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Review Article

Nanotechnology and diabetes

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Abstract

Nanotechnology offers sensing technologies that provide more accurate and timely medical information for diagnosing disease, and miniature devices that can administer treatment automatically if required. Some tests such as diabetes blood sugar levels require patients to administer the test themselves to avoid the risk of their blood glucose falling to dangerous levels. Certain users such as children and the elderly may not be able to perform the test properly, timely or without considerable pain. Nanotechnology can now offers new implantable and/or wearable sensing technologies that provide continuous and extremely accurate medical information. In the long run, nanotechnology will clearly open up many routes to treatments and cures for diabetes, as it will for many of the diseases and conditions that currently plague mankind. Nanotechnology offers some new solutions in treating diabetes mellitus. Boxes with nanopores that protect transplanted beta cells from the immune system attack, artificial pancreas and artificial beta cell instead of pancreas transplantation, nanospheres as biodegradable polymeric carriers for oral delivery of insulin are just some of them. The abilities of nanomedicine are huge, and nanotechnology could give medicine an entirely new outlook. Whilst some of these technologies are quite far-fetched, there is evidence that we will see significant advances in the treatment and management of diabetes quite soon. The purpose of this review is to throw more light on the recent advances and impact of nanotechnology on biomedical sciences to cure diabetes.

1. Introduction

The prevalence of diabetes is rapidly rising all over the globe at an alarming rate. Over the past 30 yr, the status of diabetes has changed from being considered as a mild disorder of the elderly to one of the major causes of morbidity and mortality affecting the youth and middle aged people. It is important to note that the rise in prevalence is seen in all six inhabited continents of the globe[2]. Type 2 diabetes represents approximately 90% of individuals with diabetes in the United States, while most of the remainder has type 1 diabetes. According to statistics from the Centre for Disease Control (CDC) diabetes is the sixth leading cause of death due to disease in the U.S., and the third leading cause among some ethnic populations[1].

The application of nanotechnology to medicine is called nanomedicine, it is defined as: "Research and technology development at the atomic, molecular and macromolecular levels in the length scale of approximately 1 – 100 nanometer range, to provide a fundamental understanding of phenomena and materials at the nanoscale and to create and use structures, devices and systems that have novel properties and functions because of their small and/or intermediate size." The size domains of components involved with nanotechnology are similar to that of biological structures. For example, a quantum dot is about the same size as a small protein (<10nm) and drug- carrying nanostructures are the same size as some viruses (<100 nm). Because of this similarity in scale and certain functional properties, nanotechnology is a natural progression of many areas of health-related research such as synthetic and hybrid nanostructures that can sense and repair biological lesions and damages just as biological nanostructures (e.g. white-blood cells and wound-healing molecules)[2]

2. Diabetes Mellitus

Diabetes (diabetes mellitus) is a metabolic disorder which results in high levels of blood glucose. It can be classified as either Type 1 or Type 2, depending on the reason for the high glucose levels. Type 1 diabetes means that the pancreas cannot produce insulin (a hormone which enables the uptake of glucose by the liver, muscle and fat tissue), whereas Type 2 means that the body's cells do not respond to the presence of insulin. Whilst Type 1 diabetes can be fatal if untreated, most patients today survive into old age - however, they must inject insulin several times a day to allow their body to use the glucose from their food. Our understanding and ability to treat insulin has been improving steadily, ever since the first insulin injections were carried out in the early 1920s by Banting and Best. Despite all the advances which have been made, insulin cannot be cured altogether, and a good deal of research effort is aimed at improving quality of life for diabetic patients, making their glucose tests and insulin injections as easy and non invasive as possible, and potentially devising a permanent cure for diabetes.[1, 3]

2.1 Use of nanotechnology in the detection of insulin and blood sugar: Current methods of blood glucose monitoring are invasive and often painful. The finger-prick test has been associated with non-adherence to treatment regimes by diabetic patients because of this, but it also has very limited accuracy - it cannot be performed during other activities, such as driving, or sleeping, and its intermittent nature means that it can miss important and potentially dangerous spikes and fluctuations in blood glucose levels in between tests.

