-CoV-2

HPoorly controlled blood glucose increases the risk of most of the viral infections [16,17]. Though there are no pathological correlation of COVID-19 infection in DM patients confirmed, the mortality and severity of the complications are found to be higher in diabetic patients [18]. Once the patients get infected by the virus, it attacks type 2 pneumocytes in the respiratory system and causes alveolar edema, inflammation, restricted gas exchange (hypoxemia). When the inflammation becomes systemic, it damages the vital organs like heart, liver and kidneys. DM patients with poor glycemic management are more vulnerable to these comorbidities. It would also develop DKA and other higher complications [19]. .

Diagnosis

Diabetes Meletus is usually unapparent during early stages and may stay longer in our body without manifesting any visible signs. But it is tough to manage after the disease aggravates and cause organ damages. Blood glucose estimation is a principal method used to diagnose diabetes. Considering the elevation of glucose levels in blood, it betides either due to the insufficient insulin secretion or failure of insulin reactivity [20]. Hence, investigating the blood glucose concentration by performing random plasma glucose test, fasting plasma glucose test (FPG), oral glucose tolerance test (OGT) and hemoglobin A1C (HBA1C) test. The values of those parameters for diagnosing the status of the condition are presented in the table (Table 1) [21]. Diabetes Ketoacidosis (DKA) is a severe condition of T1DM which begin with a breakdown of fats and proteins in our body for the energy, leads to the production and release of ketones into the bloodstream. Metabolic acidosis could be diagnosed by measuring ketone level, blood electrolyte and blood acidity test. It will only show normal hyperglycemic signs includes polyuria, polydipsia and intemperate dehydration. If this condition is left undiagnosed and untreated for a long period, could lead to sudden unconsciousness and eventually death [22]. C peptide chain cleaved out from pro-insulin while maturation and it reflects the level of matured insulin in the system (Figure 2). Insulin C chains are the simple and efficient diagnostic marker to measure the pancreatic insulin and it could also be used to differentiate the type 1 from type 2 diabetes. [23]. There are some other disease specific markers like Zinc transporter 8 (ZnT8) autoantibodies, insulinoma associated antigen 2 (IA-2), glutamic acid decarboxylase 65 (GAD65) and genetic testing were available to identify and categorize the condition. Some immunodiagnostic procedures like HLA typing were also followed to detect the incidence of DM at early stage. Human leukocyte antigen (HLA) are surface proteins present in immune cells, which distinguish the antigen from own body's cells, and tissue components. The HLA haplotypes associated with type 1 diabetes are HLA-DQA1, HLA-DQB1, and HLA-DRB1 [24]. These combinations encourage the destruction of beta cells by the self-immune system. Systemic detection of autoantibodies

Table 1: *Clinical criteria for the diagnosis of Diabetes Mellitus*

Markers	Normal range	Diabetes
FPG	<100mg/dl	>126mg/dl
OGT	<140mg/dL	>200mg/dL
HBA1C	<6%	>6%
RPG	-	>200mg/dL
C peptide	0.5-2.7ng/mL	<0.5ng/mL
Ketone	<0.6mmol/L	>1.6mmol/L

FPG: Fasting plasma glucose; OGT: Oral glucose tolerance; HBA1C: Hemoglobin A1C; RPG: Random plasma glucose test.

Table 2: *Summary of complementary and alternative therapies for Diabetes Mellitus*

Therapies	Description	Effects	Limitation
Phytotherapy	Using medicinal plants and their active constituents to treat various health complications	Polyphenols from medicinal herbs like Aloe vera, neem oil, gymnema, ginseng, Indian mallow, matura tea tree, etc., has been reported for their therapeutic benefits like insulin mimetic and hypoglycemic properties	Overuse of certain herbal medicine could damage kidney tissues and nephron function
Supplements	Consumption of micronutrients like, minerals, vitamins and essential biomolecules to stabilize the dysfunctional metabolism	Vitamin-C, D, E, magnesium, chromium, α-lipoic acid, coenzyme Q10 are some customary biological supplements, which has positive role in the management of DM	Could only be a supportive option in DM management
Dietary therapy	Modifying irregular and scanty diet with fibers and natural nutrient rich foods to prevent or remediate the health complications	Common fruits and vegetables like bitter gourd, ginger, broccoli, guava, Indian gooseberry, etc., improve the stability of vital organs in DM	Proper diet can reduce the complications of DM. Could only be a supportive option for other remedies.
Homeopathy	Made from minerals, chemicals, plants and animal sources. One of the most renowned complementary therapies in Malaysia and Germany	Patients who are practicing homeopathy for DM were studied and reported that they have controlled HbA1c levels and effective reduction of FPG	Currently, there are no scientific research evidence that homeopathy could cure DM
Reflexology	Reflexology involving applying little pressure to particular points in hands and feet	Reflexology or zonal treatment stabilizes the regular metabolism by improving circulation of blood, oxygen throughout the systems. It possibly rejuvenates pancreas and liver to restore its function	No validated reports are available about its effect in DM patients
Mind and body practices	Yoga, meditation, tai chi, qigong, swimming are physical practices involving a series of effective movements and breathing	Reduces physiological and emotional stress in DM patients	Promote general health, hence could be used only to manage the DM associated complications. No other benefits were scientifically validated or reported
Massage therapy	Manipulation of body tissues by applying little pressure with hands or devices	Massage therapy can improve the circulation of oxygen, lymph in our system and improve mobility	No evidential reports were available about their effectiveness in disease mechanism of progression
Aromatherapy	Using essential aroma oil (mostly derived from plants) to improve the health	It can reduce the stress and complications associated with diabetes	Aromatherapy is a supportive option could be used along with other management practices. It would not cure diabetes

