Chapter 13

Use of Nanoparticles in Diabetes Treatment

Syeda Rida Fatima[1*], Habiba Akram[1], Neha Fatima[2], Tooba Farooq[2], Sadia Ahmad[2], Amara Arshad[1], Farwa Tariq[1], Gul-e-Lala[1], Hina Kausar[1], Irmish Majeed[1].

[1]Department of Pharmacy, University of Agriculture Faisalabad.
[2]Department of Pharmacy, Lahore Medical and Dental College.
*Corresponding author: syedaridaf80@gmail.com

ABSTRACT

Increased concentration of sugar in plasma is known as diabetes and it is divided into two types: type 1 and type 2 diabetes. Several limitations have been identified in the methods of conventional treatment for diabetes. The nano-particles have been actively used for overcoming such limitations in diabetes treatment. The applications of nano-particles in the treatment of diabetes include the use of nano-particles for insulin delivery, diabetic retinopathy, diabetic cardiomyopathy, peripheral neuropathy, and diabetic foot ulcers. Recent advances also include the use of zinc oxide nanoparticles in the treatment of diabetes, the use of nanotechnology in the regeneration of islet beta cells, and the use of nano-particles in diabetic wound healing. The nanotechnology for treating diabetes has been proven to be more efficacious than conventional methods. This chapter highlights the introduction of diabetes mellitus and nanoparticles, limitations of conventional methods of treating diabetes, applications of nanoparticles in diabetes mellitus, and future perspectives.

KEYWORDS
Diabetes mellitus, Nano-particles, Nanotechnology, Insulin, Beta cells

Received: 26-May-2024
Revised: 12-Jul-2024
Accepted: 27-Aug-2024

A Publication of Unique Scientific Publishers

Cite this Article as: Fatima SR, Akram H, Fatima N, Farooq T, Ahmad S, Arshad A, Tariq F, Lala G, Kausar H, Majeed I, 2024. Use of nanoparticles in diabetes treatment. In: Rubio VGG, Khan A, Altaf S, Saeed Z and Qamar W (eds), Complementary and Alternative Medicine: Nanotechnology-I. Unique Scientific Publishers, Faisalabad, Pakistan, pp: 107-116. https://doi.org/10.47278/book.CAM/2024.051

INTRODUCTION

A Brief Overview of Diabetes

The raised levels of plasma sugar are a hallmark of Diabetes Mellitus, which is a chronic metabolic illness. Type 1 diabetes results from the pancreas producing insufficient insulin, whereas type 2 diabetes arises from the body's inability to respond to the insulin produced by the pancreas properly. In lower-middle-income nations, nine countries list diabetes among their top 10 leading causes of death, while in higher-middle-income countries, six nations do so, and in high-income countries, ten countries do the same. Globally, about 422 million persons suffered from diabetes mellitus (DM) in 2014, based on data provided by the World Health Organization (WHO). The incidence of DM is predicted to continue rising. By 2040, projections from the International Diabetes Federation (IDF) suggest that the figure will rise to 642 million (Dragan Lovic1, 2020).

Categories

There are three primary forms of diabetes mellitus (DM). Type 1 DM (T1DM of unknown cause) is characterized by an insulin shortage and requires lifelong insulin variant injection for therapy. It is alternatively referred to as juvenile or childhood-onset diabetes or insulin-dependent diabetes. Type 2 diabetes (T2DM), often termed adult-onset and noninsulin-dependent diabetes, stems from insulin resistance, which is the body's failure to appropriately respond adequately to the produced insulin (Fig 1). The state of high blood glucose during pregnancy in women who have never had diabetes before comes last: gestational diabetes. In this instance, there is a significant chance that the child may grow up with DM (Kaul et al., 2013).

Epidemiology (Disease Distribution and Transmission)

The main drivers for rising planetary incidences of type 1 diabetes which is less frequent are yet unknown. It is believed that environmental changes are altering diabetes-associated alleles, with geographic and ethnic variations in type 1 diabetes incidence and prevalence serving as the main contributing factors. The rates are lowest in Japan and the Pacific region and highest among Caucasians. Type 1 diabetes is not limited by age; however, approximately 50–60% of cases manifest before reaching the age of 20 (Baynes, 2015).

Ninety percent of those with diabetes have type 2, which is the most prevalent variety. Similar to type 1 diabetes there are significant regional and ethnic differences, although obesity is the main factor contributing to the rising incidence (Baynes, 2015).