Several improved methods for non-invasive, continuous monitoring of blood glucose have been proposed in the last few years. Many of these take advantage of the advances in medical technology made possible by nanotechnology.

A new method that uses nanotechnology to rapidly measure minute amounts of insulin and blood sugar level is a major step toward developing the ability to assess the health of the body's insulin-producing cells.[4] It can be achieved by following ways-

2.1.1 By microphysiometer: The microphysiometer is built from multiwalled carbon nanotubes, which are like several flat sheets of carbon atoms stacked and rolled into very small tubes. The nanotubes are electrically conductive and the concentration of insulin in the chamber can be directly related to the current at the electrode and the nanotubes operate reliably at pH levels characteristic of living cells. Current detection methods measure insulin production at intervals by periodically collecting small samples and measuring their insulin levels. The new sensor detects insulin levels continuously by measuring the transfer of electrons produced when insulin molecules oxidize in the presence of glucose. When the cells produce more insulin molecules, the current in the sensor increases and vice versa, allowing monitoring insulin concentrations in real time. This data could then be fed to an embedded microchip, which could send the data wirelessly to a wearable computer.[4, 5]

2.1.2 By Implantable Sensor ("smart Tattoo"): Use of polyethylene glycol beads coated with fluorescent molecules to monitor diabetes blood sugar levels is very effective in this method the beads are injected under the skin and stay in the interstitial fluid. When glucose in the interstitial fluid drops to dangerous levels, glucose displaces the fluorescent molecules and creates a glow. This glow is seen on a tattoo placed on the arm.

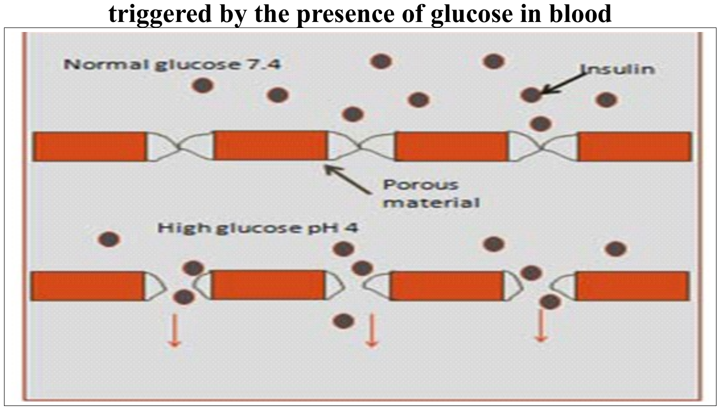
Sensor microchips are also being developed to continuously monitor key body parameters including pulse, temperature and blood glucose. A chip would be implanted under the skin and transmit a signal that could be monitored continuously.

Figure 1. The "pin-prick" glucose test could be replaced with more accurate and convenient methods using nanotechnology.

2.2 Use of nanotechnology in the treatment of diabetes:

2.2.1 Polymeric Nanoparticles: Polymeric nanoparticles have been used as carriers of insulin. These are biodegradable polymers, with the polymer–insulin matrix encloseed by the nanoporous membrane containing grafted glucose oxidase. A rise in blood glucose level triggers a change in the surrounding nanoporous membrane, resulting in biodegradation and subsequently release insulin. The glucose/glucose oxidase reaction causes a reducing the pH in the delivery system's. This can cause an increase in the swelling of the polymer system, leading to an increased release of insulin. The polymer systems examined for such applications include copolymers such as N,N-dimethylaminoethyl methacrylate and polyacrylamide. This "molecular gate" system is composed of an insulin reservoir and a delivery rate–controlling membrane made of poly[methacrylic acid-g-poly(ethylene glycol)] copolymer. The polymer swells in size at normal body pH (pH = 7.4) and closes the gates. It shrinks at low pH (pH = 4) when the blood glucose level increases, thus opening the gates and releasing the insulin from the nanoparticles. These systems release insulin by swelling caused due to changes in blood pH. The control of the insulin delivery depends on the size of the gates, the concentration of insulin, and the rate of gates' opening or closing (response rate). These self-contained polymeric delivery systems are still under research, whereas the delivery of oral insulinwith polymeric nanoparticles has progressed to a greater extent in the recent years. [2, 7]