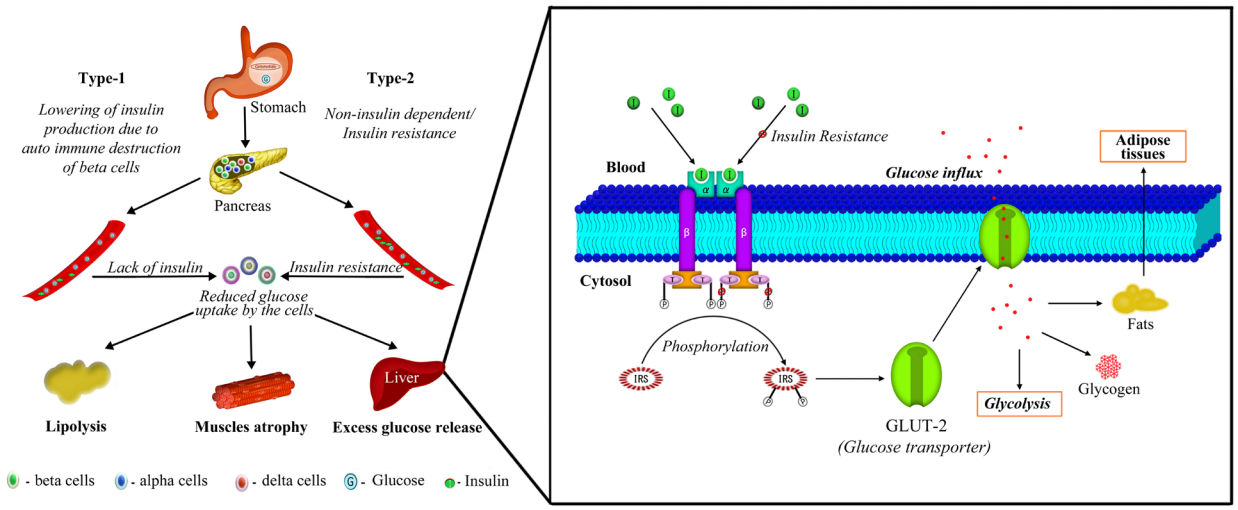

Figure 2: *Depiction of key differences between type 1 and 2 diabetes and Insulin mediated glucose uptake in liver cells: Insulin bind to the insulin receptor on the surface of hepatocyte plasma membrane and activates the insulin tyrosin kinase receptor for autophosphorylation and phosphorylation of the inner membrane protein insulin receptor substrate (IRS). It promotes the expression of glucose transporter (GLUT-2) for cellular uptake of glucose, glycogen synthesis and protein synthesis y activating PI3K-AKT and MAP kinase pathways.*

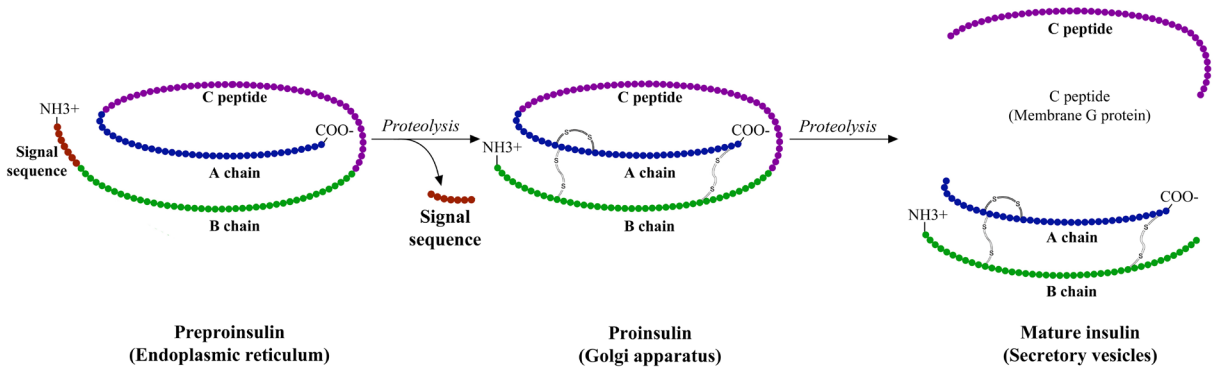

Figure 3. *Insulin hormone biosynthesis in beta cells*

from patient serum is a more sensitive method to diagnose Type 1 diabetes. Most of the established diagnostic markers for DM are blood components. Even though the non-invasive glucose estimation like from urine samples could be useful for monitoring the status, it would not be reliable marker since the renal threshold value varies for every individual. Viswanath et al., discussed the cogency of using salivary fluid for glucose estimation [25]. They have experimentally confirmed that the saliva reflects glucose level in the system. Still, it would also not helpful for categorizing the state of condition. Likewise, the positive correlation of gut microbiome rhythmicity and the chances of getting type 2 diabetes was also confirmed by Reitmeier et al. [26]..

Disease Management

Regimens of drugs for the treatment of diabetes decline the glucose level in blood by increasing insulin secretion/action promote beta cells health and function. A lot of dynamic drugs have been promoted frequently with unique revised properties like improved durability, dispersal, specificity, etc., A drug or drug combinations for individual patient is selected based on the health status, age, and other contraindication. There are huge possible ways to manage diabetes before it culminates and becoming severe, notably by following proper medication, healthy diet practices and physical activities. Besides, conspicuous technologies of modern medicine, some non-pharmacological complementary therapies subsisted to support the effectiveness of DM therapies, which includes biological therapies, homeopathy, reflexology, massage, aromatherapy, etc. (Table 2).

Oral medications

Sulfonylureas (chlorpropamide, glimepiride, glipizide, glyburide), are a class of secretagogues drug which increases the insulin secretion from beta cells. But it only acts by stimulating the inoperative beta cells to release insulin, hence it won't be effective for type 1 diabetic patients. While metformin is an initial drug choice for most of the hyperglycemic patients to reduce blood glucose level by reducing the process of hepatic gluconeogenesis and upregulation of 5' –monophosphate activated protein kinase (AMPK), a regulatory protein which stimulates glucose uptake in muscles by mediating contraction-stimulated GLUT-4 translocation. [27,28] Metformin also has some confines like, it is not suitable for patients with renal insufficiency or chronic pulmonary disease [29]. Acarbose, Linagliptin, Saxagliptin, Sitagliptin, Exenatide (Incretin), Liraglutide, Gliclezide/ Glimepiride, Glyburide, Repaglinide, Thiazolidinediones and α-glucosidase, DPP4, SGLT inhibitors are some other commonly prescribed drugs to control DM. [30,31] (Table 2) The association, specificity and responsiveness of these drugs could be improved by performing genetic alterations like altering of single nucleotide (SNPs) on the non-coding regulatory binding motifs of adipose tissues PPAR γ [32]. Immunosuppressive agents and certain medications like angiotensin-converting enzyme (ACE) inhibitor drugs (Captopril) should be avoided for the patients who are having COVID-19 infection. Indeed, ACE 2 is a target receptor for the coronavirus infection in the pneumocytes. Consuming the inhibitors of ACE 2 would affect and worsen the disease [33].

