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Review Article

CONTEMPORARY DRIFTS IN DIABETES MANAGEMENT

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ABSTRACT

Diabetes mellitus is a cumulative effect of various cellular and biochemical malfunctions which trigger the blood glucose level far beyond the normal range. From 1980 to 2014, more than 314 million individuals had diabetes. Epidemiology states that it is becoming more prevalent in low-income, middle-income, more specifically, third-world countries than the first-world countries. It showed mortality rate increased by 5% in premature ages. It was the 9th leading reason for almost 1.5 million deaths. The diagnosis clearly suggests the replacement of insulin-producing pancreatic endocrine cells. Stem cell treatment substitutes the infected or destroyed cells from pluripotent stem cells or multipotent stem cells. One of the favourite ways to understand and treat diabetes mellitus is embryonic stem cells, including pluripotent cells. The *in vitro* demonstration of iPSC-derived pancreatic cells for treating infection is a grizzled dream of scientists. Luckily, iPSC-derived cells combat the major problems that arose in this field and still, there are no legal and ethical bindings as well as immunological rejections. Later, the β cell of the pancreas has derived from PSCs from various patients who have diabetes. The study proves there is a wide possibility of demonstrating and rectification of clinical administration of these newly developing trends. The use of stem cell therapy *in vitro*, which is explicit patient research, shows various concerns related to the pathophysiology of diabetes. Successful application of procedures of screening of the apoptosis of β-cells from inbuilt cell retrieval needed to be a proper arrangement of new cell lines.

Keywords: β-cells, Insulin, Nanotechnology, Diabetes mellitus, Stem cell therapy

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INTRODUCTION

Diabetes is of two types, namely diabetes mellitus and diabetes insipidus. Sources specify that ancient Indians, Egyptians, and Greeks knew about this disease. The Latin word "Mellitus" means sweet and the Greek word "Mellitus" defines sweetness, as honey is called "Mellita". Greeks noted that people suffering from such lesions excrete sweet urine as they used to taste the patient's urine for diagnosis. The patient used to show tendencies to drink excessive water, which could not remain in their body for a very long period. The immediate excretion was demonstrated as siphoning, which was studied as "Diabetes". In the Indian subcontinent, the "Madhumeha" name was famous as the physicians noticed patients' urine enchanted ants, flies, and other insects. So, clinically these were the primitive tests to identify glucose in patients [1].

In Africa, almost 5.1% of individuals from the sub-Saharan region have diabetes. In the Caribbean and North American regions, the percentile is 11.4. This state of affairs is about to strike 8.3% of grown-up individuals aged from 20 to 79 worldwide. Third-world countries or low-income countries follow the WHO STEP wise approach to surveillance (popularly known as STEPS) tool, which was launched in 2005, whereas countries of the first world do not follow these properly. Proper lifestyle, Basal Metabolic Rate, blood pressure, and waist circumference are very important risk factors demonstrated by WHO with STEPS. FPG, along with OGTT, is advised to conduct nationwide. BMP type-1 receptor inhibitors, namely dorsomorphin and retinoic corrosive, could be the effective treatment that enhances the differentiation into PDX1 positive β-cells [2, 3]. A small molecule called Indolactum V is isolated, which initiates the differentiation of PDX1-positive cells from hESCs. The ministration of these kinds of cells is administered with SB431542, which is a TGFβ type 1 receptor. Hence this takes action on their differentiation from NGN3-positive precursor cells of the pancreas. Medications with tetrabenazine and reserpine inhibit the vesicular monoamine 2, separating PDX1 responsive cells into NGN3 responsive ancestors. For the ultimate step, these potentially separate pancreatic β-cells [4].

Pathology of diabetes

Initially, diabetes was characterized by unrestrained thirst, halitosis (a clinical term for bad odour in breath), profuse urination, presence of sugar or sweetness in urine. Back then, the biochemical pathways of diabetes were unknown to physicians. Statistical investigation shows that about 60% of the mass is distressed by diabetes. Patients who are suffering from it chronically may show various syndromes of hyperosmolar glycemia and diabetic ketoacidosis (DKA) [5]. Blurred vision, loss of vision, and floating dark strings, the red flag of diabetic retinopathy, may also occur. Acute diabetes affects the functional unit of the kidney (nephron), as a result, its function is impaired, and proteins are leaked into the urine, which is clinically termed diabetic nephropathy. In the United States, diabetes is the prime key to peripheral neuropathy.

