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Novel Approaches for Treatment of Diabetes

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ABSTRACT: Diabetes is mainly controlled by insulin to keep blood glucose level within target range. Subcutaneous delivery, the standard route for invasive insulin administration may cause pain, lipodystrophy, noncompliance, etc. Hence, to overcome these adverse effects there is need for minimally invasive or non-invasive insulin delivery. Due to evolution in technology researches are going on for novel approaches for managing and curing Diabetes. Inhaled insulin gets absorbed faster in blood stream than insulin injection. Nanotechnology can be used for biological devices, biosensors and in different forms for insulin delivery. Artificial Pancreatic system is an insulin program which uses technology for managing diabetes. Combination of GLP-1 receptor agonists and DYRK1A inhibitor can be converted into potent beta cell regenerative drug. Separation of islets from pancreas of deceased organ donor and then transplanting these cells into the person with type 1 diabetes can improve blood glucose level by releasing insulin. Probiotics treatment can reduce glycosylated haemoglobin and fasting blood glucose level. Stem cells can be differentiated into insulin producing beta cells. Gene therapy can be used for regulating glucose homeostasis or can improve insulin secretion or sensitivity. Partial jejunal diversion via a side-to-side jejuno-jejunostomy for improved glycaemic control in type 2 diabetes mellitus.

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KEYWORDS:Diabetes, Novel Approaches, Insulin, Nanotechnology, Regeneration, Homeopathy

I. INTRODUCTION

Diabetes Mellitus is a disorder that prevents your body from properly using the energy from the food you eat. Diabetes occurs in one of the following situations-

1. The pancreas produces little insulin or no insulin at all. Insulin is a naturally occurring hormone, produced by the beta cells of the pancreas, which helps the body use sugar for energy.
2. The pancreas makes insulin, but the insulin made doesn't work as it should. This condition is called insulin resistance.[1]
3. There are two main types of diabetes:

   As shown in Table 1.

TYPE 1 DIABETES	SIMILAR FEATURES	TYPE 2 DIABETES
• Autoimmune condition- insulin deficiency (prancreas)	• Onset can occur at any age.	• Progressive condition- Changes in 8 different organs.
• Treatment- Insulin	• Cause is unknown may be triggered from genetic predisposition.	• Treatment- Variety of medications.
• Immune system eliminates insulin production.	• Can cause severe other health complications.	• Insulin resistance
• Cannot be prevented.	• Increased risk of eating disorder.	• Maybe prevented/ delayed.

Table 1: An overview of types of Diabetes

WHAT IS INSULIN?

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Insulin is a peptide hormone produced by β cells of the pancreatic islets; it is considered to be the main anabolic hormone of the body (fig.1)[2].

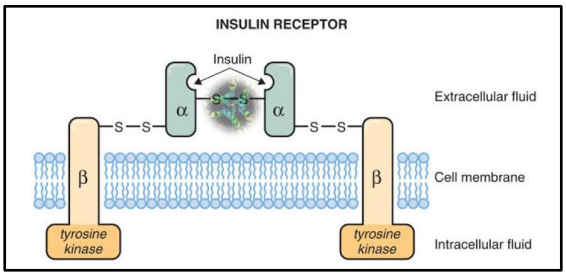

Fig 1: Insulin Receptor

The side effects that a person might experience depend on the type of insulin they are taking. The side effects may include swelling of your arms and legs, hypoglycaemia (dizziness, fast heart rate, delirium, blurred vision, slurred speech, anxiety), lipodystrophy.[3] Insulin is mainly responsible for conversion of glucose into glycogen (fig. 2)

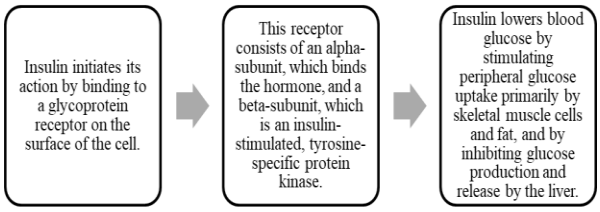

Fig 2: Mechanism of action of Insulin

Traditional treatment approaches involved oral medications for type II diabetes while the treatment of type I involves administration of insulin (Table 2)

ANALOGUE	MODIFICATION	MECHANISM
Lispro (Humalog®) Eli Lilly and Co	Pro^{B28} → Lys Lys^{B29}→Pro	IGF-I- related motif impairs dimerization
Aspart (NovoLog®) Novo-Nordisk	Pro^{B28} →Asp	Charge repulsion at dimer interface
Glulisine (Apidra®) Sanofi-Aventis	Asn^{B3}→Lys Lys^{B29}→Glu	Decreased zinc-free self-association
Glargine (Lantus®) Sanofi-Aventis	Arg^{B31}-Arg^{B32} tag Asp^{A21}→Gly	Shift in pI to pH 7 leads to isoelectric precipitation on injection
Detemir (Levemir®) Novo-Nordisk	Modification of Lys^{B29} by a tethered fatty acid	Stabilization of hexamer and binding to serum albumin

Table 2: Analogues of Insulin

NOVEL APPROACHES-

1. ORAL MEDICATIONS:

In type 2 diabetes patient's blood sugar level gets elevated due to insulin resistance. Administration of oral medications help diabetics to controls blood sugar levels along with physical exercises. The oral medications act by various mechanisms to reduce the elevated blood glucose levels (Table 3).

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CLASS	EXAMPLE	ADVERSE EFFECTS
Sulfonylurea	Tolbutamide	Dark Urine, Hypoglycaemia,Bone Marrow Damage
Meglitinide	Repaglinide	Hypoglycaemia, Lactic Acidosis
Dipeptidyl Peptidase-4 Inhibitor	Sitagliptin	Nasopharyngitis , Urinary Tract Infection, Pancreatitis
Biguanide	Metformin	Hypoglycaemia, Lactic Acidosis
Thiazolidinedione	Pioglitazone	Hepatitis, Bladder Cancer, Macular Oedema, Heart Failure
α-Glucosidase Inhibitor	Voglibose	Gastrointestinal Side Effects, Hepatitis
SGLT-2 Inhibitor	Dapagliflozin	Urinary Tract Infection, Genital Yeast Infections, Upper Respiratory Tract Infections, Dyslipidaemia
Dopamine Agonist	Bromocriptine	Hallucinations, Somnolence, Impulse Control Disorders

Table 3: Classification of Oral Hypoglycaemic Agents

Sulfonylureas are one of the most popular and the earliest categories of antidiabetic drugs that act by increasing insulin production in body.