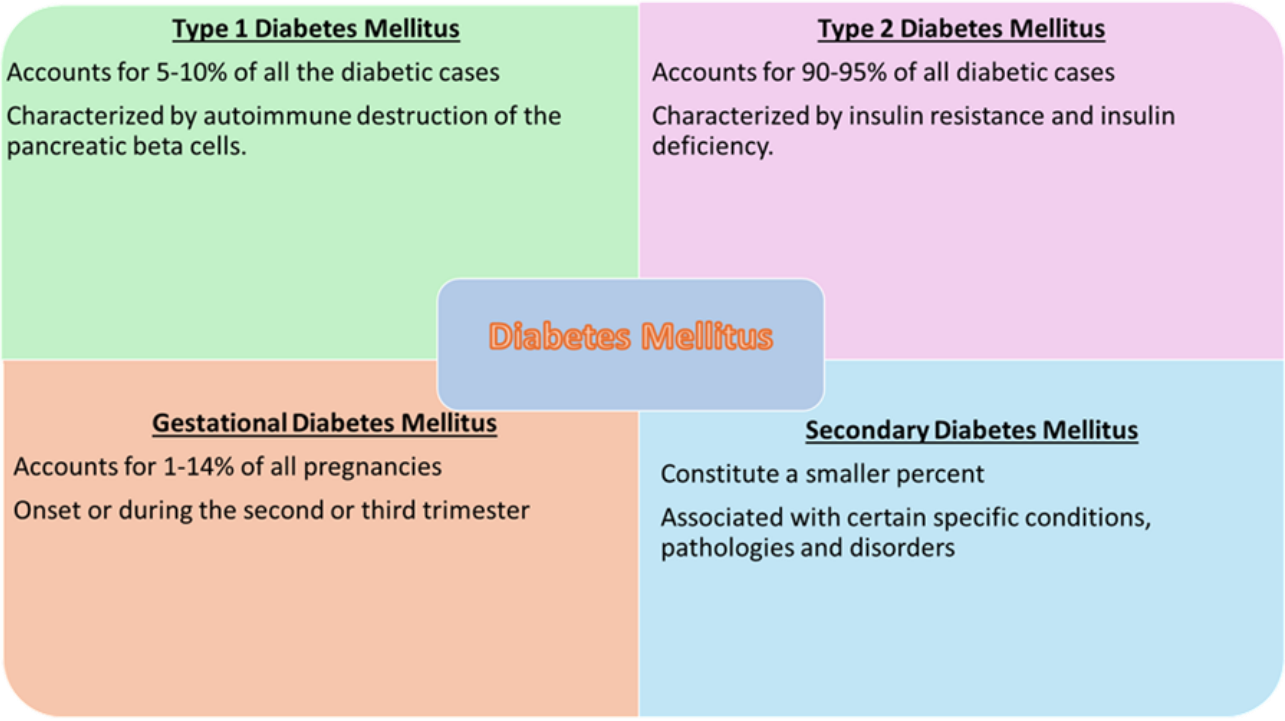

Fig. 1: The image above shadows the types of diabetes and their prevalence around the globe along with the characteristics of each type. The major portion of the diabetic population suffers from type 2DM but it can be prevented with lifestyle modifications along with pharmacological treatment. The most dangerous type is type 1 DM as it is not preventable with lifestyle modifications but needs lifetime insulin administration for survival.

Estimates of the prevalence of obesity in more obese societies fluctuate between 6-8% in the UK to 50% in the Pima Indians of Arizona. Research conducted on immigrants worldwide has shown that well-nourished populations face a risk of type 2 diabetes that is 2–20 times greater than lean populations of the same racial background (Baynes, 2015)

Etiology

Insulin insufficiency, which results from the autoimmune destruction of pancreatic β cells and leads to type 1A diabetes, is the cause of T1DM. Other underlying reasons for their insulin secretion abnormalities are hereditary. The deficiencies in glucose sensing by β cells along with other genetic and acquired disorders contribute to the condition (Yau et al., 2021).

Malfunctions in how insulin interacts with its target tissues (muscle, liver, and fat) result in type 2 diabetes mellitus (T2DM), a condition that can be exacerbated by various factors and often increase the beta cells' ability to secrete insulin diminishes, while the majority of patients with type 2 diabetes mellitus in the United States and Europe are overweight or obese (Yau et al., 2021)

Diagnosis:

Table 1: Criteria for diagnosing diabetes. Based on plasma glucose levels, diabetes can be diagnosed using either the 2-hour plasma glucose (2-h PG) value or the fasting plasma glucose (FPG) value from a 75-g oral glucose tolerance test (OGTT). This criteria also gives information on prediabetes glucose levels. (Phillips, 2012)

Parameter	Normal tolerance	Glucose impaired Tolerance	Glucose Diabetes Mellitus
Plasma glucose levels during fasting mg/dl (mmol/L).	Less than 100(5.6)	100-125(5.6-6.9)	Equal to or greater than 126(7.0)
Two hours post-glucose administration mg/dl(mmol/L)	Less than 140(7.8)	Equal to or greater than 140-199(7.8-11.0)	Equal to or greater than 200(11.1)
HbA1c	Less than 5.7	5.7-6.4	Equal to or greater than 6.5

Oral Glucose Tolerance Test

In this test, 75 or 100 grams of glucose solution should be consumed for the usual glucose tolerance-3 test (Phillips, 2012)

Complications

In the following section, complications and prevention of diabetes mellitus are described (Tripathi and Srivastava, 2006)

Acute Complications

Among these are non-ketotic hyperosmolar condition (NKHS) and diabetic ketoacidosis (DKA). Type 1 diabetes primarily leads to the former, while type 2 diabetes primarily causes the latter.

Chronic Complications

- Diabetic retinopathy
- Neuropathy
- Nephropathy
- Hypertension
- Infections
- Cardiovascular disease

Indications and Expressions

- Blurred vision
- Fatigue
- Increased thirst or polydipsia
- Increased appetite or polyphagia
- Elevated blood sugar or hyperglycemia
- Frequent urination or polyuria
- Weight loss

Management and Prevention

Type 1 diabetes is not preventable.

People may, however, take a few precautions to help avoid type 2 diabetes. Among the strategies to help avoid type 2 diabetes are;

- Keeping a healthy weight
- Maintaining a healthy diet with minimal intake of processed foods, saturated fats, and added sugars, high fiber low fat content, smoking and alcohol cessation, minimal intake of artificial sweeteners,
- Engaging in regular exercise
- Medical treatment (management)

Nanoparticles

The nanoparticles are novel dosage forms with differing compositions and properties from their respective counterparts. The nanoparticles are particulate dispersion or solid particles in a size range of 10-1000 nm (Biswas and Wu, 2005).