Regenerative Therapies

Tissue engineering

Tissue engineering is a regenerative therapy, used to repair or replace the affected tissues with ex vivo cultivated tissue scaffolds (Figure 3). In severe conditions of DM, pancreatic islets transplantation is an effective approach. The pancreatic islets are isolated from patients, proliferated using growth stimulators and implanted back into the host to restore the function of beta cells [34]. But the success of enduring outcomes of this method is limited because if the transplanted islets directly exposed into the blood or the toxins filtered from liver would stimulate instant inflammatory reactions and allograft rejection. It consequently leads to early destruction of the islets at the engraftment site [35]. Conversely, cell replacement therapy to produce functional insulin secreting non-beta cells, like reprogrammed hepatocytes; exocrine acinar cells are available to manage glucose levels. Reprograming the intestinal cells as insulin secreting cells could be achieved in different ways like modulation Forkhead box (FoxO1) gene and overexpression of nucleophosmin (NPN) proteins (Neurog3, Pdx1, MafA, Cdx2). Bioengineering of stomach tissues to produce renewable insulin cells from antral endocrine cells of gastrointestinal epithelium were proved in in-vivo mice model [36,37]. Ultrathin layer by layer encapsulation of cell surface would be a propitious approach to dampen immune reactivity as well as to provide a free environment for cellular activities and responsiveness in tissue engineering. However, encapsulation of viable cells holds number of complications to be considered, includes cytotoxicity of the polymer used for coating, stability of the polymer to stay longer, etc. Those obstacles could be resolved by maintaining the stability of the polymer coating by introducing inter-polymer covalent bonding, which allows the polymers to get moderately or neutrally charged [38].

Stem cell therapy

Stem cells are used to reconstruct the insulin producing islet beta

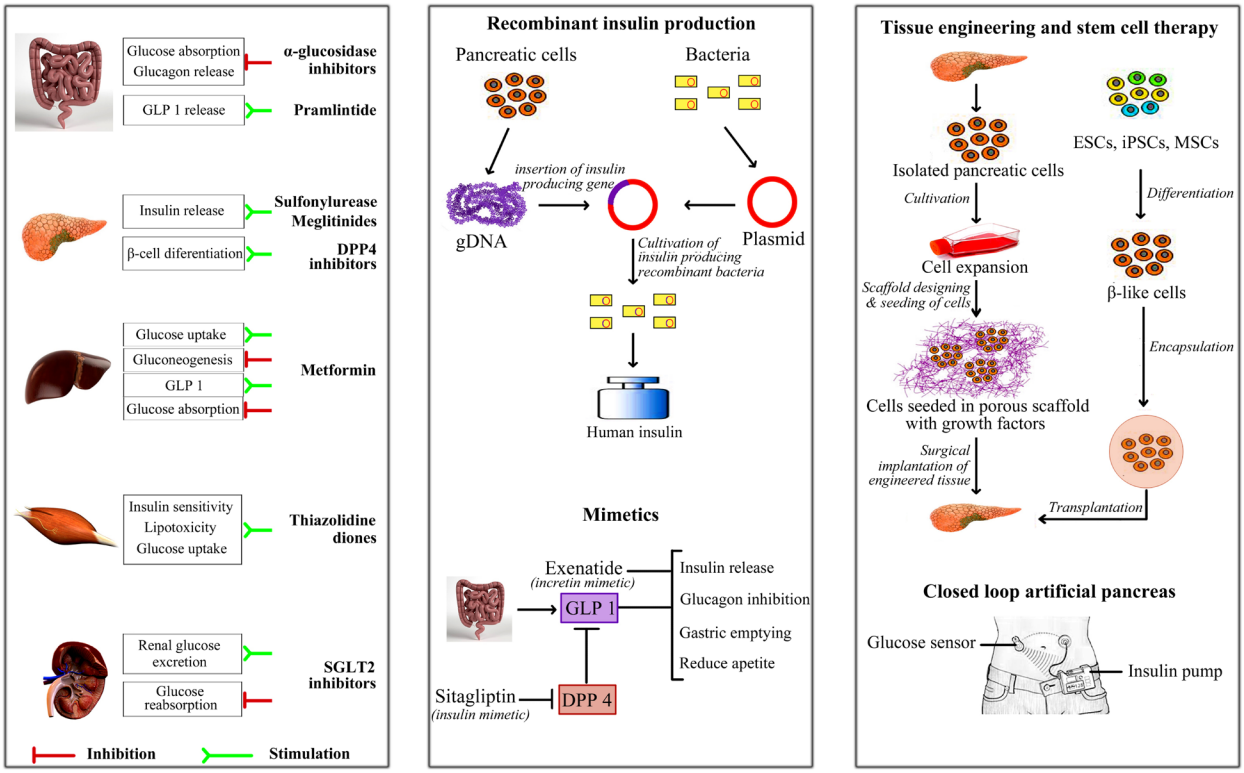

Figure 4: *Mechanisms of different diabetic medicine, tissue engineering and stem cell therapy*

cells. Islet cells are specialized cell types which executing basal insulin production which respond rapidly to the blood glucose concentration. Embryonic stem cell therapy is a flawless way to restore glucose absorption by the cells. Human Embryonic stem cells (HESC) would be differentiated into insulin producing pancreatic endoderm and it has been successfully investigated in diabetes animal models [39,40]. They could proliferate for a long term and provide protective effects on kidney neurons and circulatory endothelial cells. But HESC therapies are limited due to ethical concerns, expensiveness and experimental complication like teratoma formation due to differentiation error. Rather alternative stem cell therapies like induced pluripotent stem cells-iPSCs [41], bone marrow derived mesenchymal stem cells and umbilical cord stem cells have been successfully tested in patients. But still, immunosuppressive drugs are needed after the treatment to avoid autoimmune destruction of the newly transplanted beta cell.