In 2019, US Food and Drug Administration approved an oral tablet is Rybelsus (semaglutide) along with proper diet and exercise for controlling blood sugar in adult patients with type 2 diabetes. It is the first oral glucagon-like peptide (GLP-1) receptor agonist. The other GLP-1 receptor agonist available are to be injected. GLP-1 drugs functions by mimicking hormone Incretin and it is a non-insulin treatment for people with type 2 diabetes.[5]

The Food and Drug Administration also approved the first oral therapy of using combination of three tablets in a single pill (Trijardy XR), which comprises of linagliptin, a dipeptidyl peptidase-4 inhibitor (Tradjenta), empagliflozin, a sodium glucose cotransporter inhibitor (Jardiance), and extended-release metformin hydrochloride which is a Biguanide, as a treatment of type 2 diabetes.[6]

Now, some researchers are focused on oral delivery of insulin, which is challenging because insulin is a protein and may breakdown in stomach itself hence will further get degraded. Oramed Pharmaceuticals conducted many researches and have designed oral insulin capsule for individuals with type 1 diabetes. This oral insulin capsule completed phase 2 clinical trial. They have used enteric coating and special protection which allows the insulin to stay intact through the GI tract and reach the intestinal wall without getting degraded via special absorption enhancers. The insulin passes through intestinal wall, then enters the liver, and starts its action. It mimics the natural path of insulin in the body, by entering in to the liver first. These oral capsules

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were used at different doses during trials and the result was excellent safety profile, no occurrence of any serious drug related adverse effect, no increased frequency of hypoglycemic episodes or weight gain, compared to placebo. Decrease in A1C levels was observed which a key indicator for diabetes ~~is~~. If the oral capsules get approval to come in market then it will revolutionize the treatment of Diabetes. By the result of the trials it has the potential to be the first commercial oral insulin capsule for the treatment of type 2 and type 1 diabetes.[7]As shown in fig.3[8]

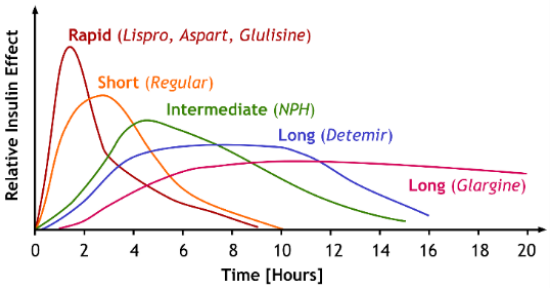

Fig 3: Insulin Analogues: Graphical Illustrations

2. INJECTIONS:

2.1. Semaglutide-

Injection is the act of putting a liquid drug into an individual's body employing a needle and a syringe. Injection is a technique for delivering drugs by parenteral administration, that is, administration via a route aside from through the alimentary canal.

OZEMPIC® (semaglutide) subcutaneous injection contains semaglutide, a human GLP-1 receptor agonist. The peptide backbone is produced by yeast fermentation. The main protraction mechanism of semaglutide is albumin binding, facilitated by modification of position 26 lysine with a hydrophilic spacer and a C18 fatty di-acid(fig 4)[9].

Fig 4: OZEMPIC® (Semaglutide) Subcutaneous Injection

Furthermore, semaglutide is modified in position 8 to supply stabilization against degradation by the enzyme dipeptidyl-peptidase 4 (DPP-4). A minor modification was made in position 34 to make sure the attachment of just one fatty di-acid. OZEMPIC®is a sterile, aqueous, clear, colourless solution. Each pre-filled pen contains a 1.5 mL solution of OZEMPIC® like 2 mg semaglutide. Each 1 mL of OZEMPIC®solution contains 1.34 mg of semaglutide and therefore the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propanediol, 14.0 mg; phenol, 5.50 mg; and water for injections. OZEMPIC®has a pH of approximately 7.4. Hydrochloric acid or caustic soda could also be added to regulate pH. Semaglutide may be a GLP-1 analogue with 94% sequence homology to human GLP-1. Semaglutide acts as a GLP-1 receptor agonist that selectively binds to and activates the GLP-1 receptor, the target for native GLP-1. GLP-1 may be a physiological hormone that has multiple actions on glucose, mediated by the GLP-1 receptors. The principal mechanism of protraction leading to the long half-life of semaglutide is albumin binding, which finally ends with decreased renal clearance and protection from metabolic degradation. Moreover, semaglutide is stabilized against degradation by the DPP-4 enzyme. Semaglutide

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reduces blood sugar through a mechanism where it stimulates insulin secretion and lowers glucagon secretion, both during a glucose-dependent manner. Thus, when blood sugar is high, insulin secretion is stimulated and glucagon secretion is inhibited. Semaglutide lowers fasting and postprandial blood sugar and reduces weight. The most common side effects of OZEMPIC® may include nausea, vomiting, diarrhoea, stomach pain and constipation. Serious allergic reactions, kidney problems, change in vision and low blood sugar are other side effects.[10]

2.2. Diamyd®Vaccine-

Vaccine is a preparation utilized to stimulate the production of antibodies and provide immunity against one or several disorders, prepared from the causative agent of a disorder, its products, or a synthetic substitute, treated to act as an antigen without inducing the disorder.

A vaccine composed of GAD_{65} protein formulated in combination with the well accepted adjuvant alum (a suspension of aluminium and magnesium hydroxide) known as "Diamyd®" (fig 5)[11].

Fig 5: Diamyd® Vaccine Vial

Because, aluminium salts preferentially induce a type 2 immune response rather than cell mediated immunity, it was used to minimize the potential of aggravating T cell mediated β-cell destruction. The purpose of this treatment is to protect the body's own ability to control the blood sugar level in children and adolescents newly diagnosed with type 1 diabetes. Present treatment strategies involve controlling the blood sugar level by adding external insulin, either by injections or by insulin pump. The aim is to attain a stable adequate blood sugar level. Constantly high and fluctuating blood sugar levels cause diabetes complications, including kidney and eye damage, cardiovascular disorder, nerve damage as well as severe hypoglycaemia and ketoacidosis. Diamyd Medical's drug development in diabetes originates from the protein GAD, which is the active substance in the Company's diabetes vaccine Diamyd® for the prevention and treatment of autoimmune diabetes. Treatment with Diamyd® is intended to prevent, delay, or stop the autoimmune attack on the beta cells. The aim is to prevent the onset of autoimmune diabetes, or to protect the body's capacity to adjust blood sugar. Studies have shown that even a very small preservation of endogenous insulin secretion and minor improvement of the blood sugar control can significantly reduce the risk of both acute and long-term diabetes complications. The mechanism of Diamyd® action is attributed to induction of a Th2 immune response. In addition, Diamyd® induced the expansion of T regulatory cell populations as measured by an increase in Foxp3+ T cells and secretion of anti-inflammatory cytokines IL-5, IL-10, and IL-13. Even though Diamyd® has been successful in preserving residual insulin secretion, it is not sufficiently effective to restore euglycemia in type 1 diabetes patients.[12]

3.GLUCAGON PEN:

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Glucagon pen contains an injection of glucagon, and works by triggering the liver to release stored sugar, raising blood glucose levels.[13]

GvokeTM comes as a single-dose prefilled HypoPen auto-injector and a single-dose prefilled syringe (fig 6)[14].

Fig 6: **Gvoke™HypoPen**

The new formulation which became available in 2020 in a single-use prefilled syringe in a single-use auto-injector. Unlike most available injectable glucagon products *GvokeTM* does not require reconstitution before administration. GvokeTM which contains the active drug glucagon is given as a subcutaneous injection the minute low blood sugar is noticed. Glucagon, made within the pancreas, is accountable for increasing blood glucose levels by signalling the body to release glucose stored in the liver into the blood. In type 1 diabetes, glucagon is impaired, and thus does not raise blood sugar correctly especially in conditions of accidental insulin overdose. When someone with diabetes has a seizure or becomes unconscious due to low blood glucose, administering glucagon will immediately raise blood glucose levels. People with diabetes who are on insulin or sulfonylureas are at the utmost risk of severe hypoglycaemia. GvokeTM belongs to a class of medications called glycogenolytic.[15]

GvokeTM is given by subcutaneous injection in the lower abdomen, the outer thigh, the outer side of the upper arm. The upcoming HypoPen involves two simple steps: first remove the cap; and then press the pen against the skin. Upon contact with the skin, the automatic injector will deliver an adjusted dose of glucagon and pull the needle back. GvokeTM has an early onset of action of about 15 minutes to raise blood sugar level. The GvokeTM HypoPen administers a liquid-stable but nonaqueous glucagon formulation that contains a human recombinant DNA–derived amino acid polypeptide similar to that used in the currently available GEK. Glucagon is an agonist for glycogen receptors, and thus initiates the conversion of stored glycogen into glucose and so increases the concentration of glucose in the blood.[16]

4. INHALERS:

Normally insulin is injected under the skin. Afrezza® is an artificial insulin powder made by MannKind Corporation that is inhaled using an inhaler device (fig 7)[17].