Nanoparticles are the basic components of nanotechnology. The nanoparticles possess unique properties due to their small size such as stability, surface area, high reactivity, strength, and sensitivity. On the nano-metric scale, nanoparticles are categorized into organic nanoparticles which include dendrimers, liposomes, and micelles the others are inorganic nanoparticles which include metal and metal oxide-based nanoparticles, and carbon-based particles. The nanoparticles are of different dimensions, sizes, shapes, and structures. The nanoparticles can either be of zero dimension, one dimension, two dimension, or three dimensions. They exist in spherical, hollow core, cylindrical, tubular, spiral, and conical, flat, or irregular shape. The nanoparticles can be amorphous or crystalline having uniform or rough surfaces. Depending on the method of preparation, drugs can be entrapped, encapsulated, dissolved, or attached to a nanoparticle matrix. The drug release rate can be controlled by nanoparticles, nano-capsules, and nanospheres preparation. In nano-capsules, the core of the drug is surrounded by a specific polymer membrane. At the same time, nanospheres are homogeneous systems in which the drug is uniformly dispersed within the polymeric matrix. The nanoparticles synthesized from chemical methods have toxic effects due to the adherence of toxic chemicals on the surface. Preparation of nanoparticles by using microorganisms is an eco-friendly alternative to chemical and physical methods. Currently, metallic nanoparticles like silver, copper, zinc, gold, titanium, magnesium, and gold are prepared using different microorganisms (Mohanraj and Chen, 2006)

Therapeutic and diagnostic nanoparticles have two categories: 1) Organic nanoparticles and 2) Inorganic nanoparticles. Inorganic nanoparticles have been used successfully for preclinical studies whereas organic nanoparticles have been used successfully in various applications ranging from vaccination to long-lasting depot delivery systems.

Methods of Preparation

The following methods are most frequently used for nanoparticle preparation:

- De-solvation
- Dialysis

- Ionic gelation
- Nano-precipitation
- Solvent evaporation
- Salting out
- Spray drying
- Supercritical fluid

Other methods we can use to prepare nanoparticles include Vacuum deposition and vaporization, Gas condensation, Chemical vapor condensation (CDC), Chemical Vapor Deposition (CVD), Chemical precipitation, Mechanical attrition, Sol-Gel techniques and electro-deposition. All these methods are widely used in the preparation of nanoparticles.

Advantages

The major functions of this novel drug delivery are to control the particle size, control the release of drug at a predetermined rate, site-specific targeting, sustain the release of the drug at auction site to acquire increased therapeutic efficacy and reduced side effects, surface characteristics can easily be manipulated to achieve active and passive targeting after parenteral administration.

Limitations

Nanoparticles do have limitations:

- The nanoparticle dosage form leads to particle-particle aggregation due to small size and large surface area.
- Due to the small size, handling of nanoparticles becomes very difficult.

The small size of nanoparticles causes their clearance by the reticuloendothelial system through opsonization.

Applications

The nanoparticles have significant applications in various fields including food, cosmetics and sunscreens, electronics, catalysis, construction, renewable energy, space exploration, transportation, medicine, and bioengineering.

Limitation of Conventional Drug Delivery System

Currently, the medications utilized in the clinical management of diabetes may encompass insulin as well as non-insulin oral hypoglycemic agents. The traditional diabetes treatment using antidiabetic medications can lead to hypoglycemia, posing significant risks to patients including behavioral and cognitive disturbances, seizure and brain damage, and potentially fatal outcomes. Hence, there is a critical need for the development of an advanced drug delivery system capable of achieving sustainable and controlled drug release (Zhao et al., 2020).

The Limitations of Conventional DDS

The medication must be administered at a precisely controlled rate and directed to the target site with utmost accuracy to achieve optimal efficacy and safety. The traditional antidiabetic medication's failure to accumulate at the intended site could potentially induce severe side effects to other organs because they have limited specificity for the target site. Furthermore, the traditional dosage forms cannot intelligently adapt to the wide fluctuations in glucose concentration, leading to a heightened risk of hypoglycemia (Zhao et al., 2020).

The diverse pH, environment and digestive enzymes serve as primary biochemical obstacles for oral drug delivery systems. The pH level fluctuates significantly throughout the gastrointestinal tract, gradually increasing from stomach to the colon ranging from 1-8. This transition from acidic to alkaline environments influences drug efficiency and bioavailability (Lou et al., 2023). The desired therapeutic concentration of antidiabetic drugs cannot be effectively achieved in specific target areas due to their susceptibility to chemical instability and proteolytic degradation in the harsh physiological environment (Zhao et al., 2020).

In the management of diabetes mellitus, the primary method of treatment often involves administering insulin via subcutaneous injection. However, patient adherence to this approach is often compromised due to concerns related to discomfort, trauma, pain, and the risk of local infection, skin necrosis, and nerve damage. To address these challenges, nanoparticles have emerged as potential carriers for insulin, offering alternative, more patient-friendly routes of administration that eliminate the need for injections (Souto et al., 2019).

The limited effectiveness of oral insulin administration stems from its low bioavailability and inadequate therapeutic impact, largely due to rapid chemical clearance. When insulin is ingested orally it encounters various obstacles in the gastrointestinal tract including acidic conditions and enzymatic degradation which can degrade the insulin molecules before they can be absorbed into the bloodstream. Additionally, the large size and hydrophilic nature of insulin molecules make it challenging for them to pass through intestinal epithelium and enter systemic circulation effectively. As a result, only a small fraction of ingested insulin enters into the bloodstream leading to rapid clearance (Souto et al., 2019).

Various strategies have been explored to ensure plasma drug concentrations remain above the minimum effective concentration while avoiding toxicity. One such approach involves administering multiple doses at regular intervals. However,

repeated dosing with conventional drug delivery systems can result in poor patient adherence (Adepu and Ramakrishna, 2021).