Insulin based therapeutics

Matured insulin from secretory vesicles maintains circulatory glucose levels in the bloodstream. The first insulin injections used was obtained from animal sources such as pigs and cattle. To overcome the allergic effects of administering animal insulin, new recombinant human insulins, Humulin, Novolin (*E. coli*) and insuman (*S. cerevisiae*) were then developed [42] (Figure 3). To improve the pharmacokinetic properties like fast absorption and different rapid acting insulins has been developed. Recently, joseph et al., studied an ultrafast monomeric insulin, which could act four folds higher speed than the existing rapid insulin shots [43].

Oral insulin

To abstain from the risk of frequent subcutaneous insulin shots, investigators sought to develop oral insulin pills. Oral delivery of a protein/peptide drug is a challenging approach in pharmaceutics. The major snag of oral insulin administration is the digestive system, where insulin could easily get broken down before start functioning. To avoid the digestive enzyme's interaction, the insulin packed with the liposome like carriers are developed. Biotinylated/ Biotin modified liposomes (BLPs) mediated oral insulin delivery concept was successfully proved by Xingwang. Here the BLPs prepared by reverse evaporation method and the bioavailability of the BLPs packed insulin were tested in laboratory rats. The study resulted, BLPs could be a perfect carrier for the delivery of insulin through oral route and in addition, it also promotes the blood absorption of insulin [44].

Insulin mimetic peptide

Costus igneus, is a prominent anti-diabetic plant and popularly known as 'insulin plant'. The oral consumption of a raw leaf of *Costus igneus* on a daily basis stabilizes the blood glucose level. Insulin like peptide (ILP) purified from *C. igneus* exhibited functional similarities with human insulin on RIN 5f cell line, oral glucose tolerance test and in streptozotocin induced diabetic mice [45]. The hypoglycemic mechanism of the ILP has validated by monitoring the glucose uptake of skeletal muscles [46]. *Urtica dioica* was tested on L6-GLUT4 myc-myoblast to study their blood glucose lowering effect. The subfractions of the *U. dioica* active extract show the presence of Insulin mimetic cyclic peptide. The mimetic cyclic peptide itself exhibited the functionality of insulin by regulating glucose uptake by the cells [47]. Visfatin is an adipocytokine hormone produced from visceral fat, it mimics insulin functions by activating the insulin receptors to diminish glucose release from liver cells and accelerate glucose consumption in adipocytes and myocytes [48,49]. Zinc (ZnII) mineral also exerts insulin mimetic effect on diabetes by counteracting on various stage of signaling pathways of insulin. Besides, there are some non-islet cells were also secreting some hormones for

regulating glucose homeostasis like asprosin. Asprosin is a fasting induced glucogenic peptide hormone secreted from white adipose tissues, which regulates glucose homeostasis by activating glucose release from hepatocytes. By modifying the levels of asprosin, the elevated glucose levels in bloodstream could be reduced [50].

Intracellular signal modification

Indeed, the insulin resistance and unresponsiveness of the skeletal muscles, hepatic, renal and adipose tissues on type 2 diabetes are known to be a molecular defect on insulin signaling cascade. Thus, monitoring and identifying the events on biochemical pathways of insulin signaling is an informative and exclusive way to develop new therapies. The glucose uptakes by cerebral cells are also found to be an insulin dependent process, the brain non-neuronal glial cells known as astrocytes have key regulation on insulin signaling and glucose sensing on cerebrum. The insulin signaling for hypothalamic glucose metabolism has experimented on astrocyte Insulin receptor knockout mice (postnatal ablation). The study revealed the role of astrocytic insulin receptors on glucose transport across the blood brain barrier [51]. Since alteration in intracellular signaling might reverse the type 2 diabetes. Defects on the IRS-1 phosphorylation would also affect insulin signaling on T2DM, to resolve such defects by modification of Ser/thr phosphorylation sites on IRS-1 have recently been reported. Similarly, dysfunctions of PI3k, Akt/PKB, PKCs and MAPK leads to insulin resistance and it could be treated by modifying the defects [52]. The potential gene targets involving in the pathophysiology of DM were collected from literature and presented in the table (Table 3). The identified 69 DM associate primary targets have various regulatory and modulatory functions against the signaling molecules and other DM associated markers.

Portable devices and analogues

Closed-loop artificial pancreas is a mechanical automated device which continuously monitors blood glucose levels in the system. Glucose sensor probe attached to the body sends alert signals to the pump for the intravenous release of insulin directly to the bloodstream (Figure 4). Several clinical trial investigations on this system have been successfully carried out with different inpatients and outpatients for the safety and effectiveness in type 1 diabetes and it is expected to reach the market within two years. There are some examinations were going on it to explore smart pumps, glucagon infusion, refinement in algorithm features, portability, etc. [53,54]. Rapid acting insulin (RAI) analogues provide the continuous steady infusion of insulin into the system. This is a portable wearing analogue, which has been tested in patients from Texas and their efficiency were recently reported by Dr. Mora in The Endocrine Society, 2020. Some artificial intelligence also has been recently developed to predict the people who are prone to get diabetes, at an earlier stage.

Table 3: *Summary of the contemporary medications used for managing Diabetes Mellitus*