People suffering from diabetes mellitus type-2 have a high risk of segmental bone injury. The prime regulating factor of the biochemical pathway of diabetes is insulin, which plays a pivotal role. The absence or imprudent quantity of this hormone produces diverse corporeal abnormalities and collateral damage in the body. The surplus in body weight and insufficient physical exertion leads to non-insulin-dependent diabetes, popularly called diabetes mellitus type-2. In this case, the body becomes incompetent to the effect of insulin. More than 95% of the human population has diabetes, suffering from non-insulin-dependent diabetes mellitus (NIDDM). Insulin is produced and released by the β-cells of the pancreas [6]. In an auto-immune disease where β-cells are destroyed, insulin production will be halted. In chronic pancreatitis, the cells of this organ become inefficient in producing insulin which regulates blood sugar levels. The illegitimate modification in insulin receptors also plays a crucial role as it is also responsible for insulin-dependent diabetes mellitus (IDDM), which is widely known as

Type-1 diabetes. Maturity onset diabetes of the young (MODY) has been contemplated in the last few decades. This shows the tendency of diabetes before the individual reaches 30 y, which can also be developed in later years. Neonatal diabetes (NDM) appears in infants' first six months when the body remains unable to produce enough insulin, followed by a hike in blood sugar level. Malformation of the pancreas or inadequate development of pancreatic β-cells may be the major reasons behind this. Excess weight during pregnancy causes gestational diabetes, as imprudent obesity reduces the effectiveness of insulin. In postpartum, the blood sugar level reaches back to its normal range, but it creates room for the reoccurrence of type-2 diabetes [2].

B-cell-production house of insulin

The human pancreas contains about 10,00,000 islets, among which there are barely 2,000 β-cells, which indicates β-cells contain about 1.5% mass of the total organ. The proper action of the cells maintains the equilibrium of body glucose. The glucagon produced by α cells plays an antagonistic role to insulin; the fine balance between these continues the sustainability of blood sugar levels [7].

Totipotent cells of embryos have the super ability to produce any cell in the body. Throughout development, the totipotent cells differentiate into pluripotent cells. These cells possess the capacity to produce three leading cell groups. Embryonic stem cells differentiate into three germ layers: ectoderm, mesoderm, and endoderm. These pluripotent cells give rise to every cell and organ of our body. The germ layers initially contain multipotent stem cells which can self-renew and regenerate a specific cell batch, such as hematopoietic stem cells differentiate into various blood cells; bone marrow stem cells differentiate into different bone cells; cardiac progenitor cells differentiate into cardiomyocytes; pancreatic progenitor cells arisen from endodermal germ layer produces pancreatic β-cells [8].

Eradication of β-cells in autoimmune interference gives rise to type 1 diabetes. The decreasing β-cell colony is decrypted as the ground reason behind the reduced insulin level, followed by hyperglycemia. Almost 65% decline in β-cells related to type-2 diabetes. 10X increase in apoptosis in β-cells is not an immune system alteration; glucose, human islet amyloid polypeptide (hIAPP), and FFA synthesize poisonous oligomers, which play a crucial role in this case [9].

Instead of suppressing the disease with various drugs, substituting β-cells could be a potential treatment for type-1 and type-2 diabetes. Islets substitution could also be a treatment choice but speculative regarding a medical course of action. Transplantation of the pancreas is also feasible, but profound immune suppression restricts its utilization. Though islets transplantation is less effective than pancreas transplantation in achieving moderation in insulin levels [10].

Biochemical assay to determine diabetes mellitus

There are various biochemical assessments to diagnose different stages of blood sugar levels. Utilizing various tests and methods, diabetic and prediabetic conditions could be assumed. These may be:

- Fasting plasma glucose (FPG) test
- Urine glucose test
- Oral glucose tolerance test (OGTT)
- Hba_1c testing
- Serum creatinine estimation
- Estimation of urine microalbumin
- Glucometer for measurements at home
- Salivary glucose as a non-intrusive type-2 diabetes biomarker

Fasting plasma glucose (FPG) test

The fasting glucose test is administered to detect diabetes or pre-diabetic condition. After a long time of fasting, a blood test takes place. This test dictates the amount of glucose in the blood at a certain time. This test is done in the morning after continuing a straight 8 h fast to obtain the best result. A little water could only be taken during this period. According to WHO, the normal range is less than 5.5 mmol/(100 mg/dl). In the cas3 of impaired fast the range is 5.5-6.9 mmol/(100-125 mg/dl). In diabetic patients, the level is 7.0-1 or higher/(126 mg/dl). This pre-diabetic condition is determined by impaired fasting with glycemia [4].

Urine glucose test

The patient's urine sample is assessed to determine the quantity of glucose present in it. The presence of sugar/glucose in the urine is medically termed Glycosuria. It could also be tested with blood or cerebrospinal fluid. Urine is examined with a dipstick along with color-sensitive pads.

A blood test has replaced this popular glucose measuring test to examine blood glucose levels, which is quick and apt for new ones.

The normal glucose level of urine is 0 to 0.8 mmol/l (0 to 15 mg/dL) in normal non-diabetic conditions; individuals may show abnormal glucose levels [6].