Role of Nanoparticles in the Diagnosis of DM

The nanocarrier-mediated drug delivery is a method of administering drugs that has several advantages over traditional methods. It offers selective targeting, enhanced cellular intake, and accumulation, improved stability, prevents offsite degradation, and prolongs the active agents' half-life in the bloodstream. This approach enhances the therapeutic efficacy of pharmaceutical agents at the intended site while minimizing off-target normal cytotoxicity (Debele and Park, 2022).

The nanoparticles (NPs) have unique biological, physical, optical, chemical, and magnetic properties that make them valuable for early disease detection and prevention. For example, their small size and specific binding ligands on their surfaces make NPs useful as imaging probes for diseased tissues or organs. Additionally, NPs can be tailored to have longer circulation times and better targeting in the body by adjusting their size, surface charge, and other properties. This makes them useful as contrasting agents for various biomedical imaging techniques, such as magnetic resonance imaging (MRI), for early diagnosis of diseases like diabetes. The NPs have a high surface-to-volume ratio, making them an ideal matrix for enzyme immobilization. This enhances enzyme-substrate interactions and enzymatic activity. Various materials, such as magnetite NPs, gold NPs (AuNPs), and carbon nanotubes, have been investigated for their potential use as matrices for enzyme immobilization. (Debele and Park, 2022).

The integration of NPs into sensors offers several benefits, including increased surface area, better electron transfer from enzyme to electrode due to excellent conductivity and small bandgap, improved stability, and the ability to incorporate additional catalytic steps. In the field of diabetes sensors, nanotechnology is commonly used to enhance standard enzymatic electrochemical glucose detection or for direct detection of glucose oxidation at an electrode, also known as non-enzymatic glucose sensors (Debele and Park, 2022).

Application of Nanoparticles in Insulin Delivery

The development of insulin through the use of biocompatible and biodegradable nano-carriers is crucial. The nano-carriers help to protect insulin from stomach acid and enzymatic degradation, thus improving its effectiveness in the intestines. The uptake of nanoparticles depends on various factors such as surface charge, shape, size, muco-adhesive properties, and the method of administration. Furthermore, the characteristics of pharmaceutical agents, such as hydrophobicity, molecular weight, pH stability, and ionization constants, also play a significant role in the cellular uptake. Understanding these mechanisms is necessary for creating effective delivery systems for oral protein drugs. Currently, researchers are focused on optimizing nano-carrier design to protect macromolecules from the gastrointestinal environment and prolonged intestinal permeation. This could potentially enhance the effectiveness of insulin (Debele and Park, 2022).

Nanotechnology and Diabetic Complications

Diabetic Nephropathy (DN)

The major reason for nephropathy is usually diabetic nephropathy (DN). There is no satisfactory preventive measure and treatment available for DN. The pathogenesis of DN is complicated, various factors and conditions exaggerate the occurrence and condition of DN, which include: glucose imbalance metabolism, endothelial nitric oxide synthase production, inflammatory reactions, along renal hemodynamic changes. Therapeutic drugs for DN significantly reduce the production of renal fibrosis factors such as TGF-β1 and fibronectin as well as inflammatory cytokines including MCP-1 and TNF-α. ("Nanotechnology in the Treatment of Diabetic Complications: A Comprehensive Narrative Review," n.d., #)

Diabetic Retinopathy (DR)

With an expansion in patients with diabetes, diabetic retinopathy is one of the major reasons for blindness. The combination of retinal damage, thickened basement membrane, blocked micro-vessels, and impaired blood-retinal barrier function lead to retinal edema and neovascularization. The silicate nanoparticles developed by some researchers showed anti-angiogenesis effects on retinal vein occlusion by inducing the formation of the protein (VEGF) vascular endothelial growth factor. ("Nanotechnology in the Treatment of Diabetic Complications: A Comprehensive Narrative Review," n.d., #)

Diabetic Cardiomyopathy (DCM)

Some studies showed that cardiac myopathy is due to the formation of free radicals that cause injury to cardiac muscle cells due to diabetes mellitus which leads to abnormal myocardial diastolic function. The common pathological features of cardiomyopathy are myocardial fibrosis and apoptosis. The PSS-loaded nanoparticles made with the help of synthetic polymer Poly (lactic-co-glycolic acid (PLGA) have shown significant improvement in DCM with improving cardiac diastolic and systolic function and ventricular wall motion. ("Nanotechnology in the Treatment of Diabetic Complications: A Comprehensive Narrative Review," n.d., #)

Peripheral Neuropathy (DPN)

The peripheral neuropathy is a chronic disease and a major reason for foot ulcers and amputation. Microvascular

changes and glucose metabolism disorder, deficiency of nerve growth factors, and vitamins are considered the factors of pathogenesis in DPN. The short-term treatment with curcumin nanoparticles showed a reduction in complications of DPN in T2DM. ("Nanotechnology in the Treatment of Diabetic Complications: A Comprehensive Narrative Review," n.d., #)

Diabetic Foot Ulcer (DFU)

The diabetic foot ulcers are a severe complication in diabetic patients and can result in amputation and death of the lower limb. The treatment of diabetic foot ulcers includes the establishment of a clear and optimal environment for the foot wound which facilitates its prompt healing. The process of wound healing is complex and involves various stages that must occur in a specific sequence. As such, the perfect wound dressing should be non-allergenic and non-toxic, while also maintaining moisture in the wound area, facilitating gas exchange, protecting the wound from microbes, and absorbing wound drainage.

The nano-technology has been extensively used in research related to wound dressing for diabetes with material like gold, chitosan, curcumin, and silver being extensively studied. There is an increasing interest in biopolymers that share similar structures, biocompatibility, and biodegradability with natural skin. Additionally, metal nanoparticles, such as silver and gold are suitable choices for the wound dressings, mainly due to their antibacterial properties and low toxicity levels.

