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Current Treatment Options for Diabetes: A Review

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Abstract:- Diabetes mellitus, a chronic condition characterized by insufficient insulin production or utilization, has a rich historical context and has evolved significantly since its early identification in ancient civilizations. This article explores the multifaceted nature of diabetes, including its types—Type 1 diabetes (T1D), Type 2 diabetes (T2D), and Latent Autoimmune Diabetes in Adults (LADA)—alongside the pathogenic mechanisms that contribute to its development. The prevalence of diabetes has escalated globally, posing a substantial healthcare burden and leading to serious complications, including cardiovascular diseases and kidney failure. Management strategies have advanced, highlighting the importance of lifestyle modifications, continuous glucose monitoring, and emerging treatments such as artificial pancreas systems, smart insulin, and gene therapy. Furthermore, the potential of stem cell therapy and nanotechnology in the management of diabetes is discussed, indicating a shift towards innovative therapeutic approaches. This comprehensive overview underscores the necessity of tailored treatment strategies and the ongoing research efforts aimed at improving the quality of life for individuals affected by diabetes while addressing the global diabetes epidemic.

Keywords:- *Diabetes Mellitus, Lifestyle Modifications, Continuous Glucose Monitoring, Gene Therapy, Smart Insulin.*

I. INTRODUCTION

The term 'Diabetes mellitus' has its origin from the Greek word 'diabetes' meaning to pass through or to siphon and the Latin word 'mellitus' that means honey. As history records it, the Greek physician Apollonius of Memphis was the first to use the term diabetes around 250-300 BC. The Yu Han dynasty, ancient Greek, Indian, and Egyptian cultures all described sweet urine as a symptom of this condition and the word Diabetes Mellitus grew out of this. Then in the year 1889, scientists Mering and Minkowski identified the pancreas as a central organ in the pathogenesis of diabetes. And in 1922 at the University of Toronto, Banting, Best and Collip were the first to achieve the successful purification of insulin from bovine pancreas tissues, and provided the much required remedy for diabetes. In particular, a lot of work over the years has enabled many discoveries to be made and various management techniques to be developed in order to combat this disease due to its ever growing importance. Alas, diabetes is still reported as one of the most common chronic conditions in both the US and the rest of the world and it is ranked as the seventh common cause of death in the United States.(1)

Diabetes is a disease that occurs in a person when there is an absolute deficiency in insulin secretion by the pancreas or when the insulin present in the body does not function efficiently. Insulin is critically important in the control of blood glucose concentrations. Poor management of diabetes leads to a condition known as hyperglycemia which may be defined as increased blood sugar levels. Chronic hyperglycemia will lead to a series of pathological changes in many organ systems such as peripheral vessels and nerves systems around the Goura.(2)

In adults aged 18 years and older, the rate of diabetes was reported at 8.5% in the year 2014. In 2019, diabetes was responsible for 1.5 million deaths, with close to half (48%) of such deaths occurring in individuals below the age of 70. Besides, an estimated 460,000 deaths due to kidney disease had even diabetes as a contributing factor and blood glucose level was said to have caused about 20% of the deaths that were due to heart diseases.(3)

Diabetes, in its pathogenesis, evolves as a manifestation of many factors. These include autoimmune destruction of the pancreatic β-cells, due to some defect(s), causing an insulin-deficient state. Insufficient insulin action on target tissues is the primary factor responsible for the metabolic derangement's that include the abnormal biochemical composition in diabetes. This occurs when there is abnormal insulin secretion, or an insulinotropic response defect, or deficiency in one or more stages of insulin's multiple action pathways. It is quite possible for a patient to have two unfavorable conditions where the first one is the secretion of insulin while the second one is the action or use of the insulin, and many times there is a confusion as to which of these, if any, is primarily responsible for the hyperglycemic disorder.(4).