- A little hike in glucose levels of urine after a nosh up generally is not a matter of concern.
- Almost 50% of pregnant ladies have excess sugar in their urine in some stages of pregnancy; this is called gestational diabetes.
- Renal glycosuria is a medical condition where the blood sugar level is absolutely normal, but the kidneys exude glucose and urine.

Oral glucose tolerance test (OGTT)

This test reveals the patient's capability to assimilate a fixed quantity of glucose among type 1, type-2, and gestational diabetes patients. Patients are instructed to uptake a minimum of 150 grams of glucose each day for three consecutive days while fasting for at least 8 h before collecting the sample. Repeated phlebotomies or BC-shielded IV catheters may be used to administer the procedure. During pregnancy, between 24 to 28 w, gestational diabetes could find out. Widely insulin is examined from people, but c-peptide and glucose estimation are administered when required. In the process of centrifugation, the platelet is isolated from serum. The serum is kept in refrigeration for further use while the platelet is discarded. This test is excellently designed to examine the rapid glucose assimilation in blood. Reactive hypoglycemia, acromegaly, insulin resistance, and decreased β-cell activity could be screened with OGTT [11].

Hba_1c testing

The haemoglobin A1c (A1C) level is a standardized marker to indicate chronic glycemia and its future risk. There is no obligation of fasting during or before the test. It's powerful diabetes screening appliance for detecting type-2 diabetes in a population-based survey. Glucose binds to the haemoglobin of RB while circulating, resulting in an aroused blood sugar level. This test evaluates the hemoglobin-bound glucose in the blood. As the RBCs survive almost three months, it examines the conspicuous blood glucose level for the last 3 mo [1].

People not suffering from diabetes generally show A1c levels below 5.6%. A1c levels between 5.7% and 6.4% forecast pre-diabetic conditions. Above 6.5% of the patient is thought to be diabetic. If the individual is suffering from anemia, a disease related to hemoglobin, pregnancy, or heavy blood loss, there is a high chance of receiving false data.

Malfunctioning of the glomerular endothelial barrier, inflammation, mechanical stress, and the effect of angiotensin II along with other various reasons give rise to the albumin level excreted from the kidney, termed albuminuria. Vascular and metabolism-related issues could also contribute to glucose level fluctuation as reactive oxygen species formation and vasodilation could impair renal functions [1].

Charles Heilig *et al.* (2006) examined the function of renal glucose transporters in the development of diabetic nephropathy in the case of mesangial cells. The primary glucose transporter is GLUT1, which

holds the responsibility of controlling extracellular matrix development. If mesangial cells overexpress GLUT1, the production of fibronectin, laminin, and type-I and type-IV collagen increases, which results in diabetes. In the case of the glomeruli, overexpressed GLUT1 produces a phenotype that is similar to the renal lesion in diabetic mice.

The plasma creatinine concentration remains constant in skeletal muscle. Nobuko Harita *et al.* (2009) confirmed that low serum creatinine levels provoke a risk of type-2 diabetes if skeletal muscle mass is reduced [2].

Estimation of urine microalbumin

The urine microalbumin test detects the protein albumin of blood in the urine, so it could be used to diagnose the very first symptoms of kidney damage. Impairment in kidney function leaks albumin into the urine. Both types of diabetes and high blood pressure require microalbumin testing.

Less than 30 mg of protein per 24 h is considered normal. In microalbuminuria, the albumin ranges between 30 to 300 mg. in macroalbuminuria, more than 300 mg of albumin is detected. Various reasons cause a high level of albumin, such as fever, urinary tract infection, other kidney lesions, strenuous exercise, hematuria, and the effect of several drugs [12].

New assays for diabetes

Glucometer for measurements at home

With the help of a glucometer, any individual can measure their blood glucose level before or after a meal whenever required. But this handy technique also has disadvantages in its usefulness. So, more accurate procedures are needed [13].

Salivary glucose as a non-intrusive type-2 diabetes biomarker

a non-invasive blood sugar monitoring strip has been developed by scientists at Newcastle University in Australia, which measures glucose levels from saliva samples of diabetic patients.

Readings of Blood glucose levels exceeding 126 mg/dL are recognized as diabetic. Saliva could be easily collected non-invasive, so researchers used this as a golden opportunity for prognosis as it contains enzymes, growth factors, hormones, microorganisms, and antibodies.

A mouth guard biosensor coupled with a telemetry system is synthesized to sense diabetes by monitoring real-time saliva glucose. A different study shows that dried saliva spots are a suitable and very reliable sampling method for biometric diagnosis [14, 15].