Drug Category	Route of administration	Mechanism of action	Effect in plasma insulin concentration	Adverse effects
Sulfonylurease *(Chlorpropamide, glyburide, glipizide, glimepiride, etc.,)*	Oral	Stimulate insulin secretion from pancreatic beta cells	Yes	Hypoglycemia, Overweight gain
Biguanides *(Metformin IR & SR)*	Oral	Prevent hepatic conversion of fats and amino acids into glucose	No	Hypoglycemia, Gastro-intestinal complications, Overweight gain, Lactic acidosis
Thiazolidinediones *(Rosiglitazone, pioglitazone)*	Oral	Selective agonist of PPARγ, increase fatty acid storage in adipocytes	No	Overweight gain, chest pain, macular edema
Glinides *(Nateglinide, repaglinide)*	Oral	Stimulate insulin secretion from pancreatic beta cells	Yes	Skin allergy, liver problem, mild hypoglycemia
α-glucosidase inhibitor *(Acarbose, miglitol, voglibose)*	Oral	Decrease carbohydrate digestion and glucose absorption	No	Nausea, diarrhea, flatulence
DPP4 inhibitor *(Sitagliptin, Vildagliptin, Linagliptin, Saxagliptin)*	Oral	Inhibit glucagon release by increasing the levels of incretin	No	Gastrointestinal complications, diarrhea, skin problems
SGLT inhibitor *(Dapagliflozin, canagliflozin, ertugliflozin, empagliflozin)*	Oral	Prevent reabsorption of glucose	No	Diabetic ketoacidosis, urinary tract infection, kidney problem, hypoglycemia
Incretin mimetic *(Exenatide, liraglutide, semaglutide, dulaglutide)*	Parenteral	Acts like incretin hormone which stimulates glucose dependent insulin release	Yes	Indigestion, diarrhea, loss of appetite
Amylin analogs *(Symlin)*	Parenteral	Assist insulin during post-meal period and reduce glucagon release	Yes	Hypoglycemia, nausea

Table 4: *List of genes associated with the progression of Diabetes Mellitus*

S. No.	Gene	Description
1	ABCC8	Control insulin secretion through instruct the sulfonylurea receptor 1(SUR1) of the ATP sensitive potassium (K(ATP)) channel in pancreatic beta cells. Mutations on this gene lead to DM
2	ACE	Angiotensin converting enzyme controls blood pressure in our body. Some studies revealed the ACE gene polymorphism is relative to diabetic nephropathy and retinopathy
3	ACLY	ATP citrate lyase is a cytosolic enzyme which is decreased on type 2 diabetes
4	ADRA 1A	Adrenoceptor alpha 1A, which functions in Phospholipase C mediated signal transduction activation
5	ADRB3	Adrenoceptor beta 3, a receptor located in adipose tissues and regulates lipolysis. Missense mutation in this gene influences the development of type 2 diabetes
6	AGT	Angiotensinogen is related to ACE gene controls blood pressure. Which is expressed in liver and it is associated with diabetic nephropathy and retinopathy
7	AKT2	A key mediator in insulin signaling pathway. Hence the variation on the gene may affect glucose metabolism.
8	AQP2	Aquaporin 2 is a water channel protein coded gene expressed in kidney. Polymorphism in this gene linked with nephrogenic diabetes
9	CAPN10	Cysteine protease calpain 10 is one of the initial susceptible genes on type 2 diabetes. Single nucleotide polymorphism of three intronic CAPN10 associated with type 2 diabetes
10	Ccl5 (RANTES)	A chemokine group has multiple roles in human. Notably, it regulates hypothalamic insulin signaling. The variation in this gene may affect the pathway and may lead to type 2 diabetes
11	CCR2	A chemokine receptor gene has a role in the development of insulin dependent diabetes in children
12	CD28	Gene coded for a protein has an important role in T cell proliferation and cytokine synthesis. The polymorphism of this gene might be associated with type 2 diabetes
13	CEACAM1	Carcinoembryonic antigen related cell adhesion molecule 1 from hepatic cells is one of the contributing factors in insulin resistance on type 2 diabetes
14	CTLA4	Cytotoxic T lymphocyte associated antigen 4, gene polymorphism of which is associated with type 1 diabetes mellitus
15	DPP4	Dipeptidyl peptidase 4 gene polymorphism is associated with the etiology of type 2 diabetes
16	ENPP1	Ectonucleotide pyrophosphatase phosphodiesterase 1, has found to be one of the reasons for insulin resistance
17	FBP1	Fructose-bis phosphatase 1 enzyme regulates gluconeogenesis. Genetic variation on this gene may lead to hyperglycemia
18	FOXC2	Forkhead box C2 has a role in mesenchymal tissue generation and it is highly correlated to the development of type 2 diabetes
19	FOXP3	Forkhead box P3 is a transcription regulator gene. Genetic variation on this gene may be the triggering factor for type 1 diabetes. Since the Imbalance in T helper and regulatory T cells are majorly contributing in autoimmune disorders
20	FTO	Fat mass and Obesity-associated gene are strongly associated with Type 2 diabetes
21	GCG	Glucagon is a pancreatic hormone perform glucose-lowering action by glycogenolysis and gluconeogenesis. Genetic variation on this gene leads to the onset of diabetes
22	GCGR	Coded for Glucagon receptor, which controls glucose level in blood and regulating hepatic glucose production
23	GCK	Glucokinase is a class of hexokinase enzyme, catalyze glucose uptake in hepatic and beta cells. Mutation on this gene lead to Maturity onset diabetes of the young, permanent neonatal diabetes and hyperinsulinemia
24	GLP1R	Glucagon like peptide receptor stimulates insulin secretion. Genetic variation on this locus cause diabetes
25	GLUT2 (SLC2A2)	Codes for glucose transporter isoform present in pancreatic beta cells have significant role in insulin secretion
26	GLUT4 (SLC2A4)	Codes for glucose transporter isoform present in hepatic cells has role in insulin secretion
27	GPD1	Glycereol-3-phosphate dehydrogenase 1 functions on carbohydrate and lipid metabolism. Genetic mutation in this gene may cause hypertriglyceridemia
28	GSK3B	Glycogen synthase kinase is an enzyme regulate glycogen metabolism. It is one of the key factors related to diabetes
29	HHEX	Haematopoietically expressed homeobox gene involved in hematopoietic differentiation and polymorphism on this locus cause type 2 diabetes