Type 1 diabetes (T1D) is an autoimmune condition characterized by the destruction of pancreatic beta cells, leading to a progressive reduction in insulin output and resultant hyperglycemia, as well as abnormalities in lipid and protein metabolism. Hyperglycemia in type 1 diabetes has been associated with both macrovascular and microvascular complications and increased risk of death, according to the DCCT-EDIC study. Subcutaneous tissue for exogenously administered insulin is essential for the survival of type 1 diabetic subjects as it ensures there is a minimum level of basal and prandial insulin concentration that would ensure similar physiological insulin profiles, avoiding consequences due to ketoacidosis and hyperglycemia.(5)

In the last few decades, type 2 diabetes has emerged as a global pandemic and has been found to be the most common

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and clinically significant metabolic disease and has become a major burden in global healthcare. Type 2 diabetes is mainly caused by insulin resistance in peripheral tissues and decreased synthesis and secretion of insulin by pancreatic beta-cells. The aetiology of type 2 diabetes is commonly thought to be linked with diets that combine excessive nutrient intake with insufficient energy expenditure, as approximately 90% of patients are obese or overweight at the time of diagnosis.(6)

Table 1 Plasma Glucose Test Levels for Normal, Prediabetes, and Diabetes. (7)

Plasma Glucose Test	Normal	Prediabetes	Diabetes
Random	Below 11.1 mmol/l Below 200 mg/dl	N/A	11.1 mmol/l or more 200 mg/dl or more
Fasting	Below 5.5 mmol/l Below 100 mg/dl	5.5 to 6.9 mmol/l 100 to 125 mg/dl	7.0 mmol/l or more 126 mg/dl or more
2 Hour Post-Prandial	Below 7.8 mmol/l Below 140 mg/dl	7.8 to 11.0 mmol/l 140 to 199 mg/dl	11.1 mmol/l or more 200 mg/dl or more

II. LATENT DIABETES OVERVIEW

Type 1 diabetes (T1D) and type 2 diabetes (T2D) represent intricate and heterogeneous conditions characterized by a diverse clinical trajectory, as not all individuals conform to the existing binary classification system. A significant subset of patients, primarily those diagnosed in adulthood, exhibits traits that overlap with both T1D and T2D, a phenomenon recognized over three decades ago. These are characterized as slowly progressive autoimmune diabetes and have serum immune markers indicated by T1D yet do not require insulin therapy at the time of diagnosis. This group, known as latent autoimmune diabetes in adults (LADA), makes up about 2–12% of the total diabetes population, with significant differences determined by ethnicity, the autoantibody used for screening (most commonly the autoantibody against glutamic acid decarboxylase [GADA]), and the setting of diagnosis (with primary care settings reporting lower prevalence than secondary care). LADA, sometimes referred to as type 1.5 diabetes, is a global problem, and an estimated 6 million people in China suffer from this disease.(8)

LADA is classified as T1D but often more akin to T2D, especially in the Western setting, where patients are typically overweight and insulin resistant. At diagnosis, patients with LADA do not usually require insulin, but many patients will require insulin over time due to a decline in beta cell function at an accelerated rate secondary to continuing autoimmune attacks. Although LADA constitutes about 10% of the diabetic population, management is not as well defined as for T1D and T2D. Therefore, the clinical challenge is to develop effective treatment strategies from diagnosis to slow beta cell decline, achieve metabolic control, and reduce complications.(9)