Nanotechnology-a new approach

After the invasion of nanotechnology in the field of disease diagnosis, medical procedures, and treatment new era has been inaugurated in science. It has become the most effective execution in daily life, ranging between 0.1 to 100 nm. Nanomaterials have idiosyncratic upshots as large surface area effects size, surface energy for quantum effect, fast increment in surface atomic ratio for the interface, and surface energy [16]. Depending on its character, it could be administered by injection, mucosal, or transdermal ways. A 3D hydrogel network system is prepared, which encapsulates effective ingredients to provide a mechanical and chemical guard. To scan, the advancement of the disease nanoparticles carries through RNA and proteins. For diabetes treatment, polymeric micelles, Ceramic nanoparticles, Polymeric liposomes, and Polymeric biodegradable nanoparticles are being used [17].

Conventional treatment approach today

Biguanides

Biguanides reduce hepatic neo glucogenesis, thus reducing sugar levels, and sugar adoption in the intestine is also decreased. The primary choice of drug for diabetes type-2 is Metformin which belongs to the class of biguanides.

Meglitinides or glinides

Meglitinides are administered orally. This treatment is exclusive to type 2 diabetes. Pancreatic β-cells possess sulfonylurea receptors (SUR1) which are associated with ATP-gated potassium channels. Glinides landing on SUR1 receptors promotes in β cells, as a result,voltage-gated calcium channel releases insulin. In type-1 diabetes, insulin is not produced, so this treatment is fruitless, where the β cells synthesize insulin but are unable to release it. This treatment is a life savior. Examples of such drugs are Repaglinide and Nateglinide [18,19].

Sulphonylureas

It works in a very indistinguishable way from that of meglitinides as its target is the potassium channels of β-cells. Individuals having a pancreatic injury cannot be administered sulfonylureas. Some drugs are: Tolbutamide, Tolazamide, Glipizide, Glibenclamide, and Glimepiride [20,21].

A-glucosidase inhibitors

A-glucosidase, which is found in the small intestine acts on complex polysaccharides and monosaccharides and converts them into simple glucose. A glucosidase inhibitors act on this substrate as competitive inhibitors and stop the production of glucose, hence lowering the blood glucose level. Some examples of inhibitors are Acarbose, Miglitol, and Voglibose (2002) [22].

Glitazones/Thiazolidinedione

Glitazones are prescribed for treating type-2 diabetes. It acts on peroxisome proliferator-activated receptors, which is a class of nuclear receptors. Consequently, the amount of fatty acid is reduced in circulation. Hence cells rely on carbohydrate oxidation; the sugar level drops. Examples of this drug are Pioglitazone, Rosiglitazone, and Lobeglitazone [22].

DPP-4 inhibitors or gliptins

Dipeptidyl-peptidase inhibitors are popularly known as gliptins. This has fewer side effects. Some of the drugs are sitagliptin, vildagliptin, saxagliptin, Linagliptin, etc [23].

Incretin mimetics or GLP-1 analogs

Incretin mimetics mimic the function of the hormone incretin. A widely known example is glucagon-like peptide-1, which enhances insulin secretion from pancreatic β-cells. These hormones, liberated after taking meals, stimulate glucose-induced insulin production. A popular GLP-1 analog is Lixisenatide which mimics the hormone GLP-1, promoting insulin production [24].

Amylin analogs

IAPP is the islet amyloid polypeptide which is also known as amyloid. It is synthesized along with insulin from pancreatic βcells. Pramlintide is an Amylin analog if administered with insulin, decreases the rate of postprandial hyperglycemia relative to only insulin. Also, Pramlintide provides full stomach feelings so food uptake is reduced [25].

SGLT2 inhibitors or gliflozinsodium-glucosecose cotransporter 2

Up to 90% of glucose is absorbed in renal tubules by the effect of Sodium-glucose co-transporter 2. When the transporter stops functioning, glucose starts to excrete with the urine, medically known as glycosuria. People suffering from renal lesions cannot be prescribed SGL2 inhibitors. Examples of the drug are Canagliflozin, Dapagliflozin, and Empagliflozin [26].

Differentiation into B cells and their biomarkers

The different cultural condition affects the differentiation and production of pancreatic β cells. Initially, hESC was thought to be utilized to develop β cells up to 12%, with a conservative response to glucose. hESC plays a vital role in β cell differentiation *in vivo*. Later, modulation in members of the TGFβ family participates in β cell formation [50].

