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Review Article

Therapeutic Efficacy of Nanoparticles in the Treatment of Diabetes Mellitus. An Overview

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Abstract

Nanotechnology can provide new solutions for diabetes management by developing more accurate .and less invasive methods for glucose monitoring and insulin delivery. For example, nanoparticles can be used as contrast agents to help diagnose type 1 diabetes at an early stage, or as carriers for oral insulin formulations that can bypass the digestive enzymes and reach the bloodstream. Nanosensors can also be implanted or worn on the skin to measure glucose levels continuously and wirelessly, reducing the need for painful finger pricks and frequent testing. Moreover, nanotechnology can enable smart insulin delivery systems that can automatically release insulin in response to variations in blood glucose levels, mimicking the function of a healthy pancreas. This review aims to highlight the recent advances and challenges of nanotechnology in diabetes treatment and prevention.

Keywords: Nanotechnology; Diabetes; Insulin; Nanopump; Artificial Pancreas

Introduction

A chronic condition that causes hyperglycemia levels due to insufficient or ineffective insulin is called diabetes mellitus (DM). Insulin is a hormone that controls blood glucose levels and is created and secreted by beta cells in the pancreas. Insulin helps glucose enter fat and muscle cells and increases glucose utilization in various tissues. Therefore, low insulin production or function results in hyperglycemia. Hyperglycemia can lead to several problems over time, such as fatty liver, atherosclerosis, diabetic nephropathy, and diabetic retinopathy [1]. According to Ogurtsova., *et al*. (2017) [2], 415 million people (aged 20 to 79) globally have diabetes mellitus. By 2038, it is anticipated that this number will reach 642 million.

There are different types of diabetes mellitus, but two main causes are recognized: lack of insulin (for example, type 1 diabetes, MODY, gestational diabetes, etc.) and resistance to insulin (such as type 2 diabetes). Type 1 diabetes usually requires insulin injections to control blood sugar levels and is often diagnosed in childhood. The most common type of diabetes in the world is type 2, which affects more than 90% of all people with diabetes. It results from a combination of insulin resistance and relative insulin deficiency. Insulin resistance means that normal levels of insulin are not enough to lower blood sugar adequately, so the pancreas has to produce more insulin to maintain normal or slightly high blood sugar levels. Elevated levels of insulin and high blood glucose levels are symptoms of type 2 diabetes. This disease has a genetic component and is influenced by various risk factors, such as aging, low physical activity, and obesity [3]. The pathogenesis, complications, and treatment of type 1 and type 2 DM are different, even though they have similar typical presentations. For instance, type 1 DM is more prone to ketoacidosis, while type 2 DM is linked to obesity, abnormal urinary acidification, and non-alcoholic steatohepatitis due to hyperinsulinemia [1].

Numerous applications of the diverse scientific field of nanotechnology exist and are intended to recover the attributes of life. A specific area of biomedicine called nanomedicine employs the concepts of nanoscience to prevent, identify, and cure a number of illnesses, including diabetes, cancer, and cardiovascular disease. The conventional treatment for diabetes is a prescription insulin supplemental treatment comprising long-acting insulin injections at meals. Diabetes patients may find insulin injections and glucose measurements uncomfortable and painful as part of their daily routine. Despite many attempts to address the limitations of injectable treatment, the need for safe, innovative, and effective diagnostic and therapeutic approaches persists [4].

Nanotechnology is a key research area for diabetes. It can help to improve the diagnosis of diabetes mellitus by providing more precise data. Nanotechnology also enables new ways of non-invasively monitoring blood glucose levels. Some examples of these methods are the molecular detection of diabetes, nanosphere-mediated oral insulin administration, the creation of artificial beta cells, and the artificial pancreas [4]. This review aims to highlight the recent advances and challenges of nanotechnology in diabetes treatment and prevention.

Diabetes mellitus

Diabetes mellitus (DM) is a term that refers to a set of metabolic conditions that cause high concentrations of sugar (hyperglycemia) due to decreased insulin secretion or action by the pancreas in the body [5].