The PLGA microspheres made with recombinant human EGF nanoparticles (NPS) embedded in wounds of diabetic rats have shown the fastest cure rate by increasing the proliferation rate of fibroblasts. ("Nanotechnology in the Treatment of Diabetic Complications: A Comprehensive Narrative Review," n.d., #)

Application of Zinc oxide Nanoparticles in the Treatment of Diabetes Mellitus

The use of zinc oxide nanoparticles (ZnO-NPs) is increasing day by day in a number of industrial products. The most popular metal, ZnO-NPs, have a wide range of biological applications due to their perfect biocompatibility, economics, and low toxicity. Zinc is widely recognized for its ability to maintain the structural integrity of insulin and play an effective role in the secretion of insulin from pancreatic cells. This is the reason that ZnO NPs are effective in the treatment of diabetes (Jiang and Cai, 2018).

A recent scientific study delved into the potential anti-diabetic properties of RSW extract, ZnO nanoparticles, and ZnO-RSW conjugate. To assess their efficacy, the researchers employed amylase and glucosidase inhibition assays. These tests allowed them to evaluate the ability of the aforementioned compounds to inhibit the activity of enzymes responsible for the breakdown of carbohydrates, which can lead to an increase in the blood glucose levels. The results of this study might have contributed to the development of new treatments for diabetes as -amylase inhibitors (Bayrami, 2018).

The results of one study revealed that only ZnO-NPs show high inhibition of pancreatic amylase. Low inhibition was shown by only RSW whereas the ZnO-RSW possesses a higher percentage of inhibition as glucosidase inhibitor. The superiority of conjugated ZnO-RSW nanoparticles is evident in their excellent performance against crude murine pancreatic glucosidase, outpacing the individual ZnO nanoparticles and RSW extract. Consider adopting these nanoparticles for enhanced activity against this enzyme (Kitture, 2015).

Effect of ZnO NPs on Lipid Profile

The combination of zinc and extract can significantly improve the body's ability to break down blood glucose, leading to a marked reduction in the lipid utilization and ultimately decreasing the risk of developing hyperlipidemia. What's particularly exciting about this is the potential correlation between the insulin-like action of ZnO-NPs and the plant extract. This promising mechanism could offer significant benefits if further studied. According to some studies, zinc may have a similar effect to a-blockers in the short-term treatment of dyslipidemic patients. A recent study examined the changes in HDL levels in different groups during a test period. The results showed that all groups that received treatment had a significant increase in their HDL levels. However, none of the treatment conditions resulted in a significant decrease in TG levels, except for the ZnO-NPs extract which showed a significant decrease in cholesterol levels (Bayrami et al., 2018).

ZnO-NPs exhibited antibacterial, antidiabetic, antioxidant and anticancer effects. Zinc is a primary trace mineral element and has an important function in the metabolism of lipids in the liver. It stimulates lipophagy in hepatic cells, decreasing lipid accumulation and promoting lipolysis. ZnO-NPs conquer liver fibrosis induced experimentally by thioacetamide and modulate liver enzymes via reducing oxidative stress (Kitture, 2015).

Regenerative Medicines

The diabetic regenerative medicine has contributed to the clinical management of diabetes mellitus and its associated problems, resulting in discoveries and advancements. Furthermore, the development of nanotechnology has given diabetic regenerative therapy a boost. The regeneration of islet β cells, retinal tissue, nerve tissue, and wound tissue cells can all be directed correctly by a nano stent. Conductive nanomaterials stimulate the formation of numerous distinct tissues. Countless other benefits and wound-healing properties of nanoparticles have resolved numerous possible challenges in the practical application of regenerative therapies (Matveyenko and Vella, 2015).

Advances in the use of Nanotechnology in Islet and Islet β Cell Regeneration

Two methods of supplementing β cells are conceivable because of the lack of insulin production induced by islet β cell function i.e., Replacement through the transplanting of islets or β cells from human embryonic stem (hESC) or induced pluripotent stem (iPSC) cells from cadavers. It happens via progenitor differentiation (neogenesis) or transdifferentiation of developed cell types.Utilizing biodegradable polymer biomaterials as drug carriers to create a nano-controlled medication system, nanotechnology offers targeted cell transplantation with good biocompatibility(Contera et al., 2020).

The Process of Stimulating Natural Regeneration

It takes place via progenitor differentiation (neogenesis) or the change of differentiated cell types (trans-differentiation). The research on pluripotent stem cells (embryonic stem cells (ESC) or inducible pluripotent stem cells (iPSC)) and allogeneic islets, particularly porcine islets, has been compelled by immunological rejection and a lack of organ donors. Using biodegradable polymer biomaterials as drug carriers to create a nano-controlled drug system, nanotechnology is targeted for cell transplantation that is both biocompatible and precise. It can enhance the differentiation, implantation, and survival of stem cells when combined with stem cells. Regenerative medicine is being aided by the use of nanomedicine, nanomedicine carriers, nano-contrast agents, and nanosensors of various kinds. The goal of islet cell transplantation is to permanently heal diabetes by using mesenchymal stem cells' limitless capacity for proliferation and creating insulin-like insulin production polymer implantation into the body (Garbayo et al., 2020).

Through this approach, the long-term survival of these cells has been established through successful encapsulation and transport that can shield them from dispersion, destruction, and immune attack. The PLA nanoparticles were used because they were non-toxic, had a long half-life, were easily biodegradable, and had good bio-compatibility (Gao et al., 2013).