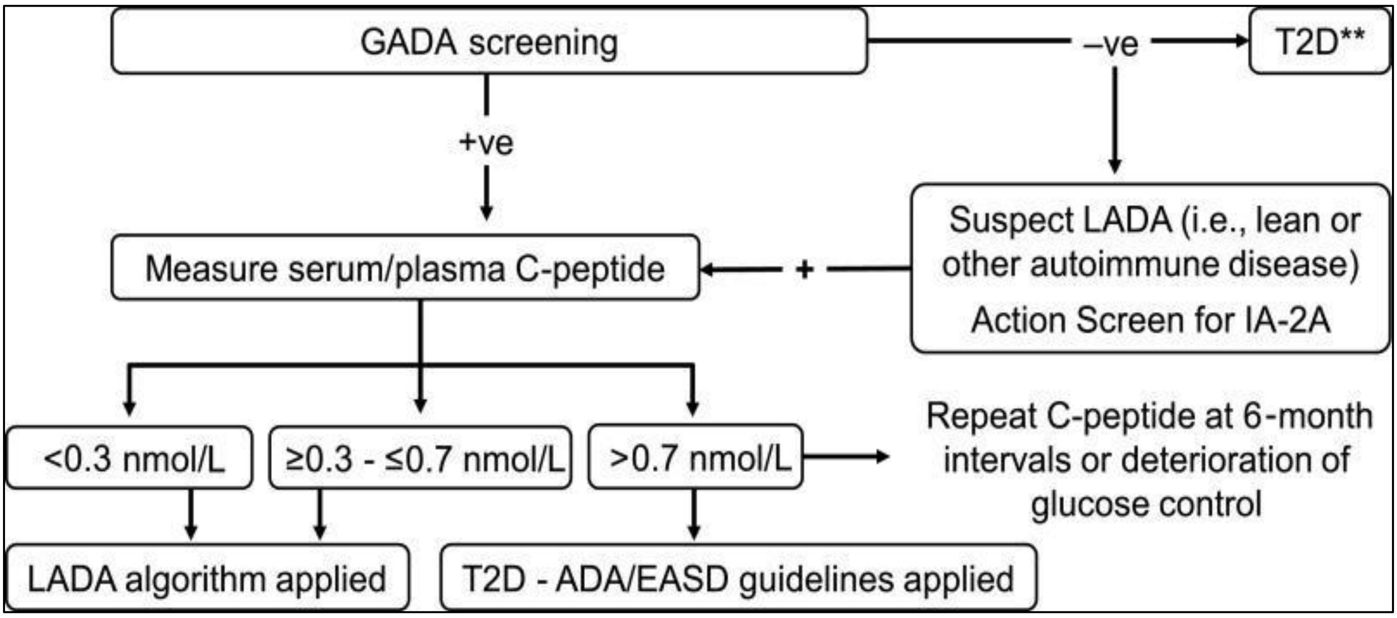

Fig 1 Diagnostic Algorithm for Latent Autoimmune Diabetes in Adults (LADA)

- *Lifestyle Modification to Control Diabetes*

Individuals who have prediabetes are more prone to developing diabetes compared to those who do not. This provides room for the development of prediabetes, allowing it to be detected and treated before diabetes happens. American Diabetes Association recommends that lifestyle changes including healthy diet, increased exercise, and managing weight can prevent people with prediabetes from developing diabetes.(11)

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Prediabetes puts individuals at risk for diabetes more than other conditions and provides an avenue for the early detection and treatment of cases to arrest further occurrences of diabetes. People with prediabetes should follow guidelines of the American Diabetes Association and make lifestyle changes in order to prevent developing diabetes. These are to be done by having a healthier diet, exercising more, and controlling weight. One must have low-fat dairy products, three ounces of whole grains per day, seven ounces of total fish per week, four or more cups of fruits and vegetables per day, less than 1500 mg of salt per day, and fewer than 450 calories of sugar-sweetened beverages per week. In the meta-analysis of six studies involving the DASH diet, the risk of coronary artery disease was decreased by 21%, and the risk of stroke reduced by 21%. This means the DASH diet may strongly lower the risk of both of these two conditions.(12)

These include greater cardiorespiratory fitness, more energy, better glucose management, reduced insulin resistance, an improved lipid profile, lowered blood pressure (BP), and weight loss maintenance among others. In randomized trials comparing supervised exercise therapies to no-exercise comparison groups, benefits in A1C, TG, and cholesterol levels have been reported in type 2 diabetes. Cohort studies have established that regular physical exercise and/or moderate to high cardiorespiratory fitness are associated with reduced cardiovascular and all-cause mortality in patients with type 2 and type 1 diabetes.(13)

III. EMERGING TREATMENTS

- *CGM(Continuous Glucose Monitor):* Every five minutes, CGM updates the glucose level display and continuously measures glucose levels, usually interstitial glucose. Most CGMs consist of three parts: (1) a monitor that displays the data (sometimes the patient's mobile device); (2) a sensor that is placed into the subcutaneous tissue; and (3) a transmitter that transmits the sensor data to the monitor.

In order to 1) detect hypoglycemic and hyperglycemic excursions, 2) predict future hypoglycemia, and 3) detect general fluctuations in glycemia, commonly referred to as glycemic variability, CGM can provide real time and retrospective information. Utilization of CGM can help a patient and their provider more precisely tailor prescription therapy and assist the patient in learning personal behavioral changes that will lead to glycemic control.

- *Professional CGM*:

Professional CGM is CGM data obtained through equipment owned by the healthcare provider. Like a 24-hour cardiac Holter monitor that transmits information regarding cardiac rhythms after they have occurred, it downloads the measurements after they have been recorded rather of necessarily providing the glucose values in real time. This allows the healthcare provider to obtain comparatively objective glucose trends throughout normal daily living. Some personal CGM devices can be operated in a blinded manner to obtain professional glucose data.