Type 1 diabetes (also known as insulin-dependent, juvenile, or childhood-onset diabetes)

A type of autoimmune disease that destroys the pancreatic beta cells that secrete insulin is the cause of this form of diabetes. Without enough insulin, the body cannot function properly, and this is known as an autoimmune reaction or cause. About 5–10% of individuals suffering from diabetes worldwide are influenced by this medical condition which usually develops faster than other types of diabetes. It is most commonly diagnosed in children and young adults, and sometimes in older adults. Patients need to take insulin regularly to stay alive. Some possible triggers for this type of diabetes are infections by viruses or bacteria, food containing chemical toxins, unknown factors that cause autoimmune response, and genetic predispositions that may also contribute to type 1 diabetes [6]. The main etiological factor for this type of diabetes has a negative impact on the immune system by attacking and destroying the cells that secrete insulin in the pancreas (autoimmunity). The symptoms include excessive urination, thirst, hunger, weight loss, changes in vision, and tiredness. These symptoms may appear suddenly [7].

Type 2 diabetes

It is a condition where the body cannot use sugar properly due to insufficient or ineffective insulin. It affects most people with diabetes worldwide and is often caused by obesity and a lack of physical exercise. It can have serious complications for the eyes, heart, and nerves if not managed well. It used to occur mainly in adults, but now it is also seen in children. Treatment involves improving insulin function and sometimes taking insulin injections. It can be prevented or delayed by following a healthy diet and exercise regimen, as shown by Behera., *et al*. (2018) [7].

Type 3 diabetes (Gestational diabetes)

Gestational diabetes mellitus (GDM) is a type of diabetes that occurs during pregnancy. It is caused by abnormal glucose tolerance and can affect around 7% of pregnancies. Risk factors include genetics, age, ethnicity, and lifestyle choices. GDM can lead to complications for both the mother and baby, but can be managed with insulin and oral medication [7].

Pathophysiology of Diabetes

Insulin and glucagon are the two hormones that have the greatest impact on the body's ability to maintain glucose homeostasis [8]. Insulin is released by beta cells in response to increased blood glucose levels.

Glucagon is secreted by pancreatic cells when the blood glucose level is low. By accelerating liver functions including glycogenolysis and gluconeogenesis, glucagon has the opposite effect of insulin; moreover, cortisol and catecholamines enhance blood glucose levels [9].

Diabetes management

The main aim of diabetes management in the current scientific field is to achieve glycemic targets that can be based on four areas: Reaching optimal glycemic control, addressing the underlying causes of the disease, using combination therapy early and aggressively, and taking a comprehensive approach. The primary objectives of diabetes management are to: (a) reduce symptoms, (b) correct related health issues and lower the morbidity, mortality, and economic burden of diabetes; (c) prevent or delay acute and chronic complications; monitor their progression and intervene promptly; and to (d) enhance the quality of life and productivity of the person with diabetes [7].

Nanotechnology application to diabetic therapy

Nanotechnology is a cutting-edge scientific field that offers modern technological technology devices for accurate and timely disease diagnosis. Nanotechnology has a wide range of applications in drug delivery, and also, to enhance the oral absorption of proteins and peptides, nanocarriers are modified with specific ligands [10]. Nanoparticles have been extensively explored for biological applications, such as drug delivery, bioimaging, and biosensing. Nanoparticles can improve the stability and bioavailability of drugs across the gastrointestinal (GI) mucosa. Size is a crucial factor that affects the uptake and cellular internalization of nanoparticles. The maximum size limit for uptake by intestinal epithelium is 10 μm, but smaller nanoparticles have higher uptake efficiency [7].

Nanoparticles-based drug delivery systems have been widely used to enhance the oral absorption of peptide drugs by offering unique advantages such as high design flexibility and *in vivo* properties [11]. These mechanisms can shield protein-based medications from GI tract destruction and facilitate their passage through mucus and epithelial barriers to enter the circulation [12]. Many oral protein treatment NPs have been developed for diabetes disease treatment using different materials and formulations [12].

The main mechanisms are receptor-mediated transcytosis and paracellular transport, which allow the passage of molecules across the cell layer [13].