30	HLA-DQA1, HLA-DQB1, HLA-DRB1	Polymorphism on these three HLA loci associated with the type 1 diabetes occurrence
31	HNF1A	Hepatic Nuclear factor 1 alpha and beta are a transcription factor regulates various hepatic genes. Mutation in these gene causes maturity onset diabetes of the young (MODY)
32	HNF1B	
33	HNF4A	Hepatic Nuclear factor 4 alpha control insulin secretion. The gene variation on the locus may cause type 2 diabetes
34	ICAM 1	Intra cellular adhesion molecule 1, the genetic polymorphism of this gene linked with diabetes and diabetic nephropathy
35	IFNG	Gene coded for cytokine, polymorphism on this Interferon gamma gene is associated with Latent autoimmune diabetes of adults (LADA) and type 2 diabetes
36	IGFBP5	Sequence variation on Insulin like growth factor binding protein 5 associate with adiponectin modulate the process and causes metabolic syndrome like diabetes
37	IL10	Locus variation of Interleukin 10 genes are highly associated with diabetic retinopathy
38	IL12B	Locus variation of Interleukin 12B has the risk of developing type 1 and rarely type 2 diabetes
39	IL2RA, IL4RA, IL6	Common polymorphism of the locus of Interleukin 2RA, 4RA and 6 has the risk of developing type 1 diabetes
40	IRS1	Variable Insulin receptor substrate 1 locus has high frequency of occurrence in type 2 diabetic patients. But they are not associated with insulin resistance
41	IRS2	Variable Insulin receptor substrate 2 genes are associated with both type 2 and gestational diabetes mellitus
42	ITPR3	Inositol 1-,4-,5-triphosphate receptor type 3 gene mutation is relative to the development of type 1 diabetes
43	KCNJ11(KIR6.2)	This gene is found in pancreatic beta and alpha cells. It is one of the key factors in insulin secretion. Polymorphism on this gene causes type 2 diabetes
44	MAPK14	Mitogen activated protein kinase 14 genes has multiple roles like cell proliferation, transcription regulation, etc., and the variation on the gene is related to the development of diabetic foot ulcer
45	NEUROD1	Neuronal differentiation 1 is a helix loop helix transcription factor. It is one among the factors regulating insulin expression gene. The genetic variation causes type 2 diabetes
46	NFKB1	Nuclear factor kappa B 1 is a type of transcriptional regulator. Polymorphism of the gene is associated with diabetic nephropathy
47	NOS3 (ENOS)	Nitric oxide synthase 3 enzyme responsible for synthesis of nitric oxide radical which act as a biological mediator for various processes. Endothelial nitric oxide synthase gene polymorphism lead to diabetic nephropathy
48	OAS1	2'-5'-oligoadenylate synthetase 1, gene is encoded for the protein 2'-5'-oligoadenylate. Polymorphism in this gene associated with type 1 diabetes
49	PARP1 (ADPRT1)	Poly (ADP-ribose) polymerase 1 has functional role in cell proliferation and tumor transformation etc., Mutation on this gene may develop type 1 diabetes
50	PDX1 (IPF1)	Pancreatic and duodenal homeobox 1 gene coded for transcriptional activator of different genes involved in glucose metabolism, includes insulin, somatostatin, glucose transporter 2, etc., Mutation of this gene lead to Maturity onset diabetes of the young 4 (MODY4)
51	PPARA	Peroxisome proliferator-activated receptor alpha is steroid hormone receptors. It disturbs specific genes involved in cell differentiation and proliferation, etc., the gene polymorphism on PPARA has important role in the development of type 2 diabetes
52	PPARG	Peroxisome proliferator-activated receptor gamma stimulates the genes responsible for adipocyte differentiation. Mutation of the gene is associated with insulin resistance
53	PPARG-C1A (PPARGC1)	Peroxisome proliferator-activated receptor gamma coactivator 1 alpha gene encoded a protein PGC-1 alpha which participate in energy metabolism and mitochondrial function. The variation in gene lead to type 2 diabetes
54	PTPN1 (PTP)	Protein tyrosin phosphatase 1 negatively regulates insulin signaling. Variations on the gene appear to be the contributing factor for metabolic syndromes like diabetes
55	PTPN2	Protein tyrosin phosphatase 2 regulates cytokine induced cell apoptosis. Hence it may one of the contributing factors in beta cell destruction and type 1 diabetes
56	SERPINE1 (PAI-1)	Gene involved in fibrinolysis and polymorphism in this gene may cause diabetic nephropathy, retinopathy and type 2 diabetes
57	SNAP23	Synaptosome associated protein 23 do vesicular transport on the cells. It is involved in the insulin resistance due to increased lipid level in cardiomyocytes. Hence this gene is directly linked to the type 2 diabetes condition

58	SOD2	Encoded protein is a member of iron/manganese superoxide dismutase family. Mutation in the gene has been associated with insulin dependent diabetes
59	SREBF1	Sterol regulatory element binding transcription factor 1 encoded protein flanks low density lipoprotein receptor and sterol biosynthesis genes. It promotes glycolysis, lipogenesis and adipogenesis. Genetic variation may cause obesity linked type 2 diabetes
60	SUMO4	Small ubiquitin like modifier 4 gene encoded with ubiquitin related modifiers. Specific genetic polymorphism (SUMO4 M55V) leads to type 1 diabetes
61	TCF7L2	Key component on Wnt signaling pathway and it has been reported for their association with type 2 diabetes
62	TGFB1	Transforming growth factor beta 1 encoded gene regulate gene expression. Polymorphism of single nucleotide in this gene lead to diabetic nephropathy
63	TNF ALPHA	Tumor necrosis factor alpha codes for multifunctional proinflammatory cytokine. Polymorphism of the particular gene may cause, Type 1, Type 2 diabetes and diabetic nephropathy
64	TNFRSF1A(TNFR1)	TNF receptor superfamily member 1A gene coded gene plays important role in apoptosis, inflammation, etc., The genetic variation may associate with type 2 diabetes
65	TNFRSF1B	TNF receptor superfamily member 1B gene coded to mediate antiapoptotic signals for protecting neurons. Polymorphism of this gene is related to type 2 diabetes and neuropathy
66	TRIB3 (SKIP3)	Tribbles homolog 3 coded for a key mediator in insulin signaling. It is associated with the cause of diabetes by affecting glucose homeostasis
67	UCP2	Uncoupling protein 2 coded for the transporter of anion and proton through mitochondrial membrane. This gene is linked to the development of type 2 diabetes
68	VAMP2, VAMP3	Vesicle associated membrane protein 2 & 3 coded protein are needed for insulin and GLUT 4 translocation in the body. Hence the variation on these locus affects insulin uptake and causes diabetes
69	VEGFA	Vascular endothelial growth factor A, encoded for the protein to perform proliferation of vascular endothelial cells and angiogenesis. Wo polymorphism on this gene (rs699947, rs2100963) is associated with diabetic retinopathy