- *Dexcom Professional:*

The Dexcom G6 Pro is approved by the FDA as of March 2018, and it works in a blinded and unblinded mode. It enables glucose trend observation, immediate feedback to support patient education, and support for personal CGM decisions. Its components—the sensor, transmitter, and receiver—are similar to the personal Dexcom G6: they have a quick startup with no calibration needed. They measure interstitial glucose levels every five minutes and have been approved for ten days of use. Data can be accessed via Dexcom CLARITY, a web-based platform for analyzing glucose data.

- *Analysis of Retrospective Data*:

All CGM device data can be retrospectively analyzed. Professional CGM sessions are also recommended for better interpretation by recording data regarding diet, physical activity, symptoms, and insulin injections. This can be done in various ways: by a patient diary, direct entry of events into the device, or with a suitable application compatible with the respective system. There are three main periods to be studied:

- Overnight : Glucose levels that drift out of the target zone at night can be corrected through adjustments to the basal amount of insulin
- Preprandial Period : The levels of glucose that were not in the target range are corrected through the adjustment from the previous meal, from the current meal, or the exercise routine .
- Post-prandial Period: Glucose levels that exceed the target range after meals can be managed by altering the immediate meal bolus, the meal composition, or the exercise regimen.(14)

- *Artificial Pancrease System:*

Individuals with type 1 diabetes are permanently dependent on insulin replacement because of the autoimmune destruction of pancreatic beta cells.(15). One of the important advances in the treatment of diabetes particularly for individuals with T1D is the artificial pancreas system. These devices, combining an insulin pump and a CGM, improve glycemic control by delivering automatic insulin supply based on real-time glucose data. Compared to conventional insulin therapy, research suggests that artificial pancreas systems can increase the percentage of time in range (TIR) by about 11.74%. Full closed-loop systems are particularly effective at controlling hyperglycemia.(16). Furthermore, real-world research has shown significant drops in HbA1c levels and increased patient satisfaction, as evidenced by studies utilizing do-it-yourself Android artificial pancreas systems.(17)

The first commercially available hybrid closed-loop system was Medtronic 670G (Minimed Medtronic, Northridge, CA). The 670G soon followed the 770G (FDA authorized, licensed for age 2 and above) and 780G (CE marked, licensed for age 7-80 years) after U.S. Food and Drug Administration clearance and Conformitè Européenne marking for ages 7 and above. The pump has Medtronic's PID algorithm built into it.(18).

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➢ *Conventional Targets in Diabetes:*

The agents that are used in the market are considered the traditional targets. Biguanides decrease the output of glucose and increase glucose uptake in the liver and skeletal muscles, in which they maintain the levels of blood glucose. SGLT-2 inhibitors cause more glucose excretion by the kidneys. A-glucosidase inhibitors facilitate the reduction of intestinal absorption of glucose and free fatty acids.(19)