Peptide drugs can be loaded with high efficiency and kept in small delivery systems by using metal ions like zinc ions (Zn^{2+}), which can bind to them [14]. Zn-insulin is more stable against chymotrypsin digestion and does not produce fibrils. By decreasing the concentration of Zn2+, Zn-insulin can be converted into free insulin. Of peptide drugs [12]. Nanotechnology and smart nanostructures are emerging fields that offer great possibilities for various biomedical applications, such as monitoring, diagnosis, repair, and treatment of human biological systems. In recent times, many nanoparticles have been explored as alternative therapies for diabetic complications and inflammation, due to their multifunctional biological activities [15]. Some examples of nanomaterials that have been used for biomedical engineering are quantum dots, metal and metal oxide nanoparticles, two-dimensional carbon-based nanostructures, and stimuli-responsive polymers. These nanomaterials have shown advantages in optical imaging, drug delivery, nanotheranostics, antiviral and antibacterial applications, and nanomedicine. However, the safety and toxicity of nanomaterials in biomedical applications are also important issues that need to be addressed carefully.

Some examples of nanoparticles that have been investigated for insulin delivery are biodegradable polymers, micelles, ceramics, dendrimers, and liposomes [16]. These nanoparticles can overcome some of the limitations of conventional anti-diabetic drugs, such as low bioavailability, rapid degradation, immunogenicity, and side effects [16]. Nanotechnology is a new field with enormous potential for diabetes therapy [17]. The creation of biocompatible nano-composites for medication administration, particularly insulin, is one of the most promising uses of nanotechnology. Currently, insulin is administered by injection into the bloodstream, which is inconvenient and painful. This method is necessary because oral insulin would be destroyed by stomach acid. However, with nanotechnology, insulin could be delivered by inhalation and released in a controlled manner into the bloodstream. This would improve the management of blood sugar levels for diabetic patients.

According to previous research, some nanoparticles have the ability to deliver drugs to specific targets based on their characteristics, which can help reduce the complications of diabetes and enhance insulin secretion. Some of these nanoparticles are made of essential elements that have antioxidant properties and can improve diabetes. Nanoparticles have a high reactivity due to their small size and large surface-to-volume ratio. Using these elements at the nanoscale and targeting specific diseases such as diabetes could be an effective treatment strategy. Examples of such nanoparticles are vanadium, zinc, aluminum, cerium, and gold [18].

Nanotechnology and diabetes diagnosis

According to Taguchi., *et al*. (2014) [19], nanotechnology can provide revolutionary sensors for precise and health-related data, including the evaluation of insulin. To reduce the risk of hypoglycemia, diabetics must routinely be able to monitor their blood sugar levels [20]. For older individuals and kids in particular, this process can be difficult and unpleasant [21].

To monitor the blood sugar levels of diabetic patients, nanostructured implantable sensors employ beads of polyethylene glycol that are coated with fluorescent molecules [22]. The beads are injected into the interstitial fluid under the skin [23]. When the glucose level in the interstitial fluid drops to a dangerous level, it displaces the fluorescent molecules and causes a glow that can be detected by a tattoo on the arm [24]. This method is regarded as very effective. Recently, a microchip-based test that can differentiate between the two main types of diabetes mellitus and enable differential diagnosis has been developed [25].

Nanostructured injectable sensors use polyethylene glycol beads that have been coated with fluorescent molecules to measure the blood sugar levels of diabetic patients [22]. The interstitial fluid beneath the skin is where the beads are inserted [23]. A tattoo on the arm can be used to detect the glow that results when the interstitial fluid's glucose level decreases to a risky level and displaces the fluorescent molecules [24].

A type of islet encapsulation that uses biopolymer hydrogel to form a very thin layer around each islet is called nanoencapsulation [26]. This technique reduces the distance between the cell and the encapsulating surface, which improves the delivery of nutrients and insulin [27]. One advantage of nanoencapsulation is that it significantly reduces the volume of the transplant by removing the empty space between the islet and the encapsulating membrane [26]. This also enhances the response time of glucose–insulin [28] and increases the oxygen supply to islets. A smaller graft size also enables islet transplantation in narrow spaces like the portal vein, which is a common site for transplanting unencapsulated islets [29]. Moreover, nanoencapsulation provides better control over the uniformity of capsule thickness and pore size to improve permselectivity. It also allows adding specific functions to each film layer, such as immune evasion by hiding surface antigens, angiogenesis, anticoagulation, and other applications [27].