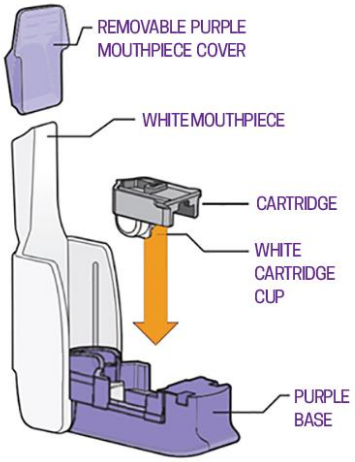

Fig 7: Inhaler device

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The inhaled insulin is absorbed into the blood stream faster than insulin that is injected. Afrezza® has an onset of 12-15 minutes and is excreted in about 3 hours. This means that Afrezza® works as a fast-acting insulin which can be used at meal time or to rapidly lower the high blood sugar level. In reality, Afrezza® works faster than the fastest injectable meal-time insulins such as Humalog, Novolog, or Apidra. The rapid on/off effects of Afrezza® can help in controlling blood sugar even better than traditional meal-time insulin and decrease the risk of hypoglycaemia because the insulin is excreted in 3 hours. It is possible to use inhaled insulin to control the blood sugar spikes with the meals, without injections. Afrezza® comes in color-coded single dose cartridges containing either 4 units (blue), 8 units (green), or 12 units (yellow) of inhaled insulin. A single cartridge is loaded into the small, hand-held inhaler device and is then inhaled. If higher doses of insulin are needed with the meal, 2 inhalations are taken per meal. Afrezza® should be taken immediately before a meal since it works very quickly. Afrezza® can be used for people with both type 1 and type 2 diabetes. Some common side effects are hypoglycaemia, decrease in lung function, possible risk of lung cancer, diabetic ketoacidosis, low potassium, allergic reaction, heart failure if taken with pill of thiazolidinedione (TZD).[18]

People with diabetes using Afrezza® have access to a novel Bluetooth accessory called BluHale that will guide them to understand if they're taking the medication properly and getting the proper dose. The idea is to build this to sooner or later to track and share all of the user's Afrezza® statistics. BluHale's chief function is to flash a green light if the Afrezza® is inhaled properly and a red light if it's not. It's being used as a training device, where doctors can view the tracked statistics and then offer their patients advice on how to best use Afrezza®. This device is compatible with Android, iPhone and Microsoft devices.[19]

5.PUMP:

An insulin pump provides continuous and steady delivery of short acting insulin throughout the day. The insulin pump is an alternative to the long-acting insulin. With a continuous insulin infusion by the pump, it can replace the multiple injections taken daily, and also aids to improve the blood sugar levels. Insulin pumps are small, computerized devices that imitate the way the human pancreas work by delivering small doses of short acting insulin. The device is used to deliver adjustable amounts of insulin when ingesting a meal. The basal insulin rates are usually set up in the pump under the guidance of a physician, there can be one or multiple basal settings programmed according to the need of the patient in the pump. The amount of insulin needed when ingesting a meal can be programme. Almost all pumps come with a built-in bolus calculator to help adjust the amount of insulin needed at mealtime based on the body glucose levels and the amount of carbohydrates eaten.

The pump, is the size of a smart phone or deck of cards, and can be comfortably worn on the outside of the body and will deliver insulin through a catheter, connected to a thin cannula, positioned

into the fat layer under the skin, typically around your stomach area. The pump can be worn around your waist in a pump case or attached to a belt or bra, in a pocket, or on an armband.

In general, there are two types of pump devices:

1. Traditional Insulin pumps have an insulin container and pumping apparatus, and attach to the body with tubing and an infusion set. The pump body has buttons that permit the programming of insulin delivery for meals, precise forms of basal rates, or suspend the insulin infusion, if essential.

2. Insulin patch pumps are worn directly on the body and have a container, a pumping mechanism, and infusion set inside a small case. The patch pumps are controlled wirelessly by a separate device that allows the controlled programming for insulin delivery from the patch during meals.[20]

Fig 8: Insulin Pump: OmniPod™

The OmniPod™ (fig 8)[21] is a small lightweight device that is worn on the skin like an infusion set. It delivers insulin according to pre-programmed instructions transmitted wirelessly from the Personal Diabetes Manager (PDM). The PDM is a wireless, hand-held device that is used to program the OmniPod™ with customized insulin delivery instructions, monitor the working of the OmniPod™, and check blood glucose levels using FreeStyle blood glucose test strips. There's no tubing connecting the OmniPod™ to the PDM. The OmniPod™ is worn comfortably and discreetly beneath the clothing, and therefore the PDM are often carried separately. Almost like currently available insulin pumps, the OmniPod™ Insulin Management System features fully programmable continuous subcutaneous insulin delivery with multiple basal rates and bolus options, suggested bolus calculations, safety checks, and alarm features.[22]

6.NANOTECHNOLOGY:

Nanotechnology is a technique of manipulating the matter on an atomic, molecular, and supramolecular scale. This technology is an emerging field in Medicine. This application of nanotechnology in medical field is termed as Nanomedicine. Nanomedicine includes drug delivery by using nanoparticles in different forms, biological devices and even nano electronic biosensors, with its growing use and research it may be possible in future to get biological machines based on this technology. Nanotechnology is a non- invasive technique for monitoring blood glucose level and delivers insulin by using nanoparticles, they can be more effective and efficient over traditional oral medicines.

1) Use of nanotechnology in monitoring blood glucose level-

• Smart tattoo-

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This nano tattoo is an innovative device which proves to be an advancement in monitoring diabetes. It is an implantable sensor which is to be implanted into the skin and can monitor individual's blood glucose level continuously. It contains biosensors array which are inserted intradermally that uses polyethylene glycol which is coated with fluorescent molecules that is in contact with interstitial fluid, which detects local changes in blood glucose level. When level of glucose decreases in interstitial fluid, fluorescent molecule gets displaced by glucose which causes implanted sensor to emit visible color changes. This color changes can be seen to the smart tattoo. Hence without pricking fingers change in blood glucose level can be detected.[23]

• Microphysiometer-

Microphysiometer is a sensor which is built from multiwalled carbon nanotubes, in which series of single walled tube are stacked on one another. These nanotubes act effectively at pH levels of living cells. It can detect even the small amount of insulin which is produced by pancreatic islets cells of Langerhans. As nanotubes are electrically conductive hence in presence of glucose, insulin gets oxidized which leads to electron transfer thus current at the electrode in the sensor increases which can be directly related to insulin concentration. It proves to have great sensitivity in detection of insulin levels.[24]

• Glucose sensors-

Use of nanostructured materials in glucose-sensors by introduction of electrochemical mediators such as ferrocene and ferrocyanide can modify nanotubes. And it can also be done by combination of Carbon nanotubes with other nanoparticles like noble metals (gold, silver, platinum) or titanium dioxide, silica. This will improve catalytic activity and sensitivity measurement of sensors.[25]