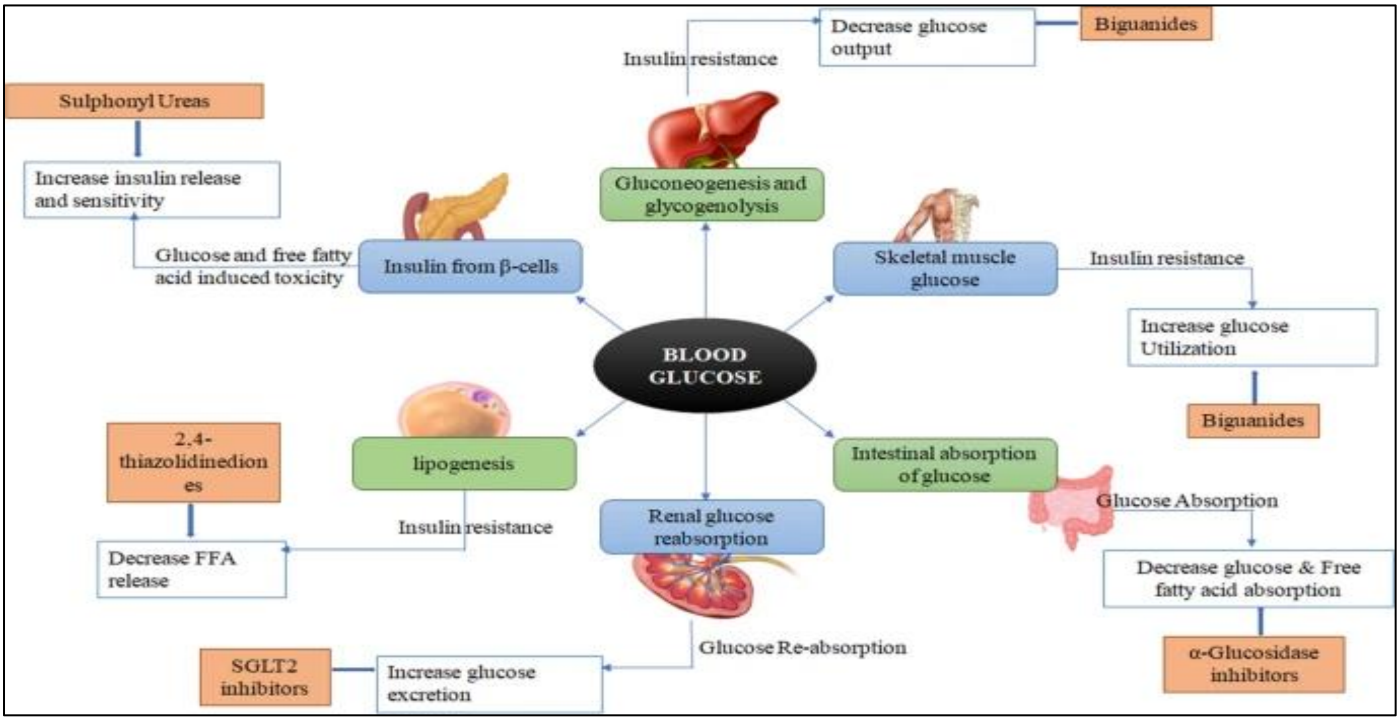

Fig 2 Traditional Therapeutic Targets and Mechanisms in Diabetes Treatment

IV. REGENERATIVE MEDICATION

➢ *Exploration of Stem Cell Therapy:*

Stem cells have the ability to self-renew and develop into almost any type of tissue or organ. Because T1DM is an autoimmune disease, the immune cells destroy and kill pancreatic β-cells; therefore, in a stem cell therapy approach, the immunomodulatory properties of stem cells plus their potential for differentiation into insulin-producing cells must be considered. More gifted stem cells credit the formation of different types of cells during early stages of embryonic life and growth of the organism. Such stem cells have an excellent ability to self-repair and differentiate into any type of specialized cell in a suitable environment. In the gut and bone marrow, the stem cells divide rapidly to replace damaged tissues. In organs such as the pancreas and heart, the stem cells are actually resident cells that divide only when required. Fig(3).(20)