A single-layer conformal coating has some drawbacks, such as its inability to maintain long-term stability, since the islet membrane turnover causes it to unravel [28]. Moreover, the coating is too thin to resist mechanical and biochemical stress, and if the islets are not fully coated, they can trigger an immune response from the host [27].

The advancement of nano-biosensors that are highly sensitive and can detect low levels of harmful substances, as well as nanomaterials that enhance the performance of glucose sensors, will eventually improve the quality of life of people with diabetes (both type 1 and type 2) [30]. One of the main reasons for developing glucose sensors in the body is to diagnose hypoglycemia in people with insulin-dependent diabetes. Nanotechnology has improved these sensors by increasing their surface area, improving their catalytic properties, modifying their operating parameters, and improving electron transfer from the enzyme to the electrode.

Nanomaterials and diabetes treatment

In recent years, nanotechnology has been applied to create new delivery methods that can potentially improve the effectiveness of anti-diabetic treatments [31]. These methods involve the use of smart materials that can achieve two main goals: (a) to protect the drug by encapsulating it into a nano-carrier system; and (b) to release the drug in a controlled and gradual way. Therefore, anti-diabetic therapies that increase insulin production or reduce insulin secretion can be given to patients with SIRD, and nano-formulations of insulin can be used for patients with insulin deficiency (SAID and SIDD) [30].

Oral administration

The most convenient way to administer insulin orally for diabetes mellitus patients is widely accepted [32]. However, the absorption of hydrophilic drugs such as insulin is hindered by the intestinal epithelium, which prevents their diffusion through the lipid-bilayer cell membranes to the bloodstream [33]. Insulin delivery systems that rely on gastric enzymes expose the insulin to degradation and transfer in the stomach [34].

Mansoor., *et al*. (2019) [35] offer polymer-based nanoparticle methodologies for insulin delivery in various ways that are thought to be more effective than commonly used oral and intravenous administration techniques. In order to create insulin delivery systems that allow for the regulated release of insulin, biodegradable, pH-sensitive polymers with a nanoporous membrane are used [35].

In animal studies, nano-pellets loaded with insulin are used to achieve oral delivery of insulin polymeric nanoparticles [35]. Some of the polymer-based nanoparticles that are used for oral insulin administration are N-isopropyl acrylamide, polyethyleneimine, and polymethacrylic acid.

By encapsulating insulin within its matrix, hydrogels, and microspheres can protect it from enzymatic degradation and act as protease inhibitors. They can also act as permeation enhancers by crossing the epithelial layer after oral administration [36]. Therefore, they can deliver insulin effectively and offer a promising strategy for oral insulin administration [35].

Chitosan nanoparticles coated with mucoadhesive chitosan can also enhance the intestinal absorption of insulin more than chitosan aqueous solutions [33]. These nanomaterials can stay longer in the small intestine [37] and infiltrate the mucus layer, creating temporary openings in the tight junctions between epithelial cells. They can also degrade due to their pH sensitivity [31] and release insulin that can pass through the paracellular pathway into the bloodstream [38].

Nanosphere for oral insulin production

The transdermal [39] or oral routes [40] are deemed patient-friendly since they are noninvasive, reasonably straightforward, and practical ways to give insulin. Previous attempts to deliver insulin via these channels were impeded by their restrictions, which included low transport across epithelial barriers, poor absorption, and unpleasant gastrointestinal conditions [40]. For minimally invasive insulin delivery, Yu., *et al*. (2015) [41] created a glucose-responsive, insulin loaded nanoscale vesicle patch with microneedles.

When blood sugar levels are high, the glucose oxidase in the vesicles utilizes oxygen by oxidizing glucose. Low levels of oxygen result from this, causes the vesicles to disintegrate and release insulin by reducing 2-nitroimidazole [41]. To avoid excessive biofouling over time, this approach may still need to be improved, perhaps incorporating nanocoating or nanofabrication techniques [42].