Fig 2: Schematic of polymeric nanoparticles with pH-sensitive molecular gates for controlled insulin release triggered by the presence of glucose in blood



2.2.2 Oral Insulin By Using Polysaccharides And Polymeric Nanoparticles: Polysaccharides are natural biodegradable hydrophilic polymers, which exhibit enzymatic degradation behavior and good biocompatibility[16]. The development of improved oral insulin administration is very essential for the treatment of diabetes mellitus to overcome the problem of daily subcutaneous injections. Insulin, when administered orally, undergoes degradation in the stomach due to gastric enzymes. Therefore, insulin should be enveloped in a matrix like system to protect it from gastric enzymes. This can be achieved by encapsulating the insulin molecules in polymeric nanoparticles. In one such study, calcium phosphate–poly (ethylene glycol)–insulin combination was combined with casein (a milk protein). The casein coating protects the insulin from the gastric enzymes. Due to casein's mucoadhesive property, the formulation remained concentrated in the small intestine for a longer period, resulting in slower absorption and longer availability in the bloodstream.[2,7]

2.2.3Insulin Delivery Through Inhalable Nanoparticles: Inhalable, polymeric nanoparticle-based drug delivery systems have been tried earlier for the treatment of tuberculosis. Such approaches can be directed toward insulin delivery through inhalable nanoparticles. Insulin molecules can be encapsulated within the nanoparticles and can be administered into the lungs by inhaling the dry powder formulation of insulin. The nanoparticles should be small enough to avoid clogging up the lungs but large enough to avoid 414 being exhaled. Such a method of administration allows the direct delivery of insulin molecules to the bloodstream without undergoing degradation. A few studies have been done to test the potential use of ceramic nanoparticles (calcium phosphate) as drug delivery agents. Porous hydroxyapatite nanoparticles have also been tested for the intestinal delivery of insulin. Preclinical studies in guinea pig lungs with insulin-loaded poly (lactide-co-glycolide) nanospheres demonstrated a significant reduction in blood glucose level with a prolonged effect over 48 hours when compared with insulin solution. Insulin-loaded poly (butyl cyanoacrylate) nanoparticles when delivered to the lungs of rats were shown to extend the duration of hypoglycemic effect over 20 hours when compared with pulmonary administration of insulin solution. The major factors limiting the bioavailability of nasally administered insulin include poor permeability across the mucosal membrane and rapid mucociliary clearance mechanism that removes the non mucoadhesive formulations from the absorption site. To overcome these limitations, mucoadhesive nanoparticles made of chitosan/tripolyphosphate and starches have been evaluated. These nanoparticles showed good insulin-loading capacity, providing the release of 75% to 80% insulin within 15 minutes after administration. [2, 8]

2.2.4 Applications Of Nanotechnology In Diabetes: Diabetes is considered to be one of the major afflictions of modern western society. To date, diabetic patients control their blood-sugar levels via insulin introduced directly into the bloodstream using injections. This unpleasant method is required since stomach acid destroys protein-based substances such as Insulin, making oral insulin consumption useless. The new system is based on inhaling the insulin (instead of injecting it) and on a controlled release of insulin into the bloodstream (instead of manually controlling the amount of insulin injected). The treatment of diabetes includes the proper delivery of insulin in the blood stream which can be achieved by nanotechnology in the following ways:

2.2.5 Development Of Oral Insulin: Production of pharmaceutically active proteins, such as insulin, in large quantities has become feasible. The oral route is considered to be the most convenient and comfortable means for administration of insulin for less invasive and painless diabetes management, leading to a higher patient compliance. Nevertheless, the intestinal epithelium is a major barrier to the absorption of hydrophilic drugs, as they cannot diffuse across epithelial cells through lipid-bilayer cell membranes to the bloodstream. Therefore, attention has been given to improving the paracellular transport of hydrophilic drugs. A variety of intestinal permeation enhancers including chitosan(CS) have been used for the assistance of the absorption of hydrophilic macromolecules. Therefore, a carrier system is needed to protect protein drugs from the harsh environment in the stomach and small intestine, if given orally. Additionally, CS nanoparticles (NPs) enhanced the intestinal absorption of protein molecules to a greater extent than aqueous solutions of CS in vivo.