Conclusion

DM patients are more likely to develop severe complication and death from COVID19 infection. Proper management of blood glucose and insulin levels would be helpful to avoid such difficulties in patients. It is apparent that there are distinct therapies available to the people living with DM for effective management. The emergence of recombinant therapeutic products, stem cell and gene therapy reinvigorate the strategies on diabetes treatment. With these headways, we could engineer the defected or mutated genes or reintroduce the cultured stem cells and proliferate them inside the target to achieve sustainable or complete recovery from the disease. But it isn't possible to perform on every individual with DM due to certain risks like immune rejection, possibility of normal cell damage, infection and expensiveness. Progression of modern therapies promotes the rate of survival of the patients against various life-threatening diseases like coronary heart disease, stroke, respiratory disorders and diabetes etc. Since most of the modern chronic disorders like diabetes mellitus could be controlled through proper medication and healthy diet practices. But DM remains deadliest for decades because of the increasing number of cases every year and its serious comorbidities. There are multiple risk factors influencing the fatality rate of DM and each patient has unique levels of responsive mechanism against COVID-19 infection based on their health status. Thus, education about available therapeutic interventions is one of the effective ways to reduce mortality in DM.

Conflict of Interest

All authors declare that there are no conflicts of interest.

References

1. Association AD. Diagnosis and classification of diabetes mellitus. *Diabetes care*. 2009; S62-S67.
2. Jeong IK, Yoon KH, Lee MK. Diabetes and COVID-19: Global and regional perspectives. *Diabetes Research and Clinical Practice*. 2020; 166: 108303.
3. Vink MA, Bootsma MC, Wallinga J. Serial intervals of respiratory infectious diseases: a systematic review and analysis. *Am J Epidemiol*. 2014; 180: 865-875.
4. Huang C, Wang Y, Li X, Ren L, Zhao J, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *The Lancet*. 2020; 395: 497-506.
5. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*. 2019; 157: 107843.
6. Yoon JW, Kim CJ, Pak CY, McArthur RG. Effects of environmental factors on the development of insulin-dependent diabetes mellitus. *Clin Invest Med.* 1987; 10: 457-469.
7. Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. *Int J Med Sci.* 2014; 11: 1185-1200.
8. Okin D, Medzhitov R. The Effect of Sustained Inflammation on Hepatic Mevalonate Pathway Results in Hyperglycemia. *Cell*. 2016; 165: 343-356.
9. Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. *Phys Ther.* 2008; 88: 1322-1335.
10. Kolseth IB, Reine TM, Parker K, Sudworth A, Witczak BJ, et al. Increased levels of inflammatory mediators and proinflammatory monocytes in patients with type I diabetes mellitus and nephropathy. *J Diabetes Complications.* 2017; 31: 245-252.
11. Elmonem MA, Amin HS, El-Essawy RA, Mehaney DA, Nabil M, et al. Association of chitotriosidase enzyme activity and genotype with

the risk of nephropathy in type 2 diabetes. *Clin Biochem.* 2016; 49: 444-448.