Table 1: The prospect of nanotechnology in diabetes treatment

Nanotechnology	Prospects
Vesicular system	• Consisted of an aqueous core in company with one or more lipid bilayers • Fixed location drug delivery [26]
Liposome	• Vesicles containing phospholipid bilayer • High tolerance for *in vivo* • High production cost • Low stability in the intestine [27-29]
Nanocochleates	• Prolonged stability in the intestine • Drugs could be delivered in every possible way in the body, such as parenteral, rectal, topical, sublingual, mucosal, nasal, ophthalmic, subcutaneous, intramuscular, intravenous, transdermal, spinal, intra-articular, intra-arterial, bronchial, lymphatic, an intrauterine/intra-vaginal way [30-32]
Niosomes	• Consisted of non-ionic surfactants • Cholesterol and lipids • Transports lipophilic and amphibolic drugs • Non-immunogenic [33]
Phytosome	• Consisting of phyto-compounds and phospholipids • Pyrosome-aspiring drug molecule carrier [34, 35]
Polymeric nanoparticle	• Instinctive polymer nanoparticle [36] • Synthetic polymer-based nanoparticle
Inartificial polymer-type nanoparticles	• Nontoxic • Biocompatible
Chitosan-based nanoparticles	• loosens up the tight junction between epithelial cell • releases drug quickly • dissociates readily in intestinal juice [35-37]
Alginate/chitosan-based nanoparticles	• slow drug release • exhibits better hypoglycemic effects [37]
Gum-based NPs and gum chitosan-based NPs	• remarkable stability in a broad range of pH • hydrogel formation with naturally occurring gums [36-38]
Dextran-based NPs	• Outstanding water solubility • Highly efficient in reducing mitochondrial depolarization, apoptosis, and glucose-induced oxidative stress [39].
Synthetic polymer-based NPS	• The basic components are poly-vinyl alcohol (PVA) • poly-lactic acid (PLA) • poly-lactic-co-glycolic acid (PLGA) • poly ε-caprolactone • Widely regulate synthetic processes [30]
PLGA-based NPS	• Biocompatible • Bio-degradable • The rate of drug delivery could be changed as per the requirement • Protects drugs from degrading • Carry hydrophobic drugs and hydrophilic drugs [32, 33]
PLA, PCL and PVA based NPS	• Improves the glycemic condition of blood • Enhances bioavailability of certain antibiotics [34, 35]
Polyethylene glycol surface modification	• Reduced immunogenicity • Hydrophilic • Less toxic • Blood-correspondent polymer [38, 40]
Micelles	• transfers β cells efficiently • increases oral bioavailability [39]
Lipid-based nanoparticles	• low production cost • water-insoluble drugs • smoothly assimilated through the GI tract [39]
Solid-lipid nanoparticles (SLNs)	• antioxidant • anti-diabetic • reduced SNARE protein with anti-insulin properties [41-43]
Nanostructured lipid carriers (NLCs)	• composition of solid and liquid lipids • lesser *in vitro* toxicity [39, 44]
NEs	• consisted of the emulsifying medium, water, and fat • manage antioxidative stress • show anti-diabetic properties [45, 46]
SNEDDS	• blend of triglyceride, surfactant, and co-surfactant • excessive requirement of surfactant • stubby encapsulation • glyceride oxidation [47]
Metallic nanoparticles	• show enhanced antidiabetic effects of plant-based compounds [47]
Mesoporous silica-based nanoparticles	• honey-comb-like structure • huge capacity to capture different drug molecules [48, 49]

PSCs can be widely marked with OCT4, NANOG, and SOX2 biomarkers. In the very initial steps of differentiation Activin A, Wnt3A, and PI3k antagonists influence the process. Sod, pyruvate, IDEs, and GDF8 also contribute to the itinerary. In the next step, RA, Noggin, FGF10,

SU5402, CYC, and Indolactam V play pivotal roles in differentiation. These cells are SOX2 positive, FOXA2 positive, and BMP2 positive. These are the biomarkers for the cells. The pancreatic progenitor cells are PDX1-positive cells. DAPT and SB431542 (inhibitor of TGFβ) play the foremost parts in the upcoming stages. The new endocrine progenitor cells are NGN3 positive and PAX4 positive. For the ultimate and major part of this way, an adenylate cyclase activator-Forskolin, hepatocyte development factors such as HGF, adreno-cortical steroid–Dextra-methasone, insulin-like development factor 1 (IGF1) are principal components playing the key role. The β-cells are exclusively marked with insulin, MAFA, and GLUT2. The whole biosynthetic pathway is depicted in fig. 1.

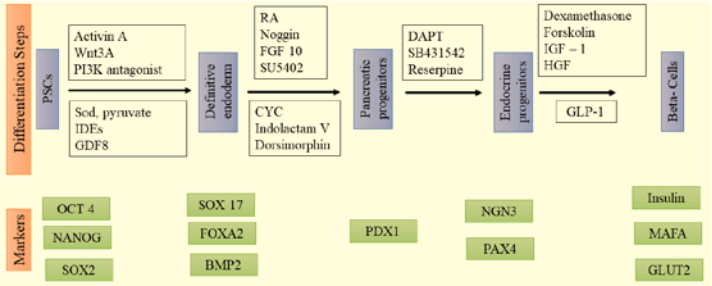

Fig. 1: Differentiation and development of pancreatic beta cell, the contribution of regulating genes and factors [50]

In vitro method

PSCs to β cells

The arrangement of DE is upgraded by hESC treatment with bone morphogenic protein 4 (BMP4) or Wnt3A. endodermal separation is recorded in some cases where Wnt3A or CHIR99021 treatment is administered. CHIR99021 performs more precisely than Wnt3A in the advancement of SOX17-and FOXA2-positive cells of endoderm. GDF8 (myostatin), a TGFβ family protein, successfully animates DE. hESC treatment may be performed with little atoms such as IDE1 and IDE2, almost 80% of total ESCs to separate into SOX17-positive DE cells [51].