The insulin loaded NPs coated with mucoadhesive CS may prolong their residence in the small intestine, infiltrate into the mucus layer and subsequently mediate transiently opening the tight junctions between epithelial cells while becoming unstable and broken apart due to their pH sensitivity and/or degradability. The insulin released from the broken-apart NPs could then permeate through the paracellular pathway to the bloodstream, its ultimate destination.

2.2.6 Microsphere For Oral Insulin Production: The most promising strategy to achieve oral insulin is the use of a microsphere system which is inherently a combination strategy. Microspheres act both as protease inhibitors by protecting the encapsulated insulin from enzymatic degradation within its matrix and as permeation enhancers by effectively crossing the epithelial layer after oral administration.

2.3 Artificial Pancreas: Development of artificial pancreas could be the permanent solution for diabetic patients. The original idea was first described in 1974. The concept of its work is simple: a sensor electrode repeatedly measures the level of blood glucose; this information feeds into a small computer that energizes an infusion pump, and the needed units of insulin enter the bloodstream from a small reservoir.

Another way to restore body glucose is the use of a tiny silicon box that contains pancreatic beta cells taken from animals. The box is surrounded by a material with a very specific nanopore size (about 20 nanometers in diameter). These pores are big enough to allow for glucose and insulin to pass through them, but small enough to impede the passage of much larger immune system molecules. These boxes can be implanted under the skin of diabetes patients. This could temporarily restore the body's delicate glucose control feedback loop without the need of powerful immunosuppressant that can leave the patient at a serious risk of infection.

Scientists are also trying to create a nano-robot which would have insulin departed in inner chambers, and glucose level sensors on the surface. When blood glucose levels increase, the sensors on the surface would record it and insulin would be released. Yet, this kind of nano-artificial pancreas is still only a theory.[1, 2, 8]

3. The Nanopump

The nanopump is a powerful device and has many possible applications in the medical field. The first application of the pump, introduced by Debiotech, is Insulin delivery. The pump injects Insulin to the patient's body in a constant rate, balancing the amount of sugars in his or her blood. The pump can also administer small drug doses over a long period of time.[9]

4. Summary And Conclusion

Diabetes mellitus, often simply referred to as diabetes—is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). It is the most common endocrine disorder and by the year 2012, it is estimated that more than 200 million people worldwide will have DM and 300 million will subsequently have the severe diabetic complication such as retinopathy, neuropathy, nephropathy, cardiovascular complication and ulceration.

Nanotechnology can be defined as the monitoring, repairing, construction and control of human biological systems at the cellular level by using materials and structures engineered at the molecular level. It is useful in detection of insulin and blood sugar by the help of microphysiometer and implantable sensors. By using nanotechnology the nanoparticles were formed and these nanoparticles are also useful in treatment of diabetes. In which a) a polymeric nanoparticle these polymeric nanoparticles have been used as carriers of insulin for giving targeted site of action b) oral insulin administration by using polysaccharides and polymeric nanoparticles the development of improved oral insulin administration is very essential for the treatment of diabetes mellitus to overcome the problem of daily subcutaneous injections c) insulin delivery through inhalable nanoparticles in this insulin molecules can be encapsulated within the nanoparticles and can be administered into the lungs by inhaling the dry powder formulation of insulin, this will be an effective in treatment of diabetes. And its applications in developments of oral insulin, microsphere for oral insulin production, development of artificial pancreas, nanopumps the pump injects Insulin to the patient's body in a constant rate, balancing the amount of sugars in his or her blood. The pump can also administer small drug doses over a long period of time. These are all about the disease diabetes in which the nanotechnology helps in the treatment of diabetes and its recent advances used for diabetes treatment.

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