2) Use of nanotechnology for drug delivery-

• Use of polymers

Polymeric nanoparticles are solid colloidal particles in range of 10-1000nm. These are formulated from the polymers, which have the nature of bio-compatibility, bio-adaptability and are bio-degradable. The polymers used for formation of polymeric nanoparticles can be either natural or synthetic. Insulin is hydrophilic in nature hence cannot permeate intestinal epithelium. Hence this approach is to improve insulin absorption from GIT and modulate insulin release. Chitosan is a natural

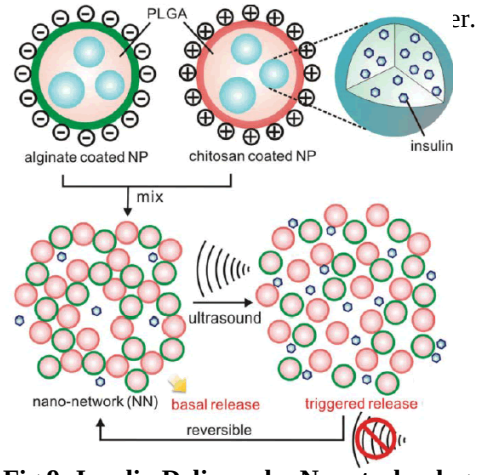

Fig 9: Insulin Delivery by Nanotechnology

By encapsulating insulin in the shell of carboxylated chitosan (fig 9)[26] grafted poly (methyl methacrylated) nanoparticle can make insulin delivery more efficient. Some insulin loaded nanoparticles which are prepared by using biodegradable polymers such as poly(lactide-co-glycoside), polyanhydride and polyalkyl cyanoacrylate, poly(E-caprolactone) combined

with acrylic polymer are absorbed from intestinal epithelial cells and transport insulin through intestinal mucosa. Lectin-polystyrene nanoparticles causes two-fold increase in absorption. Some preparation methods used are Complex coacervation method using chitosan or sodium alginate, Ionic gelation method using chitosan/ poly(γ-glutamic acid) or alginate.[2728]

• Dendrimers-

Dendrimers are well-defined 3-D homogenous nanosized structures and has tree-like branches. The characteristics of dendrimers like high branching, a well-defined globular structure, excellent structural uniformity, variable chemical composition, multivalency and having high biological compatibility, makes these compounds ideal carrier for drug. Polyamidoamine (PAMAM) is often used as a dendrimer due to its absorption-enhancing effects which can improve insulin absorption via the nasal route of administration without damaging surrounding epithelial tissue which is important factor for insulin delivery through nasal route. The positive charge of PAMAM may have a role in this characteristic. This was studied in a research which was conducted by Department of Biopharmaceutics, Kyoto Pharmaceutical University, Japan. More research is going on to study dendrimers for administration of drugs, because of its impressive characteristics.[29]

• Nanogels-

Nanogels are 3-D hydrogel materials on a nanoscale formed by cross-linked swellable polymer networks that are able to retain large amounts of water without being solubilized. By using pH sensitivity release insulin can be properly regulated. When it gets bind to glucose, amino phenylboronic acid (PBA) functionalized nanogels causes shift in their ionization equilibrium, and thus increases the anionic charge density of the gel, causing gel to swell. Once the gel gets swollen it leads to release of insulin and after that gel shrinks once glucose levels return to normal. In a certain research hydroxypropyl methylcellulose (HPMC) nanogels were synthesized without the need for a surfactant and thus with no use of organic solvent, making this a green environmentally friendly method. This system showed that release of insulin from nanogel is temperature and pH dependent.[30]

• Micelles-

Micelles are nanosized colloidal dispersions prepared from amphiphilic molecules and have a hydrophilic head and a hydrophobic tail. The hydrophobic core which is the tail part plays a role of reservoir for hydrophobic drugs and this hydrophobic core is stabilized by hydrophobic shell. These polymeric micelles are formed by amphiphilic copolymers which self-assembled to nanosized aggregates above the critical micellar concentration. The mechanism of insulin delivered by Nano micelles is dominated by endocytosis, that is greatly affected by the surface properties of the nanocarriers used. Some of preparation methods are Dialysis method which uses materials like [PEG-b-P(Asp-co-AspPBA) and P(Asp-co-AGA) and the other method is Film formation using N-octyl-N-arginine chitosan.[31]

3) Nanopump-

Nanopump is a smart and flexible infusion pump. It can control delivery of insulin which is almost

close to the natural physiological secretion of insulin due to microfluidic technology. This pump also allows the subcutaneous infusion of many other pharmaceutical compounds with feature of freely adjustable delivery profile as required. The first application of the pump of insulin delivery was introduced by Debiotech. The pump injects insulin to the patient's body at a constant rate, maintaining the amount of sugars in individuals' blood. The pump can also administer smaller doses of drug for a long period of time.[32]

4) Nanocapsules-

A recent research which was carried out by Dr. Hani Al-Salami, from the Curtin Health Innovation Research Institute (CHIRI) and the School of Pharmacy and Biomedical Sciences at Curtin University about tiny capsules developed using bio-nanotechnologies and it was filled with a combination of the lipid-lowering drug Probucol and human-based bile acids. They found out that this combination could target the inflammatory effects of diabetes in mouse models for about a period of six month. These nano capsules protected the active drugs during the process of digestion and absorption, that enhanced uptake of bile acids and Probucol in the liver and pancreas, which are typically inflamed in diabetes. Hence it was found effectual in reducing inflammatory effects related to diabetes and reducing high-blood sugar levels in animal models with diabetes.

These advances in nanotechnology have expanded many potential routes for insulin delivery. Nano-insulin delivery has widened the choices for treatment of diabetes which is giving a lot of support to researchers. With an aid of nano delivery high bioavailable doses can be delivered.[32]

7. ARTIFICIAL PANCREATIC SYSTEM:

Hybrid Closed Loop Systems, they take an insulin program and uses technology to produce better results. It includes a continuous glucose monitor, an insulin pump, and a computer program known as algorithm that takes data from insulin pump, continuous glucose monitor and automatically adjusts basal insulin delivery, mimicking some function of healthy pancreas thereby maintaining blood glucose level closer to specific target. [33]

Medical algorithm is computerized health diagnostic approach which is used with a purpose to improve and standardize decisions made in the delivery of medical care.

If patient uses CGM and pump, it is possible to get good time in range with well-timed meal boluses, counting carbs, managing your diet and hence eating relatively low-carb.[34]

Some closed loop systems developed are Medtronic's 670G™ hybrid closed loop system (fig 10)[35], loop, Open APS™, etc.

Fig 10: Hybrid Closed Loop Systems: Medtronic's 670G™

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The first FDA approved system was the Medtronic 670G™. Recently FDA authorized an algorithm that enables the second artificial pancreas system that is The Tandem® Control-IQ advanced hybrid closed loop technology. It's the first algorithm authorized as an interoperable automated glycaemic controller. The algorithm can be used with Tandem's t: slim X2 insulin pump® and Dexcom's G6 Continuous glucose monitor®.

This system requires Patient's accurate information, such as basal profile, insulin:carb ratio, insulin sensitivity factor. This system reduces hypoglycaemia (low blood sugar), increases time-in-range (70-180 mg/dl), and lowers A1C.[36]

Advantages of this program-

1) Gives automated boluses- It gradually increases basal insulin by increasing CGM value and administers 60% correction boluses once an hour to correct for high blood sugars.

2) Does not require finger sticks from users for CGM calibration.

3) Smooth Basal Rate Attenuation- It smoothly decreases or discontinues basal delivery based on falling CGM values to help prevent hypoglycaemia.