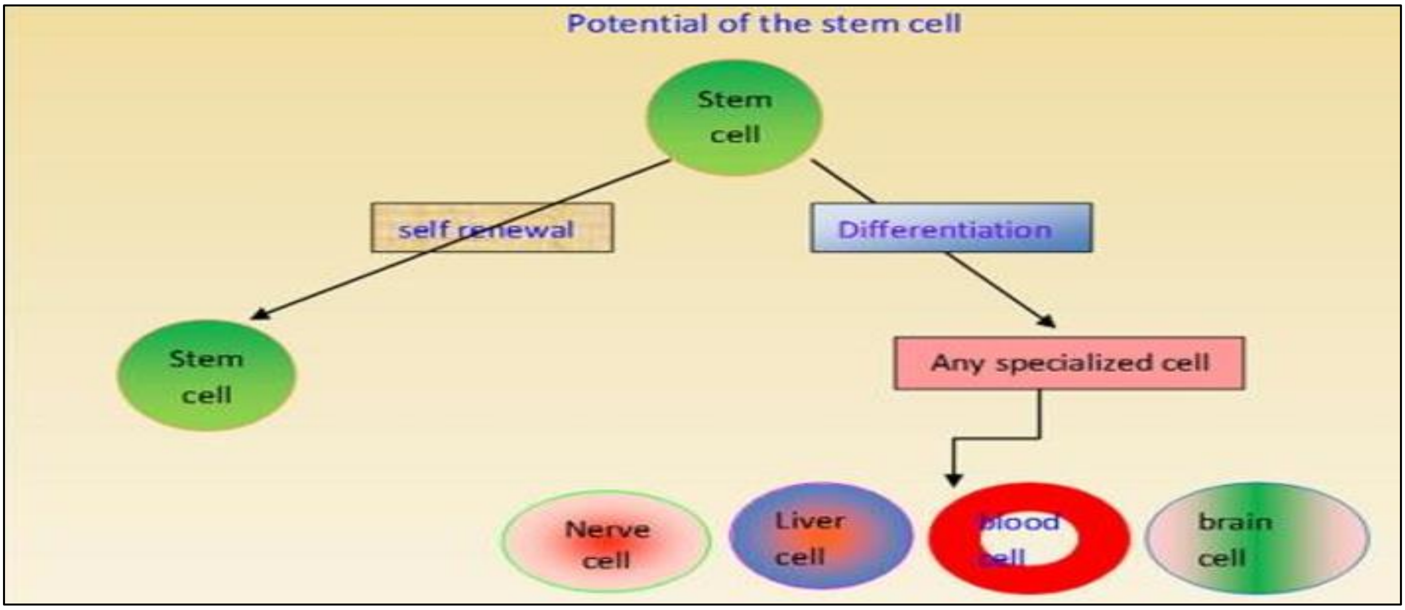

Fig 3 Stem Cell Therapy Approaches for Type 1 Diabetes Treatment

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V. POTENTIAL FUTURE TREAMENTS

➢ *Smart Insulin:*

To date, standard of care for managing BGLs in type I and advanced type II diabetes has been regular monitoring of BGLs by measuring blood glucose concentrations in intervals of a few hours followed by intravenous or subcutaneous infusion of exogenous insulin. In such patients, for most subjects, regular insulin injections render it possible to be treated in a manner quite like normal life, although enormous problems remain to be resolved by this approach. Variations in BGLs during real time are poorly related to the supply of exogenous insulin. In addition to preventing the effective regulation of diabetes, delayed delivery of insulin may cause unchecked hyperglycemia. Secondly, since insulin is only effective for a relatively short period, patients frequently require to administer it via injections two or three times per day. Generally, common injection of insulin faced with the following challenges including; discomfort, excruciating pain, skin condition, variations in BGLs and hypoglycemia. Several researchers have put a lot of effort trying to overcome these challenges.

On the other hand, smart insulin pumps were advanced in order to provide insulin in a "closed-loop" manner directly to true real-time BGLs. A minute amount of insulin is dispensed when the BGLs fall within the norm; supplemental insulin is used to fight hyperglycemia once the BGLs elevate and exceed the normal range. The BGLs are automatically kept in communication with the real-time insulin supply, and it uses the BGLs to correctly calculate the dose of insulin. In this way, the risk of immediate hypoglycemia can be significantly minimized, insulin use can be highly maximized, and BGLs can be maintained at a normal range with less fluctuation.(21)

➢ *Gene Therapy:*

Gene therapy is a type of therapy applied to modify the DNA of an individual's cells for the purpose of treating disease; several objectives are aimed at while doing gene therapy: trying to introduce a new or modified gene into the body that might help in the treatment of the disease, rendering an inoperative disease-causing gene that is not functioning as it should, or substituting an active, disease-causing gene with a normal version of the gene. Gene therapy is now in research for the common conditions like infectious diseases, cancer, and autoimmune and genetic disorders. There are various types of gene therapy like plasmid DNA, bacterial, viral, and human gene-editing technologies along with the patient-derived cellular gene therapy products.(22).

Gene therapy for type 1 diabetes may possibly reprogram other cells to undertake tasks that the original insulin-producing beta cell would perform. Producing insulin is part of having diabetes, but because the reprogrammed cells would be sufficiently different from betaCells, when there, will not trigger the response from your immune system about the presence of new cells- exactly what T1D presents.(23).