Insulin nanogel

Based on glucose-responsive hydrogels, an innovative approach of injecting insulin may release insulin in response to changes in blood glucose levels. Gel-based systems demonstrate uncontrolled insulin leakage, weak mechanical strength, and postponed response times [43].

After a single injection, such devices have successfully maintained glycemic control in diabetic mice for up to 10 days. Similar systems that elicited an appropriate glucose response in diabetic mice for roughly 2 hours during a glucose tolerance test have been described with several and more diversified chemistries (e.g., polyethylene glycol-based nanogels) [44]. A novel insulin administration method is based on glucose-responsive hydrogels, which can release insulin in response to changes in blood sugar levels. Gel-based devices have poor mechanical strength, a high rate of insulin leakage, and delayed response times [43].

Gu., *et al*. (2013) [43] developed a very efficient insulin administration method based on an injectable gel comprised of pH-sensitive dextran nanoparticles loaded with the enzyme glucose oxidase, which converts glucose into gluconic acid. Due to improved glucose penetration into the gel, large amounts of gluconic acid are formed when the levels of glucose are sufficient. Insulin in the dextran spheres is then slowly broken down and released as a consequence of the resultant acidic environment.

The limited supply of donor tissue and the requirement for stringent immunosuppressive regimens are two obstacles to employing allogeneic islet transplantation to lower blood sugar levels in diabetic patients [45]. To get around these restrictions, various research teams have concentrated on creating more effective ways to differentiate induced pluripotent stem cells (IPCs), which can be created from the patient's own cells into cells that make insulin [46].

Through the development of cutting-edge methods for diagnosis, monitoring, and treatment, nanotechnology has a tremendous opportunity to enhance the treatment of patients with diabetes. To assess the usefulness, affordability, and efficacy of different kinds of nanotechnologies in clinical settings, additional study is nonetheless required. For instance, it is still unknown whether minute variations in the activity of immune cells or cell mass may accurately identify diabetes at an early stage. Despite the fact that nanoparticles can enable minimally invasive imaging of the pancreas. Similarly, while blood glucose measurements are the gold standard for diagnostics and monitoring, more research is needed to assess the benefits, cost-effectiveness, and feasibility of using nanotechnology for improved glucose sensibility, reliability, and strength, as well as a tool for assessing other metabolic products besides glucose that may be associated with the development or progression of disease [47].

Several preclinical investigations have demonstrated the significant potential of nanotechnology to enhance glucose detection and insulin system delivery. To assess the long-term safety and efficiency of such systems in regulating blood sugar levels in diabetic patients, further study is nonetheless required. Additionally, gene and cell therapies may help create insulin-producing cells through controlled cell differentiation or reprogramming, which may help find new treatments for diabetes [48]. Additionally, numerous nanoscale methods have been created for regulated gene delivery and differentiated cells *in vitro* and *in vivo* [49], though there is still little knowledge of the application of these methods in the field of treating diabetes.

Inhalation

A nanotechnology-based system of insulin delivery is being developed, that involves inhaling instead of injecting insulin. This enables the controlled release of insulin into the bloodstream [32] Compared to the gastrointestinal route, inhaler systems have low enzyme levels and a neutral pH [50]. Different inhaler systems can deliver active substances [51], such as dry powder formulations and solutions [52]. By encapsulating the insulin in nanoparticles, the dry powder formulation can be inhaled into the lungs, preventing insulin degradation and ensuring its delivery to the bloodstream [53]. However, this method requires regular lung function tests for the patients before the treatment, increasing its cost [32]. Since insulin is a water-soluble medication that diffuses poorly across the intestinal epithelium, chitosan nanoparticles are well suited for creating an inhalation delivery system for type 2 diabetes therapy [54].

Insulin absorption can be improved by chitosan [55]. By grafting carboxylated chitosan with poly(methylmethacrylate), advanced composite nanomaterials can be produced to enhance the controlled release of insulin [31].