Noggin inhibits the function of BMP, whereas SU5402 inhibits the FGF receptor. This antagonistic play throttles the hepatic separation in the therapy of diabetes. The suppression of bone morphogenic protein (BMP) signals the dorsal endoderm, which is primary for pancreatic isolation if the functional pancreatic cells are formulated; the BMP labelling is thought to be carried on with PDX1 union. This could also be operated by Indent and Sonic HedgeHog pathways, where cyclopamine is a potent Hedge Hog inhibitor that has been potentially used to communicate with PDX1 flagging cells. This PDX1 has a crucial role in the course of progression of the endocrine cells of the pancreas. The fibroblast development factor, popularly known as FGF10 can communicate with NOTCH, which assists with the extension of PDX1-positive pancreatic cells. The structurization of NGN3 with pancreas cells occurs as a result of reduced NOTCH signalling. Some inspections show that DAPT, a potent gamma-secretase inhibitor, obstructs NOTCH signalling [52, 53].

To improve β cell development, these cells are given treatment with a potent adenylate cyclase activator, namely forskolin and adrenocortical steroid hormone dexamethasone, hepatocyte development factor, IGF1 or insulin development factor, and GLP1 or glucagon-like peptide 1. *In vivo* maturation of PDX1 flagging cells into pancreatic β cells requires NKX6.1. In the case of a diabetic mouse, NKX6.1 reduces hyperglycemia. Some other flagship biomarkers of insulin-secreting pancreatic βcells are MAFA, NEUROD, ISL-1, GLUT-2, INS, and C-peptides [54, 55].

Overexpressed PAX4 in hESC, found in insulin-secretingβ cells, communicates with PDX1, GLUT 2, C-peptide, and INS. Comparatively, FOXA2 shows less effect while differentiating hESC into βcells [56].

Human-induced PSCs (hiPSCs) to β cells

Likewise, hESCs and hiPSCs were possibly isolated into β-cells after a step-by-step segregation protocol into SOX17-positive cells (DE), PDX1-positive cells (pancreatic forebears), and NGN3-positive cells (endocrine progenitors). By administering the same procedure to hESC to produce β-cells, using a four-step separation, skin fibroblasts differentiate into β-cells, which show receptors to glucose [57, 58].

In vivo method

The result has been standardized from *in vivo* microenvironment studies in transplantation β cell development. Transplanted juvenile β-cells give rise to potent insulin-secretingβ cells *in vivo*. If the mice are treated with streptozotocin (STZ) or mice have excessive body fat, hESC-derivedβ cells differentiate into effective β-cells [59]. If these hESC-derived cells are translocated into macro encapsulated form, still mature β-cells arise. In type 1 and type 2 diabetes, iPSC-inducedβ cells instantly secrete insulin in hyperglycemic conditions. Altogether, these experiments prove that *in vivo* treatment is primarily for the PSC-derived insulin-secreting cells; taken together, these discoveries recommend that *in vivo* development has the fate of transplantation and forming potent pancreatic β-cells [60, 61].

Rates of β-cell turnover in humans

Finegood *et al.* (1995) examined the turnover of βcells using BrdU or thymidine present in rodent cells in turned out to be 2% each day in mice.1 in every 1400 β cells start replication every day, calculatingly the multiplication rate is 0.0701% every day because there is no trans-differentiation rate from the new islet of Langerhans. in human, performing a similar experiment is tough but considering the frequency of Ki67 β-cell turnover rate is slower than mice. During pregnancy growth of β-cells in the pancreas proves that there are certain conditions through which the turnover of these cells possibly be extended [62, 63, 75].

Derivation of diabetic patient-specific pluripotent stem cells

There are various subtypes of diabetes that perceive various pathogenicity. Constructing an *in vitro* model of diabetes of hereditary characteristics and factors gives important calls to the different limits and analyses. The implantation of different stages of stem cell-derived insulin-secreting cells relies upon test organisms, subduing medical conditions, and hardcore research work. To understand the deep molecular and biochemical pathways to discover various aspects of the treatment, a deep *in vitro* study is to be perceived.