Fig(4). Schematic diagram of a gene transfer process. The gene of interest is identified, which is then engineered into a plasmid and bone marrow derived dentritic cell , before being transferred into the biological system.(24)

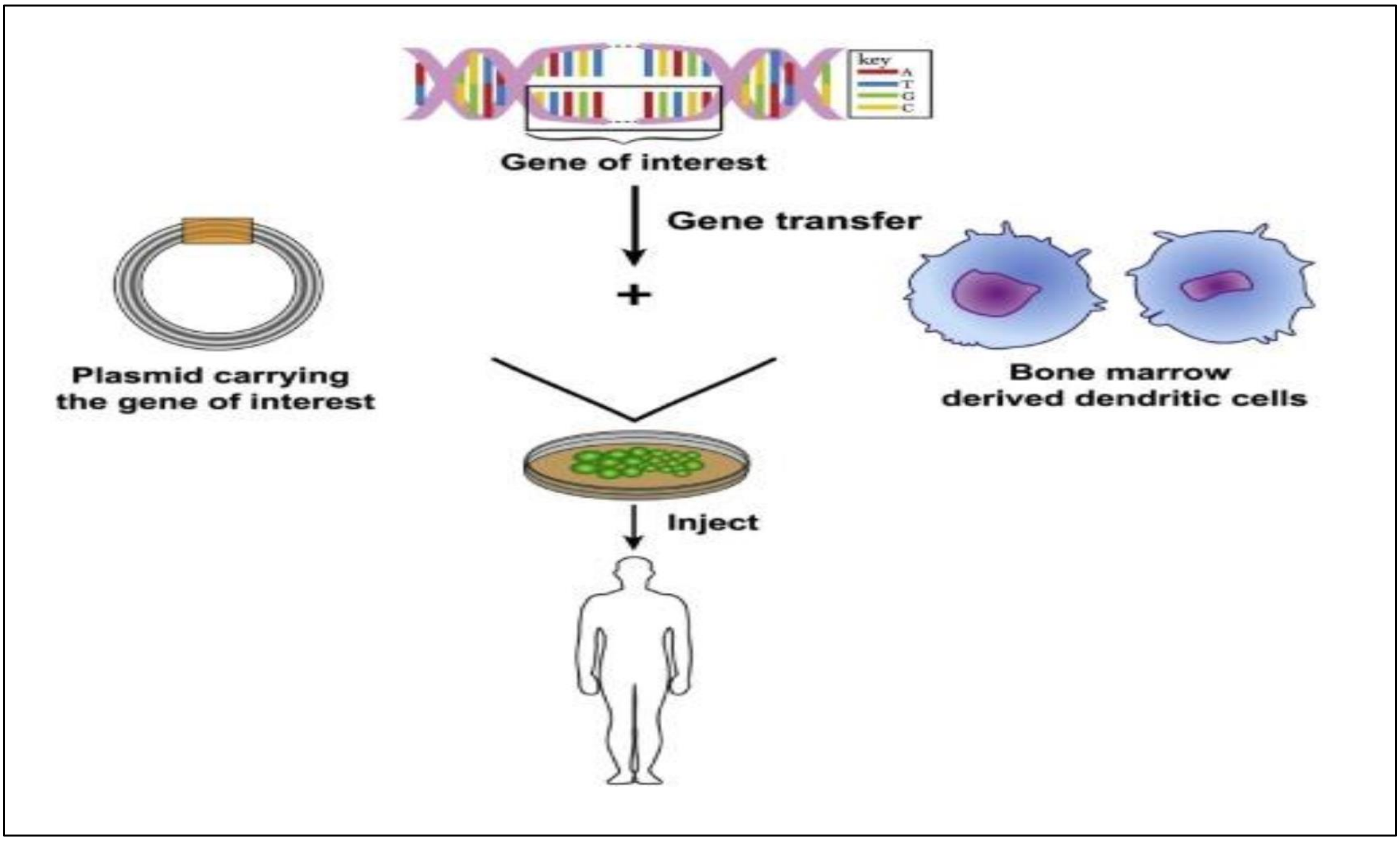

Fig 4 Gene Transfer Process in Diabetes Gene Therapy

➢ *Nanotechnology:*

Among many potential benefits of using nanotechnology in medicine, the possibility of analyzing small amounts of analytes and accessing small, therapeutically relevant cell regions is included. Additionally, the development of quantum effects leads to some interesting and useful physical properties, such as nanoscale carbon being better in electrical conductivity, more pliable, luminescent, and stronger than steel.(25)