This technology is not used for patient-

1) Under the age of six

2) Who requires less than 10 units insulin per day

3) Who weighs less than 55 pounds

Many more organizations are working to bring automated insulin delivery into the market. Some are still under research; few are under trial and few are under FDA review.[37]

8. BETA CELL REGENERATION:

Beta cells are a kind of cell found in pancreatic islets of Langerhans which synthesize, store and secrete amylin and insulin (fig 11)[38].

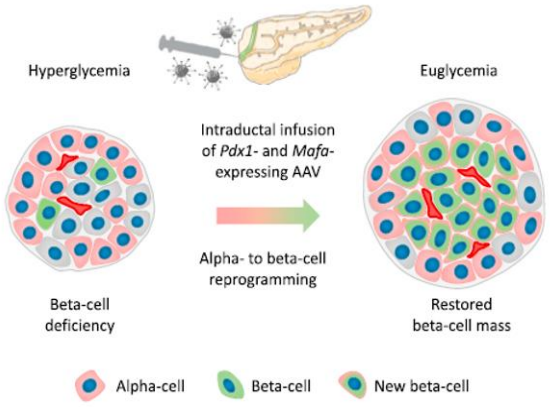

Fig 11: Beta Cell Regeneration

Beta cells make up 70% of the cells in human pancreatic islets. Insulin plays a crucial role for regulating glucose level in blood. Beta cells immediately responds to rise in blood glucose levels by secreting some of their stored insulin and amylin while simultaneously producing more. Insulin helps the cells to absorb glucose, which provides energy thus reduces blood sugar level. In type 1 diabetes autoimmune reaction takes place destroying insulin producing beta cells.

With increasing prevalence of diabetes, researchers are working on many potential treatments one of them being beta cell regeneration. As beta cell plays a crucial role for insulin production, hence researchers are working on various strategies and approaches for beta cell regeneration.

A recent study conducted at Icahn School of Medicine at Mount Sinai, published in Science Translational Medicine about a novel combination which proliferate beta cells. They wanted a drug

which can increase the proliferation rate of beta cells. They found out that when GLP-1 receptor agonists, which is employed to treat type 2 diabetes when combined with any member of the DYRK1A inhibitor class then it can be converted into "potent beta-cell regenerative drugs". This combination shows high levels of replication, within the range of 5% to 8% and in some case, it may show higher which can be up to 20%. This study shows that using islets from organ donors, from individuals without diabetes, and also from islets of individuals with type 2 diabetes. It enhances their beta-cell proliferation rate and increases their ability to secrete insulin. They took SCID mice, made them diabetic, then transplanted only enough human islets which will bring them just close to improving their diabetes. They further found when these mice are treated with Harmine and the GLP-1 receptor agonist exenatide (Byetta, AstraZeneca), their diabetes improved almost completely.

Limitations of this research:

1) Human islets live in tissue culture for only few days; hence it is not possible to conduct studies for longer time.

2) It is still not studied about how long will be the proliferation time and what will happen if drug delivery is stopped, will it stop proliferation or not.

3) GLP-1 receptor agonist acts on beta cells and also few other cell types like hypothalamus which stimulates some intestinal action. So, there are high chances of other cells such as of intestine or hypothalamus may proliferate which can create a problem because we only want beta cell proliferation.

Till now no molecule is identified which will only act on beta cells.

Hence there is need to find a way to proliferate beta cells, but delivery method is yet to be found.[39]

9. ISLET CELL TRANSPLANTATION:

The pancreas contains group of cells that produce and secrete hormones. These groups are known as islets. In an islet several different type of cells can be found. One of the types is beta cells that is responsible for production of hormone insulin that helps the body to use glucose for energy and thus lowering the glucose level. Islet cell transplantation is one of the ongoing researches for treatment of Diabetes. It is a process of separating the islet cells from a pancreas of deceased organ donor and then transplanting these cells into a person with type 1 diabetes. These cells begin to make and release insulin, which will improve the blood glucose level (fig 12)[40].

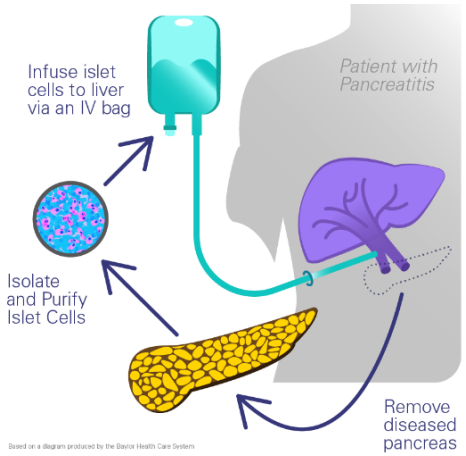

Fig 12: Islet Cell Transplantation

The biggest advantage of this treatment is that people with type 1 Diabetes can live without daily insulin injection.[41 42]

This therapy has some challenges which we need to overcome. Transplantation of islets is not like

transplanting a solid organ such as a heart or kidney. While transplanting a solid-organ, the organ's blood vessels are surgically connected to the patient's circulatory system, so right away the transplanted tissue gets good blood flow and plenty of oxygen. But during islet cell transplantation it involves isolating just the islets from the pancreas of a deceased donor by insertion of a thin, flexible tube which is known as catheter through a small cut in the recipient's upper abdomen. X-rays and ultrasound techniques are used to guide the catheter into the portal vein of the liver. The islets are slowly infused through the catheter and into the liver by gravity. Alternative to it, a minimally invasive open procedure can be used to directly visualize a vein near the liver to insert the catheter. These cells are not directly injected into pancreas because the pancreas is a fragile organ that also synthesize digestive enzymes. If pancreas gets disturbed it tends to start digesting stuff, which is very harmful. After transplantation of islet cells, it is very important that those cells should get a proper blood supply otherwise they may die because due to lack of blood supply cells won't get enough oxygen to stay alive. After injecting these cells in liver there can be chances of development of antibodies against the donor cells. Hence immunosuppressants are given as long as transplanted cells are working. [43]

Clinical trials have shown that in patient with type 1 diabetes islet transplantation is the only method, other than transplanting whole pancreas, which can restore the process of natural insulin production in patients. Still this method is not so common because more research and clinical trials are going on to overcome the challenges. [44]

10. USE OF PROTEIN ADIPSIN:

The major problem associated with type 2 diabetes is that the beta cells do not function properly and eventually start to die. The protein Adipsin, which is produced in body fat is a serine protease synthesized by adipocytes, that helps in protecting the pancreatic beta cells which secrete insulin from destruction in type 2 diabetes. Among most of the middle-aged adults, higher levels of the protein in the blood is directly proportional with protection from type 2 diabetes. Some of the medicines available in the market that target beta cells have side effects, such as extreme lowering of blood glucose levels. Patients with type 2 diabetes that have dysfunctional beta cells have to inject insulin to keep their blood glucose levels stable. After various studies, it has been found that protein Adipsin had a continuing positive effect on diabetes by not only improving blood sugar levels but also by increasing insulin levels while helping in preventing beta cell death.

After studies were conducted in the laboratories on beta cells, it was understood that the protein Adipsin activates a molecule called C3a, which protects and supports beta cell function. Later they found that C3a suppresses an enzyme called DUSP26 which causes damage to beta cells and kills those cells. The researchers then directly blocked the activity of DUSP26 in human beta cells and found that this treatment protected the beta cells from fading away. Likewise, when they suppressed DUSP26 activity in mice, beta cells became healthier, secreted more insulin. Either of

these therapies may prevent type 2 diabetes patients from developing beta cell failure and from requiring insulin injections.