Utilizing their small molecular weight, nanoparticles can seamlessly transport drugs and imaging agents through a variety of barriers, allowing them to be implanted into the body or regenerated islets or β cells to produce an accurate and clear image. In addition, nanoparticles can alter their surface groups, such as polyethylene methylation and methylation, which help them avoid being removed by macrophages and maintain a stable presence in the body. As such, monitoring islet function is essential (Wang et al., 2014).

Using biopolymers as its foundation, multifunctional nanoparticles (NPs) are engineered as specialized nano tools to monitor the functionality of transplanted tissues and cells. The primary focus of their actions is the β cell membrane-expressed glucagon-like peptide 1 receptor, or GLP-1R. One naturally occurring ligand for GLP-1R is glucagon-like peptide-1 (GLP-1). High affinity exists between them. Its short half-life in the body prevents it from achieving blood sugar management at a fine level. Therefore, GLP-1 simulations are used in the current treatment. Exendin-4, a synthetic version of the naturally occurring peptide, is the most well-known. It combines chitosan-PGA nanoparticles with detecting agents for enhanced multimodal imaging techniques such as MRI, SPECT, and multispectral photoacoustic tomography (MSOT)) (Dinnyes et al., 2020).

According to recent research, MSC-derived nanoscale exosomal miR-146a reverses islet β cells' dedifferentiation through the miR-146a-5p/β-catenin pathway, enabling its differentiation into the necessary cell subtypes, enhancing β cell function, and lowering insulin resistance to better serve diabetic patients' needs.(He et al., 2021)

Nanoparticles in Diabetic Wound Healing

A wound is an interruption in the epidermal layer of one's body. Generally, wounds result from any external invasion of skin-like injury. So, it's normal that anyone can get wounded in daily life. The diabetic patients are the ones who are susceptible to delayed wound healing which ends up in horrific amputations (Qin et al., 2022).

Normal wound healing has four phases including hemostasis, inflammation, proliferation, and remodeling. Soon after the injury, hemostasis begins immediately to produce clots through fibrin and release pro-inflammatory mediators like cytokines and growth factors through platelets. These cytokines activate the inflammatory phase by accumulating monocytes and neutrophils in the wound area. Hemostasis takes 2-3 hours. The inflammatory phase can take weeks or even months in chronic disease (Diabetic Foot Ulcer). Whenever injury occurs it causes blood vessels to rupture and formation of extracellular matrix which closes the wound. During the proliferation phase, endothelial cells and fibroblasts proliferate to direct angiogenesis and new extracellular matrix formation. The old ECM is broken down by proteases. The surface of the wound is covered by crust in the remodeling phase which can last for months (Qin et al., 2022).

Diabetic wounds are impaired due to hypoxia which is either the result of reduced O_2 supply or increased O_2 usage by the wound during neuropathy and inflammation, respectively. Hypoxia increases the ROS levels resulting in delayed wound healing. Diabetic wounds have reduced angiogenesis and increased inflammatory mediators (Qin et al., 2022).

Diabetic individuals often experience poor wound healing due to various physiological factors. These factors include:

- Impaired migration and proliferation of keratinocytes and fibroblasts.
- Abnormal cytokine and growth factor function.
- A compromised angiogenic response.
- Impaired response to infection.

These factors can significantly impede the wound healing process in individuals with diabetes.

Polymeric Nanoparticles

They are usually used embedded in scaffolds. Chitosan is studied based on its properties like biocompatibility, biodegradability, and antimicrobial activity. Chitosan NP loaded with drug curcumin, embedded in collagen scaffold heals the wound faster. It is also involved in decreasing inflammation and promoting angiogenesis (Gupta, Sharma et al. 2022).

Silver Nanoparticles

Silver nitrate and silver sulfadiazine have been used but they have certain limitations of staining and irritating the tissues (silver nitrate) and inactivating silver at the wound site (silver sulfadiazine). ACTICOAT, silver loaded dressing has been introduced to deal with these limitations. These dressings can release additional silver when the silver is inactivated by wound fluid, maintaining sustained and steady active silver availability. The silver has wide antimicrobial activity by inhibiting DNA replication (Choudhury et al., 2020).

Hydrogel

The nanocomposite hydrogel, based on alginate and positively charged Eudragit nanoparticles, has been used to load Edaravone, a drug having wound healing properties by scavenging ROS. This HG loading increases its scavenging capacity, stability, and solubility at the wound site (Fan et al., 2019)

An effective approach towards the treatment of chronic wounds is scavenging reactive oxygen species (ROS). This hydrogel serves this purpose well. Solubility and stability of Edaravone is increased by Eudragit nanoparticles while the Alginate hydrogel servesfor protection and sustained release of Edaravone. The dose dependent approach of this hydrogel shows the dual role of ROS where low dose speeds up the wound healing while high doses inhibit it.

Ferulic Acid Nanoparticles

Diabetic Rats are tested with Ferulic acid nanoparticles for their hypoglycemic and wound healing effects. The FA-NPs are prepared by encapsulating ferulic acid in PLGA (poly-lactic-co glycolic acid) having an average size of 240 nm and spherical. The FA-NP dispersion is for oral administration while FA-NP-based hydrogel is prepared using Carbopol 980, for topical administration. The FA-NPs increase hydroxyproline which plays a role in collagen stability thus speeding the epithelialization of wounds (Bairagi et al., 2018).

Future Perspectives

Exogenous insulin is the only cure currently available for Type 1 DM since it is an autoimmune disease. By understanding the mechanisms, and various changes in the pancreatic beta cells as the disease progresses, several different immunotherapies are designed. The main concern in this respect is the quick clearance and inability to maintain glucose homeostasis for a longer duration. Recent studies have shown that combining nanotechnology with these immunotherapies not only provides the targeted and controlled delivery of immune modulators to desired localized sites but also slows down disease progression (Nigam et al., 2022)

Moreover, nanotechnology is being employed in preparing artificial cells and implants. Biocompatible scaffolds, mimicking extracellular matrices, have been prepared by employing nanoparticles for tissue regeneration (Simos et al., 2021). Even at this emerging stage, it is expected that this combinational approach will provide means to treat this autoimmune disorder shortly.