The design and development of innovative nano-sensors for the quick, precise, and sensitive detection of blood glucose is one of nanotechnology's most important contributions to the field of diabetes. Strong insulin delivery systems that allow for the direct transfer of insulin molecules into the bloodstream, avoiding the stomach's acidic environment, has been made possible by nanotechnology, providing an alternative for daily subcutaneous injection. Additionally, nanotechnology is used to create bio-functional meals or nanodrugs to treat prediabetes.(26)

➢ *Main Types of Nanoparticles used in the Management of Diabetes:*

Nanoparticles are biocompatible and biodegradable systems that are spherical in shape and contain biological or conventional medications such as oligonucleotides and peptides. On the nanometric scale, nanoparticles are small, usually ranging between 100 and 300 nm. Their administration may be done parenterally or orally. As drug carriers, they can convey their drug payload to the appropriate bodily compartments, shield the drug from the environment at the administration site, and release the medication in response to environmental cues at the target site. They can also perform non-viral cell transfection in vitro and in vivo by delivering oligonucleotides to target cells, repairing aberrant gene expression. Liposomes, lipid nanoparticles, polymeric nanoparticles, and polymeric nanocapsules are the most commonly used types of nanoparticles in diabetes treatment. Fig(5)

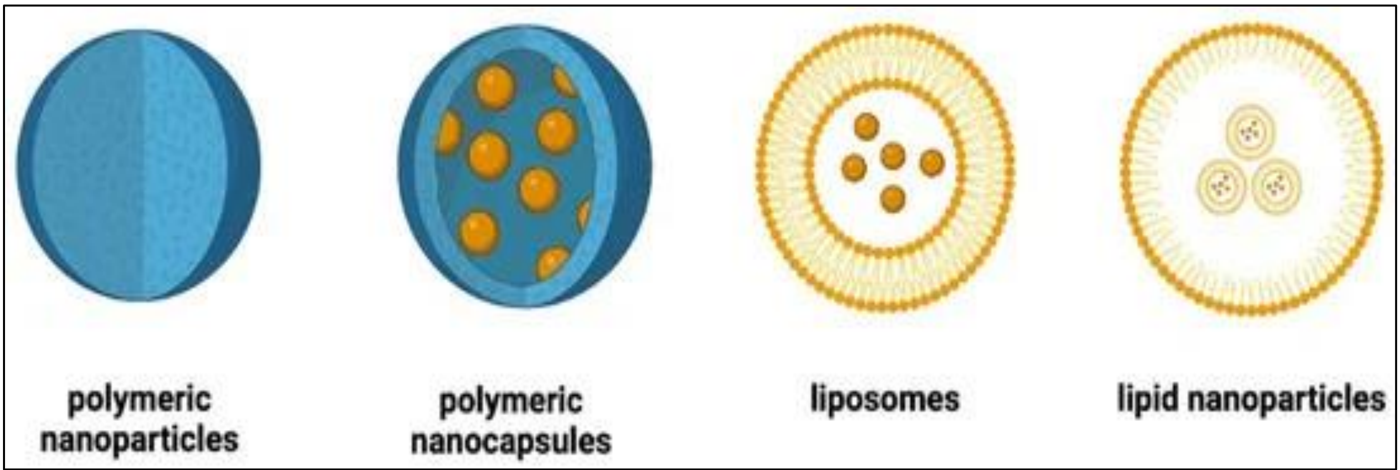

Fig 5 Types of Nanoparticles Used in Diabetes Management

VI. CONCLUSION

Diabetes mellitus has a rich historical background and significant milestones in understanding and treatment. Despite extensive research and implementation of management strategies, diabetes remains a prevalent and concerning health issue globally. The classification of diabetes into type 1, type 2, and latent autoimmune diabetes in adults (LADA) reflects the complex and heterogeneous nature of the condition. Lifestyle modifications play a crucial role in preventing the development of diabetes, particularly for individuals with prediabetes. Emerging treatments like continuous glucose monitoring (CGM), artificial pancreas systems, gene therapy, and nanotechnology hold promise for improving glycemic control and enhancing the quality of life for individuals with diabetes. These advancements offer hope for more effective and personalized approaches to managing this impactful health condition**.** Overall, the article highlights the complexity of diabetes treatment, emphasizing the need for continued research and innovation to improve patient outcomes and reduce the burden of this chronic condition.

➢ *Declarations*

- **Conflict of interest:** The authors declare no conflict of interest.

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