People with the highest level of Adipsin had more than a 50% reduction in diabetes incidence compared to the people with the lowest level of Adipsin. Also, Adipsin levels are correlated with the amount of subcutaneous fat, which is stored just under the skin, rather than visceral fat, stored within the abdomen.

Further studies are needed to know whether a better level of Adipsin in humans will protect them from developing diabetes and whether increasing Adipsin levels would scale back the danger of developing diabetes in society.[45]

11. USE OF PROBIOTICS:

Diabetes Mellitus has become major threat to human health because of its growing incidence. Majority of diabetic patients have Type 2 Diabetes Mellitus which is metabolic disorder characterized by increase in fasting glucose level and glycosylated haemoglobin (Hb1Ac), insulin deficiency and resistance. Other than this it also alters the other functions like Gastrointestinal function, physical activities and dietary behaviour. In some recent studies it was proved that host's gut microbiota plays a crucial role in development of Diabetes Mellitus especially in Type2 DM. [46]

Type 2 DM is associated with gut microbial dysbiosis. It has been observed that population of harmful microbe increases and there is reduction in beneficial microbes. This dysbiosis favours an increased ratio of Firmicutes to Bacteroidetes, the two dominant phyla within the GI tract, and a reduced presence of lactic acid producing species from the genera Lactobacillus, Bifidobacterium, and Streptococcus. Therefore, improving the gut microbiota can help in managing Diabetes. The main function of gut microbial flora is to carry out proximal digestion of carbohydrates and ferment indigestible oligosaccharides, and synthesizes short-chain fatty acids (SCFA), such as acetate, butyrate and propionate by local fermentation. SCFA stimulates release of two hormones, one is glucagon-like peptide-1 (GLP-1) which promotes glucose homeostasis and decreases appetite by stimulating central nervous system action, delays gastric emptying thus regulates postprandial glucose and the other hormone is peptide YY gastrin found in enteroendocrine cells also regulates food intake, insulin secretion and regulates intestinal gluconeogenesis. Both these hormones inhibit gastric juice secretion and peristalsis action. Therefore, T2DM related factors like fasting blood glucose level, weight, insulin secretion can be regulated.[47]

Probiotics are live microorganisms (usually bacteria) that are almost like to beneficial microorganisms found with the human gut that has are useful for the body hence may be taken as dietary supplements or found in foods. When administered in adequate amounts, confer health benefit on host because of its health promoting property. Probiotics exert many positive health effects throughout the body including production of short- chain fatty acids (SCFAs), inhibition of harmful bacterial growth, stimulates immune response, modification of GI tract pH balance,

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manages intestinal disorder. It has beneficial effect on glucose metabolism and improves insulin sensitivity. The administration of probiotics containing bacterial species from the genera Lactobacillus, Bifidobacterium, and Streptococcus could identify this metabolic alteration by inducing Favorable shift in microbial profile, positively modify glucose metabolism, and improve glycaemia outcomes.

Many studies have been conducted for studying effect of probiotics. Some shows that probiotics treatment reduces glycosylated hemoglobin (HbA1c), Fasting blood glucose (FBG) or insulin resistance (IR) significantly in T2DM patients while other studies did not find significant difference. But researchers are still working on this and trials are been conducted.

Hence probiotics can be a new approach for managing Type 2 Diabetes Mellitus through correction of diabetogenic gut microbial dysbiosis by administration of probiotics.[48]

12. HOMEOPATHY TREATMENT:

Homeopathy is one of the most prevalent alternative system of medicine based on the two fundamental principles “law of similarities” and “minimal dilution”. Homeopathy follows the natural laws of healing and uses medicine made from natural substances viz. animal, vegetable and mineral origin. Some significant homeopathic oral hypoglycaemic drugs are *Rhus aromatica*, *Syzygium jambolanum*, *Uranium nitricum*, *Gymnema Sylvester* and *Acid Phos*.[49]

Fig 13: Homeopathy Treatment: *Syzygium Jambolanum*

Syzygium jambolanum(S jambolanum) (fig 13)[50] is said to be the most useful remedy with an immediate effect against diabetes mellitus. There is no other remedy that shows such a marked degree of diminution of sugar in the urine. Mother tincture of *S jambolanum* is widely used by homeopathy doctors for control of diabetes. Mother tincture is defined as the original tincture prepared with the aid of alcohol, directly from the crude drug. It acts as the precursor for the preparation of diverse potencies and the preparatory point for the production of homeopathic medications. In the past few years, the number of preclinical studies aiming at the activity and efficacy of homeopathy medicines has increased. The scientific studies on homeopathic remedy for diabetes is very little. The study has been conducted to determine the pharmacological activity of *S jambolanum* on Streptozotocin (STZ) induced diabetic animal model. The motive is to find out the anti-diabetic mechanism of action on these animal models in connection to the partial destruction of β-cell of the

islets which leads to deficient release of insulin and thus increases the blood glucose levels namely hyperglycaemia. Administration of homeopathic remedy *S jambolanum* has a stimulatory effect on remaining β-cells to produce insulin or regeneration of pancreatic β-cells to significantly reduce the elevated blood glucose level. The corrective effect of the *S jambolanum* was observed from the assessment of the activities of hepatic hexokinase, glucose-6-phosphate dehydrogenase those are significantly increased in mother tincture treated diabetic group, indicate the insulinotropic effect as these enzymes are regulated positively by insulin. Significant decrease in the activity of hepatic glucose-6-phosphatase by this drug indicates insulinotropic effect of the drug as this enzyme is regulated negatively by insulin. This result was supported from the increased levels of glycogen in liver and skeletal muscle in mother tincture treated group which shows that the effect on hyperlipidaemia may be due to the control of hyperglycaemia. Oral administration of *S jambolanum* to diabetic rats significantly decreased the activities of the responsible enzymes, and thus showing hepatoprotective nature of *S jambolanum* mother tincture. Consequently, from the study it was understood homeopathic drug *S jambolanum* indeed has positive effects on diabetes management in rats. Recently, a study demonstrated that ethanolic extract of *S jambolanum* has a great potential in therapeutic use as anti-diabetic drug. Although the exact mechanism is unknown, which can be determined by doing more research. However, an ameliorative effect of mother tincture of *S jambolanum* on diabetic complication in STZ-induced diabetic animals has been observed.[51]

13. PARTIAL JEJUNAL DIVERSION:

Partial jejunal diversion (PJD) involves the creation of side-to-side anastomosis that allows a portion of nutrients to bypass the intact loop of bowel while the remaining portion of nutrients follows the common path of intestinal transit. Partial jejunal diversion may provide an anatomy sparing, low-risk, potentially reversible, metabolic procedure for patients with poorly controlled T2DM, which does not impose significant alterations in lifestyle.[52]

This was a single-arm first-in-human pilot study designed to evaluate the technical feasibility, safety, and clinical performance of the Incisionless Magnetic Anastomosis System (IMAS) to create a Partial Jejunal Diversion (PJD). Fifteen patients with obesity and Type 2 diabetes mellitus, prediabetes, or no diabetes were enrolled. A PJD to the ileum was attempted in all patients under general anaesthesia. The IMAS was delivered through the working channel of a colonoscope, with laparoscopic supervision. The patients were not required to participate in an intensive lifestyle/diet management program. Endoscopic visualization of the anastomosis was obtained at 2, 6, and 12 months. Patient weight, glycaemic profile, and metabolic panels were acquired at 0.5, 1, 2, 3, 6, 9, and 12 months.