Patient specific-embryonic stem cells

Substantial cell atomic exchange, termed SCNT, is gaining popularity for the production of customized ESC from the body cell of an individual. This approach is particularized as the nucleus of a considerable cell is transferred into a potential egg cell, where its nucleus is eliminated. Hence this emergent entity is completely identical to the filial cell. SCNT procedure came to light after the successful creation of “cart the sheep” in 1997, which was the very first warm-blooded animal. The formation of hESC from SNCT faced some issues, though after troubleshooting latest procedures show efficiency in synthesizing human body cells by SCNT. The latest reports essayed the in distinguishability between hESC and hiPSC so that these do not call for immune reactions in the wake of the

transplantation of isolated cells [59]. Though attaining success, this ESC production faces moral and ethical questions in collecting human oocytes, causing practical complications. PGD, namely pre-implantation hereditary determination, serves as a method to deliver hESC colonies with genetic lesions by undeveloped organisms brought into play. Through the procedure of PGD genetic deformity of an undeveloped individual might be taken into consideration [64]. Various examples show the production of proper hESC lines from a few genetic lesions of the potential and primordial organism with the help of PGD. These experiments direct the medicinal treatment wide way to treat chromosomal irregularities, study deformed genetic models *in vitro*, and drug screening in a test organism followed by subsequent treatment [65].

Patient-specific-induced pluripotent stem cells

As embryonic stem cells have a huge constraint to becoming the perfect material for genetic disorder exposition, researchers have concentrated on additional techniques exploiting the providence of iPSC of late. The primary hiPSCs are developed from skin fibroblastic cells of type 1 diabetic patients, bringing OCT4, KLF4 and SOX2 into play [57]. Later, hiPSCs are utilized for monogenic diabetes ODY *in vitro*. MODY2 patients developed hiPSCs, showed by the research of Hua *et al.* (2013) showed the variation in the quality of glucokinase encoding [66]. These patients are heterozygous for partial-loss-of-function (hypomorphic mutation) of GCK, which affects the pancreatic β cells compared to control cells [67, 68].

iPSCs along with indolent GCK alleles, exhibit reduced capability while differentiating into β-cells. In the case of MODY2 patients who have changed GCK, response with low glucose secreted from β cells. MODY2 positive iPSCs manifested for GCK quality modification can set apart insulin-secreting β cells with classic glucose responsiveness. There is a wide range of MODY lines, such as MODY1 (HNF4A positive), MODY2 (GCK positive), MODY3 (HNF1A positive), MODY5 (HNF1B positive), and MODY8 (CEL positive). This research uses a polycistronic lentivirus vector with higher effectivity than regular retroviruses, so the purposive MODY-derived hESC never shows a karyotypic bolt [69].

Though practical inspections assure that cellular aging blocks the recycling process, the latest reports examine hiPSC on epidermal keratinocytes in culture-free or serum-free conditions in older individuals suffering from type-2 diabetes. Keratinocyte-derived iPSCs collected from diabetic and all non-diabetic individuals are strongly hESC positive and give rise to each ancestry, like pancreatic β-cell. There are many variations among the patients in β-cell producing iPSCs, which might show effective differences in iPSCs.

The reconstruction of body cells in iPSC occurs by using viral transfers. But the crucial constraints of this reconstruction of unreliable genome editing, which can nip the bud, are vector spine and integration of the transgene into the original genome. This combination may give rise to transformation, which may stop the general ability of iPSC. Their responsiveness cause tumorigenesis. To fight the problem, some experiments have proclaimed iPSCs using adenoviral reprogramming technologies, mainly an adenovirus that liaises with SO2, OCT4, KLF4, and c-Myc. These needs extended candour to redesign constituents. Several other channels are fabricated to put an end to transgene from iPSC. Transgene-free iPSC formation is going by combing Cre with Lox/P [67].

Congruous coercion of straddling transposons is employed to produce vector transgene of iPSC in mice. Moreover, various tests claimed that iPSCs could be structured by instantaneous bequest of recombinant protein recycling factors without using infections. The sans transgene of hiPSCs has been manufactured from individuals suffering from type-1 diabetes and type-2 diabetes employing non-incorporating viral vectors. The harmonized iPSCs disoriented the Sendai viral genome in the core 8-12 sections without substituting the pluripotency [70].

Difficulties and future perspectives for precision

The inspections have reconnoitred the latest developments to make use of PSCs to apprehend the pathogenesis of different diabetes by producing each diabetic patient-specific stem cell by *in vitro* methods, followed by their differentiation into β-cells and its effectivity treating the disease completely. But there are still some difficulties that are required to be disposed of before bringing PSCs completely take the whole charge of clinical treatments of diabetes. To avoid the malignant growth of the cancerous cell, stimulating the experienced concordat thoroughly for differentiation of the PSC into the pure insulin-secretingβ cell is prioritized. The use of hESC in rejuvenating remedies gives out a few questions in connection with virtuous worries. Being the contrary, immunologically, their clinical implementation is limited [70].

Although the invention of iPSC marks a crucial discovery, a few impairments in this field must be worked on. The *in vivo* assessments are considered to explain the differences of β-ells in the iPSC in the transformation process [57].