In type 2 DM, the nanotechnology is being used for targeted delivery and controlled release (over an extended period) of oral hypoglycemic agents. Metallic nanoparticles, the nanoparticles containing trace elements involved in glucose homeostasis like zinc, vanadium, chromium, selenium, and lithium, have also been developed. Nanoparticles containing glucose-responsive smart polymers have been developed that release the drug when the blood glucose level is high and vice versa. In another scenario, these nanoparticles are designed first to release the initial dose of the drug providing the immediate effect followed by slow release to attain glucose homeostasis for a longer period (Simos et al., 2021). Formulations developed by nanotechnology are found to be effective in treating various DM complications like diabetic retinopathy, diabetic nephropathy, cardiomyopathy, peripheral neuropathy, and diabetic wound healing.

A novel therapeutic approach to treat type 2 DM is gene therapy which is the non-viral delivery of GLP-1 plasmid DNA (p-DNA) complex coding for a specific protein. The protein is synthesized in the cells of the small intestine on receiving the p-DNA complex and goes to systemic circulation. Here, nanotechnology serves for the targeted delivery of genes (Simos et al., 2021).

Overall, treatment with techniques and formulations employing nanotechnology and smart polymers are more efficacious than conventional treatments at the same potency (dose). However, the reproducibility and stability of nano-carriers are some of the setbacks being encountered. It is anticipated that soon researchers, with in-depth knowledge of nanotechnology, will successfully overcome the current limitations and introduce further novel approaches to combat DM. (Simos et al., 2021)

REFERENCES

Adepu, S., and Ramakrishna, S. (2021). Controlled drug delivery systems: current status and future directions. *Molecules*, 26(19), 5905.

Aguayo-Mazzucato, C., and Bonner-Weir, S. (2018). Pancreatic β cell regeneration as a possible therapy for diabetes. *Cell Metabolism*, 27(1), 57-67. .

Bahmad, H. F., Poppiti, R., and Alexis, J. (2021). Nanotherapeutic approach to treat diabetic foot ulcers using tissue-engineered nanofiber skin substitutes: a review. Diabetes and Metabolic Syndrome: *Clinical Research and Reviews*, 15(2), 487-491

Banday, M. Z., Sameer, A. S., and Nissar, S. (2020). Pathophysiology of diabetes: An overview. *Avicenna Journal of Medicine*, 10(04), 174-188.

Barkai, U., Rotem, A., and de Vos, P. (2016). Survival of encapsulated islets: More than a membrane story. *World Journal of Transplantation*, 6(1), 69.

Baynes, H. W. (2015). Classification, pathophysiology, diagnosis and management of diabetes mellitus. *Journal of Diabetes and Metabolism*, 6, 1-9. Retrieved March 30, 2024.

Bayrami, A., Parvinroo, S., Habibi-Yangjeh, A., and Rahim Pouran, S. (2018). Bioextract-mediated ZnO nanoparticles: microwave-assisted synthesis, characterization and antidiabetic activity evaluation. *Artificial Cells, Nanomedicine, and Biotechnology*, 46(4), 730-739.

Biswas, P., and Wu, C.-Y. (2005). Nanoparticles and the environment. *Journal of the Air and Waste Management Association*, 55(6), 708-746.

Chen, G., Zhang, Y., Li, C., Huang, D., Wang, Q., and Wang, Q. (2018). Recent advances in tracking the transplanted stem cells using near infrared fluorescent nanoprobes: turning from the first to the second near infrared window. *Advanced Healthcare Materials*, 7(20), 1800497.

Cierpka-Kmiec, K., Wronska, A., and Kmiec, Z. (2019). In vitro generation of pancreatic βcells for diabetes treatment. I. β-like cells derived from human pluripotent stem cells. *Folia Histochemica et Cytobiologica*, 57(1), 1-14

Contera, S., De La Serna, J. B., and Tetley, T. D. (2020). Biotechnology, nanotechnology,and medicine.*Emerging Topics in Life Sciences*, *4*(6), 551–554. https://doi.org/10.1042/ETLS20200350

Debele, T.A., and Park, Y. (2022). Application of Nanoparticles: Diagnosis, Therapeutics, and Delivery of Insulin/Anti-Diabetic Drugs to Enhance the Therapeutic Efficacy of Diabetes Mellitus. *Life*, 12(12):2078. DOI: 112122078

Dinnyes, A., Schnur, A., Muenthaisong, S., Bartenstein, P., Burcez, C. T., Burton, N., Cyran, C., Gianello, P., Kemter, E., and Nemeth, G. (2020). Integration of nano and biotechnology for beta cell and islet transplantation in type 1 diabetes treatment. *Cell Proliferation*, 53(5), e12785.

Dragan Lovic, A. (2020). The Growing Epidemic of Diabetes Mellitus. *Current Vascular Pharmacology*, 18, 104-109. Retrieved March 30, 2024, from 1.

Evans, J. L., Balkan, B., Chuang, E., and Rushkaoff, R. J. (2016). Oral and Injectable (Non-Insulin) Pharmacological Agents for Type 2 Diabetes.

Gao, Y., Cui, Y., Chan, J. K., and Xu, C. (2013). Stem cell tracking with optically active nanoparticles. *American Journal of Nuclear Medicine and Molecular Imaging*, 3(3), 232.