Mean HbA1c and fasting blood glucose were found to be significantly lower by 2 weeks after PJD, and continued to decrease over 12 months. Eight of 15 patients (53.3%) had a >2% absolute reduction and

11 of 15 patients (73.3%) had a >1.5% absolute reduction in HbA1c 12 months post-PJD, and 7 patients (46.7%) had achieved a HbA1c <7.0%. Compared with baseline at 12 months post-PJD, Oral Glucose Tolerance Test (OGTT) showed a significant decrease in blood glucose area under the curve (AUC), a significant increase in β-cell function, a significant increase in GLP-1 AUC, and an increase in whole-body insulin sensitivity. Based on the improvements in oral glucose tolerance in a rodent model of diet-induced obesity and metabolic impairment, PJD demonstrated potential as a surgical approach to treat Type 2 diabetes mellitus. The data shows that PJD is mildly or non-malabsorptive depending on distance of the intestinal loop along the GI tract. The data show that PJD has the potential to benefit oral glucose handling without causing pronounced or drastic significant malabsorption or changes in body weight in a pre-clinical rat model. We do not yet know if, or, how these findings will translate to PJD in humans.[53]

14.STEM CELL THERAPY:

Stem cells are undifferentiated or partially differentiated cells which has ability to differentiate into various types of cells and divide indefinitely to produce more of the same stem cell. They are specialized cells found in body which can differentiate into any specific cell, thus can be of therapeutic use.

The different types of stem cells are-

1. Embryonic stem cells-These stem cells come from embryos that are three to five days old. Embryo at this stage is called a blastocyst and has about 150 cells. They are harvested during a process known as in-vitro fertilization. These embryonic stem cells are known as pluripotent stem cells. They have ability to divide into many other stem cells and then can differentiate into any human cells.
2. Adult stem cells-These stem cells are found in brain, blood vessels, pancreas of adult, bone marrow or fat. Adult stem cells have a limited ability to differentiate in to various other cells of the body, as Compared to embryonic stem cells. These stem cells play an important role for maintenance and repair of the tissue in which they are found. This type of stem cells remains dormant for years and are activated by disorder or some tissue injury.
3. Induced pluripotent stem cells-These stem cells are derived from skin or blood cells that have been genetically reprogrammed in laboratory back into an embryonic-like pluripotent state that enables the development of an unlimited source of any type of human cell needed for therapeutic purposes. Therefore, they can be used in treatment of a disorder tissues or organ.
4. Perinatal stem cells-These stem cells are derived right before or after birth. Perinatal stem cells include those obtained from the umbilical cord blood and tissue, amniotic tissue and amniotic fluid and the placental blood and tissue. These stem cells also possess the ability to change into specialized cells.[54]

By using stem therapy, we can differentiate stem cells into insulin producing beta cells which can help in treatment of diabetes (fig 14)[55].

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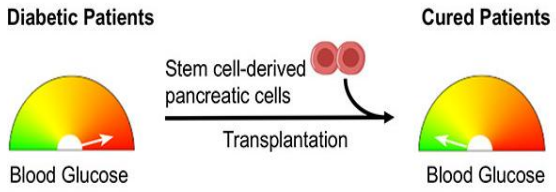

Fig 14: Stem Cell Therapy

Researchers conducted a study by differentiating human embryonic stem cells into functional β cells by in vivo process. The other types of stem cells as mentioned above like adult stem cells and induced pluripotent cells also have potential to produce insulin-producing beta cells. Hence this can help in increasing and maintaining insulin levels in the body.

As there is complexity in current in vitro beta cell differentiation protocols due to the high number of differentiation steps. The current beta cell differentiation process requires almost 20 signaling proteins and small molecules to regulate the growth and differentiation of the cells and lasts for few weeks. While undergoing this multi-step process not all cells differentiate into the targeted cells because some opt for wrong pathway which can lead to a highly heterogeneous cell population with some beta cells being nonfunctional. To overcome this problem researchers have studied and developed an improved pluripotent stem cell differentiation protocol to generate beta cells in vitro which will give superior glucose response and insulin secretion at Technical University of Munich (TUM) and Miltenyi Biotec. The researchers developed an approach to enrich the quality of stem cell culture with highly specialized pancreas progenitors (they are already specified at the endoderm stage) which could lead to a more targeted differentiation into beta cells. They wanted possibility to better control the quality of the endoderm and its differentiation into specified pancreas progenitors. They identified a monoclonal antibody called CD177 which marks a subpopulation of the endoderm that efficiently and homogenously differentiates into specified pancreatic progenitors. Proper differentiation was seen by using CD177. And this didn't lead to heterogenous cell population. It caused improvement in homogeneity of beta cells, which were more mature, more functional and similar to beta cells found in human body. There was collaboration between Helmholtz Zentrum München, the German Center for Diabetes Research (DZD), Technical University of Munich (TUM) and Miltenyi Biotec for this study. It was funded by the German Center for Diabetes Research (DZD), the EU consortium HumEN.[56]

So according to various studies stem cell can be a potential permanent treatment for diabetes.

Comparative studies are required for its future use.

More clinical trials are going on for proving it effectiveness and overcoming all the drawbacks.

ViaCyte® presented positive preliminary data from the PEC- Direct® trial. The data shows that their PEC-01 cells are capable of manufacturing C-peptide in patients with Type 1 diabetes. C-peptide may be a short chain of amino acids that's co-produced within the formation of insulin by the pancreas and is co-released into the blood proportionally to insulin. It is a calibre biomarker in the field for evaluating the amount of functional insulin-

producing pancreatic beta cells, used because its measurement is not bemused by injected insulin.PEC-01 cells are derived from stem cells and designed to mature into human pancreatic islet cells, including glucose-responsive insulin-secreting beta cells, following implant.PEC-01 cells are pancreatic precursor cells derived from CyT49 pluripotent stem cell line. PEC-01 cells are implanted in both the PEC- Direct® and PEC-Encap®. The data show initial detection of C-peptide and insulin production through histological and biochemical measurements at multiple time points in multiple patients; detection of C-peptide has correlated with engraftment efficiency. Previous histological data have shown that, after PEC-01 cells are implanted under the skin and when properly engrafted, they will mature into functional beta cells and other cells of the islet that are responsible for controlling blood glucose levels.The PEC- Direct® trial focuses on implanting PEC-01 cells in patients with Type 1 diabetes who are considered to be at high risk for complications, including coma and death, and still requires the use of immunosuppressive drugs. Many of these patients are also eligible for cadaver islet transplants, however cadaver islet cells are in short supply. PEC-01 cells, which may be produced during a lab in potentially unlimited quantities, provide a possible solution to the availability issue.ViaCyte®is currently conducting another trial using an equivalent PEC-01 cells called PEC-Encap®, which might deliver the cells from an encapsulated device and wouldn't require the utilization of immunosuppressants. The positive data reported from the PEC- Direct® trial is good news for PEC-Encap® also.[57 58]

15. GENE THERAPY:

Gene therapy for diabetes is a longstanding idea, and this topic was studied several years ago. Gene therapy is a stratagem correcting or compensating the symptoms of disorders caused by malfunctioning or abnormal genes through introduction of exogenous normal genes. The benefit of gene therapy is that the disorders could be cured by a single treatment and thus brings new treatment option to the field of medicine. At present, the manipulation of genetic material is restricted to not only gene addition but also to gene regulation and editing.

Potential targets can be used for Type 2 Diabetes Mellitus gene therapy.

1.Genes regulating glucose homeostasis are:

- Glucose Transporters re-absorption of filtered glucose from the kidney into the bloodstream.
- Sodium-Glucose Co-Transporters plays a fundamental role in the muscle and liver glucose fluxes.
- Fibroblast Growth Factors plays significant roles in glucose homeostasis.
- Sirtuin 6 is associated with increased glycolysis and glucose transporters expression.