Some genetic distortions are possibly inherited from rebuilt fundamental cells. These deformities and transformations might unfavourably crash the particulars collected from iPSC of diabetic patients. PSC-derivedβ cells are not fully functional since they are not greatly responsive to glucose. The reason may be the insufficient growth of insulin-secreting cells. To achieve completely grown β-cells, various assignments are to be performed to a greater extent. It could further improve treating infection corroboration and entreaty cell therapy [57, 62].

As the previous examinations confirm variation among patients in case of differentiation of iPSC into β-cells, administration of personalized iPSCs is needed. These differentiate into various useful β-cells. More assessments are anticipated to reduce the clonal variations, which opens a new horizon for customized medicinal treatment for diabetic individuals [58].

Along with hESC, the hiPSC should also be highlighted, as this may acquire basic research work resolving the topical issues in the research field of microorganisms.

DISCUSSION

Genuine and specific procedures are required for the assessment of diabetes. On-chip nano biosensors are disposable. It is designed with a precise sensitivity level. The cumulative result indicates that diabetes diagnosis has turned into a molecular diagnosis in a non-invasive technique using salivary tests [28]. Drugs brought about through nanotechnology have lesser side effects and work more target-oriented. The release of drugs is more sustainable, so the action time is more précised. It acts more efficiently when administered in a low dose [33]. It has the properties of diffusing into the bloodstream directly without causing any damage to the endothelial tissues. Its efficacy is enhanced by protecting it from enzymatic degradation in the body. Researches show that if drugs are enveloped with liposome and provided to the patient, they will show a more sustainable efficacy by enhancing the bioavailability of that drug [35]. Yucel *et al.* (2018) proposed when Resveratol is encased within nanopolisomes and administered to streptozotocin-induced diabetic patients' β-TC3 cells. It shows great anti-diabetic properties as the antioxidant properties are prolonged compared to the single administration of that drug [39]. The distinctive spiral shape of particular drugs helps them to bind except for any chemical bonding; hence the medicinal property remains unchanged. As the phospholipid bilayer has both hydrophilic and hydrophobic properties, it can convey all kinds of drugs that are hydrophilic, hydrophobic, and amphiphilic. This property provides the nanocochleates the unique versatility. Yucel et. al experimented with nanocochleates, they developed resveratrol seated with nanocochleates and examined pancreatic β TC3 cells and they discovered that this drug performed better than the liposome technique even in low concentrations of parent drug Resveratrol [44]. Niosomes containing lycopene exert anti-diabetic characteristics *in vivo* which resembles Glibenclamideemblem is an unceremonious component if ensheathed in noisome by thin film hydration technology, shows various anti-diabetic properties in STZ-enhanced mice; it also shows antioxidant effects by super oxidase dismutase, hypoglycemic effects better than Repaglinide. It reduces lipid peroxidation, hence producing inference as a useful drug delivery system to fight against diabetes [71]. Experiments by Rani

et al. (2019) show nanoparticles loaded with glycyrrhizin exhibit super anti-glycemic effects and anti-lipidemic effects in diabetes mellitus type 2 in mice and similar effects shown by Metformin [38, 59, 72-74]. The treatment of diabetic animals with gold nanoparticles results in a lower level of glycosylated haemoglobin, demonstrating the antidiabetic effects of gold nanoparticles. With all these experiments potency of metallic nanoparticles came to light [70, 75]. Optimizing the use of existing therapies to ensure adequate glycemic, blood pressure, and lipid control and reduce complications, improving patient adherence to lifestyle and pharmacologic interventions, lowering barriers to early use of insulin, educating patients on diabetes self-management, and improving the delivery of health care to people with chronic conditions are all current challenges in the management of diabetes.

CONCLUSION

The coordination between the iPSC cell's pluripotency with the tumorigenesis shows such properties, which reveal a way to produce iPSC oncogenes. Recent studies show the destructive ability of MYC, which keeps away genetic changes. Patients who have type-1 diabetes patients exhibit iPSC development by using OCT4, KLF4, and SOX2, which stops the malignancy of c-Myc. Obokata *et al.* (2014) innovated the reconstruction of substantial cells as possible with sublethal doses, as minimum pH, and named this remarkable innovation the acquisition of pluripotency (STAP). Unlike ESCs, STAP is able to give rise to underdeveloped and placental tissue. Moreover, these proceedings never ask for atomic changes for genetic regulation. With the development of treatment procedures, hESC and hiPSC are becoming the future of diabetes treatment. The immunologically vulnerable patients could be administered SCNT-induced hESC. The report shows that, albeit the pluripotent nature of hESC and hiPSC, some characters communicate with DPPA4, LIN28A and LIN28B, exhibiting the treatment could give striking results in a month or two.

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CONFLICTS OF INTERESTS

Declare none

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