Garbayo, E., Pascual Gil, S., Rodríguez Nogales, C., Saludas, L., Estella Hermoso de Mendoza, A., and Blanco Prieto, M. J. (2020). Nanomedicine and drug delivery systems in cancer and regenerative medicine. Wiley Interdisciplinary Reviews: *Nanomedicine and Nanobiotechnology*, 12(5), e1637.

He, Q., Song, J., Cui, C., Wang, J., Hu, H., Guo, X., Yang, M., Wang, L., Yan, F., Liang, K., Liu, Z., Liu, F., Sun, Z., Dong, M., Hou, X., and Chen, L. (2021). Mesenchymal stem cell-derived exosomal miR-146a reverses diabetic β-cell dedifferentiation. *Stem Cell Research and Therapy*, *12*(1), 1–16. https://doi.org/10.1186/S13287-021-02371-0/FIGURES/7

He, Y., Al-Mureish, A., and Wu, N. (2021). Nanotechnology in the treatment of diabetic complications: a comprehensive narrative review. *Journal of Diabetes Research*, 2021, 1-11.

Kaul, k., Tarr, J. M., Ahmad, S. I., Kohner, E. M., and Chibber, R. (2013). Introduction to diabetes mellitus. In advances in experimental medicine and biology (Vol. 771). *Retrieved March 30*, 2024.

Kitture, R., Chordiya, K., Gaware, S., Ghosh, S., More, P. A., Kulkarni, P., and Kale, S. N. (2015). ZnO nanoparticles-red sandalwood conjugate: a promising antidiabetic agent. *Journal of Nanoscience and Nanotechnology*, 15(6), 4046-4051.

Li, D., Liu, Y., and Wu, N. (2022). Application progress of nanotechnology in regenerative medicine of diabetes mellitus. *Diabetes Research and Clinical Practice*, 190, 109966.

Lou, J., Duan, H., Qin, Q., Teng, Z., Gan, F., Zhou, X., and Zhou, X. (2023). Advances in oral drug delivery systems: Challenges and opportunities. *Pharmaceutics*, 15(2), 484.

Matveyenko, A., and Vella, A. (2015). Regenerative Medicine in Diabetes. *Mayo Clinic Proceedings*, *90*(4), 546–554. https://doi.org/10.1016/J.MAYOCP.2015.01.019

Mohanraj, V., and Chen, Y. (2006). Nanoparticles-a review. *Tropical Journal of Pharmaceutical Research*, 5(1), 561-573.

Nigam, S., Bishop, J. O., Hayat, H., Quadri, T., Hayat, H., and Wang, P. (2022). Nanotechnology in Immunotherapy for Type 1 Diabetes: Promising Innovations and Future Advances. In Pharmaceutics (Vol. 14, Issue 3). MDPI.

Phillips, P. J. (2012). Oral glucose tolerance test. Australian family physician, 41. Retrieved March 30, 2024, from https://www.racgp.org.au/afp/2012/june/oralglucose-tolerance-testing

Qin, W., et al. (2022). "A comprehensive review of the application of nanoparticles in diabetic wound healing: therapeutic potential and future perspectives." *International Journal of Nanomedicine*, 17: 6007.

Sabek, O. M., Farina, M., Fraga, D. W., Afshar, S., Ballerini, A., Filgueira, C. S., Thekkedath, U. R., Grattoni, A., and Gaber, A. O. (2016). Three-dimensional printed polymeric system to encapsulate human mesenchymal stem cells differentiated into islet-like insulin-producing aggregates for diabetes treatment. *Journal of Tissue Engineering*, 7, 2041731416638198

Simos, Y. V., Spyrou, K., Patila, M., Karouta, N., Stamatis, H., Gournis, D., Dounousi, E., and Peschos, D. (2021). Trends of nanotechnology in type 2 diabetes mellitus treatment. In Asian Journal of Pharmaceutical Sciences (Vol. 16, Issue 1, pp. 62–76). *Shenyang Pharmaceutical University*. https://doi.org/10.1016/j.ajps.2020.05.001

Souto, E. B., Souto, S. B., Campos, J. R., Severino, P., Pashirova, T. N., Zakharova, L. Y., Silva, A. M., Durazzo, A., Lucarini, M., and Izzo, A. A. (2019). Nanoparticle delivery systems in the treatment of diabetes complications. *Molecules*, 24(23), 4209

Tripathi, B. K., and Srivastava, A. K. (2006). Diabetes mellitus: complications and therapeutics. *Medicine Science Monit*, 12(7), 130-147.

Wang, Y., Zhou, M., Wang, X., Qin, G., Weintraub, N. L., and Tang, Y. (2014). Assessing in vitro stem cell function and tracking engraftment of stem cells in ischaemic hearts by using novel iRFP gene labeling. *Journal of Cellular and Molecular Medicine*, 18(9), 1889-1894.

Yamaguchi, Y., and Igarashi, R. (2006). Nanotechnology for therapy of type 2 diabetes. Nihon rinsho. *Japanese Journal of Clinical Medicine,* 64(2), 295-300.

Yau, M., Maclaren, N. K., and Sperling, M. A. (2021). Etiology and pathogenesis of diabetes mellitus in children and adolescents. Endotext [Internet]. Retrieved march 30, 2024, from https://www.ncbi.nlm.nih.gov/books/NBK498653/ HYPERLINK "https://www.ncbi.nlm.nih.gov/books/NBK498653/"

Zhao, R., Lu, Z., Yang, J., Zhang, L., Li, Y., and Zhang, X. (2020). Drug delivery system in the treatment of diabetes mellitus. *Frontiers in Bioengineering and Biotechnology*, 8, 880.

Zhou, Q., and Melton, D. A. (2018). Pancreas regeneration. *Nature*, 557(7705), 351358