2.Genes improving insulin secretion and/or sensitivity are:

- Glycogen Like Peptide and its analogues/agonists increase beta-cell survival, stimulate insulin gene expression, and secretion.

- G protein–coupled receptors and their agonists stimulate insulin and Glycogen Like Peptide secretion.
- Cholera Toxin B Subunit and Active Peptide from shark liver promotes insulin secretion and insulin resistance.
- IκB kinase ε and TANK-binding kinase 1 are associated with weight reduction, insulin resistance, fatty liver, and inflammation.

3.Genes ameliorating diabetic induced complications are:

- IL-1b is associated with inflammation and b-cell failure.
- Adiponectin ameliorates diabetic nephropathy.
- Transforming Growth Factor-α plays a role in diabetic kidney disorder associated with nephron reduction.
- Nucleotide-Binding Oligomerization Domain-like receptor Protein 3 ameliorates diabetic cardiomyopathy.
- Cyclin-Dependent Kinase Inhibitor 2A/2B are associated with T-cell phenotype modulation and chronic inflammation.
- Heat Shock Protein 70 is associated with mitochondrial bioenergetics and diabetic sensory neuropathy.
- MicroRNAs involved in regulating the diabetic microvasculature.

The accomplishment of gene therapy requires suitable gene delivery systems or vectors to provide the therapeutic effect where it may be needed. Therefore, understanding of how to deliver the genes is equally important as the identification of gene target. Depending on the vectors used for loading/delivering genes, these methods can be classified into viral gene delivery and non-viral gene delivery. Virus packaged genes can be either injected or orally administered by taking advantage of the natural ability of viruses to enter cells and to transfer their genetic material to the nucleus and express proteins. In recent years, delivery systems based on bacteria like probiotics have been quickly developed and orally applied, and provide more efficient alternatives to traditional non-viral delivery systems.[59]

16. STEM CELL THERAPY+GENE THERAPY:

Using induced pluripotent stem cells produced from the skin of a patient with a rare, genetic form of insulin-dependent diabetes called Wolfram syndrome, researchers transformed the human stem cells into insulin-producing cells and used the gene-editing tool CRISPR-Cas9 to correct a genetic defect that had caused the syndrome. Patients with Wolfram syndrome develop diabetes during childhood or adolescence and quickly require insulin-replacement therapy, requiring insulin injections multiple times each day. Most go on to develop problems with vision and balance, as well as other issues, and in many patients, the syndrome contributes to an early death. Wolfram syndrome is caused by mutations to a single gene, providing the researchers an opportunity to determine whether combining stem cell technology with CRISPR to correct the genetic error also might correct the diabetes caused by the mutation. The CRISPR-Cas9 technique may hold promise as a treatment for diabetes, particularly the forms caused by a single gene mutation, and it also may be useful one day in some patients with the more common

forms of diabetes, such as type 1 and type 2.In this study, they took the additional steps of deriving these cells from patients and using the CRISPR-Cas9 gene-editing tool on those cells to correct a mutation to the gene that causes Wolfram syndrome. Then, the researchers compared the gene-edited cells to insulin-secreting beta cells from the same batch of stem cells that had not undergone editing with CRISPR. In the test tube and in mice with a severe form of diabetes, the newly grown beta cells that were edited with CRISPR more efficiently secreted insulin in response to glucose. Diabetes disappeared quickly in mice with the CRISPR-edited cells implanted beneath the skin, and the animals' blood sugar levels remained in normal range for the entire six months they were monitored. Animals receiving unedited beta cells remained diabetic. Their newly implanted beta cells could produce insulin, just not enough to reverse their diabetes. In the future, using CRISPR to correct certain mutations in beta cells may help patients whose diabetes is the result of multiple genetic and environmental factors, such as type 1, caused by an autoimmune process that destroys beta cells, and type 2, which is closely linked to obesity and a systemic process called insulin resistance.

The researchers said that the process of making beta cells from stem cells should get easier. For example, the scientists have developed less intrusive methods, making induced pluripotent stem cells from blood and they are working on developing stem cells from urine samples.[60]

17. IMMUNOTHERAPY:

Immunotherapy is the treatment for disorder which works by either activating or suppressing the immune system. As we know that Type 1 Diabetes is an auto immune disorder where the immune system detects insulin-producing beta cells as foreign and destroys them. A major player in this autoimmune response is a group of immune cells called T-cells. For this reason, the immune system also including the T-cells, becomes a target for managing the underlying cause of T1D. By inhibiting of the attack of T-cells it may help in protecting beta cells. So, to target inhibition of immune system mainly T-cells, antibodies can be used. Some approaches for inhibiting autoimmune response are

1) Antibodies are being developed that targets a molecule called CD3 for suppressing auto immune response. These antibodies get bind to CD3, thus preventing CD3-mediated activation of T-cells. Teplizumab is a monoclonal antibody which is anti-CD3. Thus, it prevents beta-cells from getting destroyed and preserve its function. Furthermore, in a recent study, it delayed the onset of T1D in individuals with high risk. This observation highlights it as a potential preventative treatment.

2) Other antibodies that can be used for T1D therapy are the one that acts against interleukin-1 and tumor necrosis factor-alpha (TNF-α), which are signaling molecules involved in inflammation and destruction of beta cells. Antibodies against IL-1 and TNF-alpha, will inhibit these molecules and hence prevents beta cells destruction which will benefit T1D patient. Recently Imcyse is developing an immunotherapy that involves injecting a molecule that makes the system produce a new

type of immune cell. These cells will specifically target those immune cells that destroys pancreatic cells and will kill them. This mechanism is specific to Type 1 diabetes and to pancreas, hence there is no harm to general immune defenses or other organs. If this research proved to be effective then this treatment could stop destruction of insulin-producing cells. Especially those who are recently diagnosed with disorder. Early after diagnosis, between 3 to 6 months, it is estimated that around 10% of the insulin-producing cells are still alive and produces insulin. After termination of the autoimmune process, the remaining beta cells would be protected and could continue producing insulin. But trials are still going for this. Earlier results suggest that this therapy could be promising and hence can move further with trial.

3) Administration of certain immunomodulatory cells may help alleviate the aggressive immune response against beta cells. A group of cells called tolerogenic dendritic cells are known to suppress the immune response through various mechanisms. A clinical study was conducted and it was found that by administrating these cells with regulatory T-cells can prevent or reduce beta-cell destruction by the immune system.

4) One of the new approaches is to develop regulatory T-cells expressing certain receptors that enable the cells to specifically target the pancreatic beta cells (CAR-T cells). This would reduce any unwanted effects of the cells at other non-target regions of the body and thus increases the effectiveness of the therapy.

Such many new approaches are being studied. The future of type 1 diabetes treatment will not be limited to insulin injections. By using Immunotherapy an individual can get a permanent treatment for Diabetes. [61 62 63]

CONCLUSION:

In our article we have covered some of the novel ways for treating diabetes which is going to expand with the continuous advancement in research and development. Newer diabetes treatment includes usage of large range of devices, stem cells, immunotherapy, cell transplantation working on different methodologies. Researchers are working on many novel approaches and we have better evidence-based information which helps in improved treatment. This has proved to be beneficial for diabetic patients in improving health and managing complications associated with it. The research is not just limited to drug delivery, but includes monitoring and control of blood glucose level. In near future the face of diabetes treatment will progress and will not be limited to just insulin therapy.

CONFLICT OF INTEREST:

The authors declare that they have read the policy and guidelines of the journal and there are no conflicts of interest.

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