12. Otto-Buczkowska E, Dryżałowski M. Review/Praca poglądowa. *Pediatria Polska*. 2016; 91: 142-148.
13. Politi C, Ciccacci C, D'Amato C, Novelli G, Borgiani P, et al. Recent advances in exploring the genetic susceptibility to diabetic neuropathy. *Diabetes Res Clin Pract.* 2016; 120: 198-208.
14. Cavan D, Makaroff L, da Rocha Fernandes J, Sylvanowicz M, Ackland P, et al. The Diabetic Retinopathy Barometer Study: Global perspectives on access to and experiences of diabetic retinopathy screening and treatment. *Diabetes Res Clin Pract*. 2017; 129: 16-24.
15. Liao Y-R, Li Z-J, Zeng P, Lan Y-Q. TLR7 deficiency contributes to attenuated diabetic retinopathy via inhibition of inflammatory response. *Biochem Biophys Res Commun*. 2017; 493: 1136-1142.
16. Rhee JJ, Zheng Y, Liu S, Montez-Rath ME, Hamill RJ, et al. Glycemic Control and Infections Among US Hemodialysis Patients With Diabetes Mellitus. *Kidney Int Rep.* 2020; 5(7): 1014-1025.
17. Erener S. Diabetes, infection risk and COVID-19. *Mol Metab.* 2020; 39: 101044.
18. Kumar A, Arora A, Sharma P, Anikhindi SA, Bansal N, et al. Is diabetes mellitus associated with mortality and severity of COVID-19? A meta-analysis. *Diabetes Metab Syndr.* 2020; 14: 535-545.
19. Chee YJ, Ng SJH, Yeoh E. Diabetic ketoacidosis precipitated by Covid-19 in a patient with newly diagnosed diabetes mellitus. *Diabetes Res Clin Pract*. 2020; 164: 108166.
20. Pippitt K, Li M, Gurgle HE. Diabetes Mellitus: Screening and Diagnosis. *Am Fam Physician.* 2016; 93: 103-109.
21. Okosun IS, Seale JP, Lyn R, Davis-Smith YM. Improving Detection of Prediabetes in Children and Adults: Using Combinations of Blood Glucose Tests. *Front Public Health.* 2015; 3: 260.
22. Delaney MF, Zisman A, Kettyle WM. Diabetic ketoacidosis and hyperglycemic hyperosmolar nonketotic syndrome. *Endocrinol Metab Clin North Am*. 2000; 29: 683-705.
23. Gomes KFB, Semzezem C, Batista R, Fukui RT, Santos AS, et al. Importance of Zinc Transporter 8 Autoantibody in the Diagnosis of Type 1 Diabetes in Latin Americans. *Sci Rep.* 2017; 7: 207.
24. Noble JA, Valdes AM. Genetics of the HLA region in the prediction of type 1 diabetes. *Curr Diab Rep.* 2011; 11: 533-542.
25. Viswanath B, Choi CS, Lee K, Kim S. Recent trends in the development of diagnostic tools for diabetes mellitus using patient saliva. *TrAC Trends in Analytical Chemistry*. 2017; 89: 60-67.
26. Reitmeier S, Kiessling S, Clavel T, List M, Almeida EL, et al. Arrhythmic Gut Microbiome Signatures Predict Risk of Type 2 Diabetes. *Cell Host Microbe*. 2020; 28: 258-272.e6.
27. Miller BR, Nguyen H, Hu CJ, Li, C, Nguyen QT. New and emerging drugs and targets for type 2 diabetes: reviewing the evidence. *Am Health Drug Benefits.* 2014; 7: 452-463.
28. Mackenzie RW, Elliott BT. Akt/PKB activation and insulin signaling: a novel insulin signaling pathway in the treatment of type 2 diabetes. *Diabetes Metab Syndr Obes.* 2014; 7: 55-64.
29. Sheehan MT. Current therapeutic options in type 2 diabetes mellitus: a practical approach. *Clin Med Res.* 2003; 1: 189-200.
30. Adeghate E. Visfatin: structure, function and relation to diabetes mellitus and other dysfunctions. *Curr Med Chem*. 2008; 15: 1851-1862.
31. Barnett AH, Charbonnel B, Donovan M, Fleming D, Chen R. Effect of saxagliptin as add-on therapy in patients with poorly controlled type 2 diabetes on insulin alone or insulin combined with metformin. *Curr Med Res Opin.* 2012; 28: 513-523.
32. Soccio RE, Chen ER, Rajapurkar SR, Safabakhsh P, Marinis JM, et al. Genetic Variation Determines PPARγ Function and Anti-diabetic Drug Response In Vivo. *Cell*. 2015; 162: 33-44.
33. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, et al. SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*. 2020; 181: 271-280.e8.
34. Amer LD, Mahoney MJ, Bryant SJ. Tissue engineering approaches to cell-based type 1 diabetes therapy. *Tissue Eng Part B Rev.* 2014; 20: 455-467.
35. Giraldo JA, Weaver JD, Stabler CL. Enhancing clinical islet transplantation through tissue engineering strategies. *J Diabetes Sci Technol.* 2010; 4: 1238-1247.
36. Ariyachet C, Tovaglieri A, Xiang G, Lu J, Shah MS, et al. Reprogrammed Stomach Tissue as a Renewable Source of Functional β Cells for Blood Glucose Regulation. *Cell Stem Cell*. 2016; 18: 410-421.
37. McCauley HA, Wells JM. Sweet Relief: Reprogramming Gastric Endocrine Cells to Make Insulin. *Cell Stem Cell*. 2016; 18: 295-297.
38. Gattás-Asfura KM, Stabler CL. Bioorthogonal layer-by-layer encapsulation of pancreatic islets via hyperbranched polymers. *ACS Appl Mater Interfaces.* 2013; 5: 9964-9974.
39. Rezania A, Bruin JE, Riedel MJ, Mojibian M, Asadi A, et al. Maturation of human embryonic stem cell-derived pancreatic progenitors into functional islets capable of treating pre-existing diabetes in mice. *Diabetes*. 2012; 61: 2016-2029.
40. Szot GL, Yadav M, Lang J, Kroon E, Kerr, J, et al. Tolerance induction and reversal of diabetes in mice transplanted with human embryonic stem cell-derived pancreatic endoderm. *Cell Stem Cell.* 2015; 16: 148-157.
41. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006; 126: 663-676.
42. Sandow J, Landgraf W, Becker R, Seipke G. Equivalent Recombinant Human Insulin Preparations and their Place in Therapy. *Eur Endocrinol.* 2015; 11: 10-16.
43. Mann JL, Maikawa CL, Smith AAA, Grosskopf AK, Baker SW, et al. An ultrafast insulin formulation enabled by high-throughput screening of engineered polymeric excipients. *Sci Transl Med.* 2020; 12: eaba6676.
44. Ma Y, Fang S, Zhao S, Wang X, Wang D, et al. A recombinant slow-release PACAP-derived peptide alleviates diabetes by promoting both insulin secretion and actions. *Biomaterials*. 2015; 51: 80-90.
45. Zhang X, Qi J, Lu Y, Hu X, He W, et al. Enhanced hypoglycemic effect of biotin-modified liposomes loading insulin: effect of formulation variables, intracellular trafficking, and cytotoxicity. *Nanoscale Res Lett.* 2014; 9: 185.
46. Joshi BN, Munot H, Hardikar M, Kulkarni AA. Orally active hypoglycemic protein from Costus igneus N. E. Br.: an in vitro and in vivo study. *Biochem Biophys Res Commun.* 2013; 436: 278-282.
47. Hardikar MR, Varma ME, Kulkarni AA, Kulkarni PP, Joshi BN. Elucidation of hypoglycemic action and toxicity studies of insulin-like protein from Costus igneus. *Phytochemistry*. 2016; 124: 99-107.
48. Domola MS, Vu V, Robson-Doucette CA, Sweeney G, Wheeler MB. Insulin mimetics in Urtica dioica: structural and computational analyses of Urtica dioica extracts. *Phytother Res.* 2010; 2: S175-S182
49. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. *Science.* 2005; 307: 426-430.

50. Romere C, Duerrschmid C, Bournat J, Constable P, Jain M, et al. Asprosin, a Fasting-Induced Glucogenic Protein Hormone. *Cell*. 2016; 165: 566-579.
51. Drucker DJ. Evolving Concepts and Translational Relevance of Enteroendocrine Cell Biology. *J Clin Endocrinol Metab.* 2016; 101: 778-786.
52. García-Cáceres C, Quarta C, Varela L, Gao Y, Gruber T, et al. Astrocytic Insulin Signaling Couples Brain Glucose Uptake with Nutrient Availability. *Cell*. 2016; 166: 867-880.
53. Fröjdö S, Vidal H, Pirola L. Alterations of insulin signaling in type 2 diabetes: a review of the current evidence from humans. *Biochim Biophys Acta.* 2009; 1792: 83-92.
54. Kudva YC, Carter RE, Cobelli C, Basu R, Basu A. Closed-loop artificial pancreas systems: physiological input to enhance next-generation devices. *Diabetes care*. 2014; 37: 1184-1190..

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