Micro physiometer

A device called the Microphysiometer was constructed using multiple layers of carbon nanotubes, which resemble thin carbon sheets rolled into tiny cylinders. The nanotubes can conduct electricity, and the amount of insulin in the chamber is directly proportional to the electric current at the electrode. The nanotubes also function well at the pH levels typical of living cells. The current methods of measuring insulin production require taking small samples at regular intervals and testing their insulin levels. The new sensor can monitor insulin levels continuously by measuring the electron transfer that occurs when insulin molecules react with glucose in the presence of oxygen. The sensor's current increases or decreases depending on the insulin production of the cells, allowing real-time measurement of insulin concentrations [56].

Implantable sensor

Scientists use fluorescent-coated polyethylene glycol beads to track blood sugar levels in diabetes patients. The beads are placed under the skin and remain in the fluid between the cells. The fluorescent molecules are replaced by glucose when the blood sugar level becomes too low, causing a glow that can be detected by a tattoo on the arm. Another technology being developed is a sensor chip that can measure vital body signs such as pulse, temperature, and blood glucose.

The chip would be implanted under the skin and send a signal that can be monitored constantly [57].

Nanopump

A gadget with enormous promise for medical usage is the nanopump. According to Barkam., *et al*. (2013) [58], it comprises a tiny volumetric pump with two check valves integrated inside a chip made of micro or nanoelectromechanical systems (MEMS or NEMS). Three layers that are bonded together make up the chip. The two Pyrex plates that sit on top of the Silicon-on Insulator (SOI) layer at the top contain microfabricated pump structures. The primary use of the nanopump is to deliver insulin [59]. The nanopump can continuously pump insulin into the patient's bloodstream, controlling blood sugar levels. Additionally, it is capable of dispensing low amounts of medication continuously [60].

Artificial pancreas

Many studies have focused on micro or nano-based islet immunoisolation systems and tested the efficacy of encapsulated islets using *in vitro* and *in vivo* platforms. The advantages of an implantable nano-pancreas include the absence of external devices, the patient's lack of need to decide the amount of insulin to deliver, and the fact that the microcontroller completely controls the operation in a precise and effective way. Some notable accomplishments include the molecular diagnosis of diabetes, oral insulin delivery using nanospheres as biodegradable polymeric carriers, and the construction of artificial beta cells and an artificial pancreas [4].

A bioartificial pancreas consists of a functional tissue that can produce insulin, surrounded by a protective microenvironment that prevents inflammation and immune attacks, and enclosed in a selective membrane that allows glucose detection and insulin delivery. A bioartificial pancreas would overcome the challenges of grafting, survival, and rejection. It would also solve the problem of organ shortage by using unlimited sources of insulin-producing cells, such as pig islets or stem cell-derived beta cells [61].

A "smart" device that can adjust its release according to the body's needs is described by [62]. It has a bundle of over 100 microneedles that are filled with insulin and enzymes that can sense glucose levels [41]. Another research project involves the development of a nanorobot with glucose level detectors on its surface and insulin stored in its inner chambers. The surface detectors can detect any increase in blood glucose levels and activate selective insulin release [63].

Conclusion

The study and manipulation of matter at the nanoscale is called nanotechnology. This is a scale where atoms and molecules, which are very small units of length can be controlled and arranged. Nanotechnology has many potential applications in various domains, such as medicine, electronics, energy, and materials. Nanotechnology can help create new nanomaterials that have unique properties and functions and can be used to improve the diagnosis and treatment of diseases. For example, nanotechnology can help develop an artificial pancreas, oral insulin, smart cells, and implantable sensors for diabetic patients. These are new tools that can help regulate blood sugar levels, deliver insulin orally, monitor glucose levels, and prevent complications. These methods take advantage of the nanoparticles' ability to interact with biological systems, target specific cells or organs, and release drugs in a controlled manner. Nanotechnology can thus offer new solutions and benefits for diabetic patients and extend their life span. It is one of the most promising scientific fields of this century, as it can bring new innovations and contributions to modern medicine and other fields. The next generation of nanocomposites-mediated insulin, in conjunction with improved nanodevices, is predicted to improve diabetic patients' daily lives in the future.

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