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Review Article

Nanotechnology in Diabetes Management

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Abstract

Nanotechnology is an interdisciplinary scientific field with a great number of applications, which are developed in order to improve the quality of life. Nanomedicine is a specialized branch of medicine that applies the fundamentals of nanotechnology to the prevention, diagnosis and treatment of various diseases, such as cancer, cardiovascular diseases and diabetes. Diabetes mellitus is considered to be among the major afflictions of modern western society. The common approach of this condition is a prescribed insulin replacement therapy, including injections of long-acting insulin at mealtimes. Regarding the everyday routine, insulin injections and glucose tests can be painful and time consuming for diabetic patients. Many efforts are given to overcome the drawbacks of injection therapy, but there is the need for new safe and cost-effective technologies for diagnosis and treatment. Nanotechnology has obtained increasing importance in the research of diabetes. Nanotechnology-based tests can provide more accurate information for the diagnosis of diabetes mellitus. Several therapeutic methods have been proposed for non-invasive monitoring of blood glucose, based on nanotechnology. Some representative achievements include the molecular diagnosis of diabetes, the oral delivery of insulin with the use of nanospheres as biodegradable polymeric carriers, the development of artificial beta cells and artificial pancreas. The aim of this review is to provide insights into the role of nanotechnology in diabetes diagnosis and treatment, shedding light on the potential of nanotechnology in this field and discussing the future prospects.

Keywords: Nanomedicine; Nanotechnology; Diabetes mellitus; Nanomaterials; Diagnosis; Treatment

Introduction

Nanotechnology is a scientific and technological combination, integrating various fields, such as physics [1], chemistry [2], biotechnology and engineering [3]. It is considered as the manipulation of matter with at least one dimension sized from 1 to 100 nanometers [4]. The interesting potential of nanotechnology, due to the special properties of nanomaterials, leads to a great number of applications, which are developed in order to improve the quality of life [5]. Nanomedicine is a specialized branch of medicine that applies the fundamentals of nanotechnology to the prevention and/or the treatment of various diseases [6]. Thus, nanomedicine involves the utilization of nanostructured materials for diagnosis, delivery, detection or actuation purposes in a living organism [7]. There are numerous companies specializing in the fabrication of new forms of nanosized matter, with anticipated applications that include medical therapeutics and diagnostics, energy production, molecular computing and structural materials [4,8]. Nanotechnology can enhance drug delivery to those areas which were unfavorable for macromolecules to approach [9]. Furthermore, it offers new implantable sensing technologies, providing accurate medical information [10]. Cancer and cardiovascular diseases diagnosis and treatment, dental applications and development of bone implants are among the most famous applications of nanomedicine [11-16]. Diabetes is considered to be among the major afflictions of modern western society. Recent studies demonstrated that around approximately 9.3 percent of the global adult population suffered from diabetes in 2019 [17]. According to mathematical models, based on clinical data, by the year 2045, this percentage is expected to rise to almost 11 percent [17,18]. Diabetes is typically characterized by increased thirst, excessive weight loss or excessive desire to eat, increased urge for urination and thus resulting in abnormal increase in blood glucose level [19,20]. It is classified as Type 1, Type 2 or gestational diabetes mellitus, depending on the reason for high blood sugar [19-21]. In type 1-diabetes, the body cannot produce insulin due to loss of β-cells, as a result of T-cell mediated autoimmune attack [22]. The common approach of this condition is a prescribed insulin replacement therapy, including injections of long-acting insulin at mealtimes [23]. An insulin-resistance combined with insulin deficiency is found in patients, suffering from type 2-diabetes [24]. Exercise and regulation of the meals is suggested for the initial treatment of type of diabetes [25]. Diabetes can lead to serious long-term health complications, such as cardiovascular disease, chronic kidney disease, stroke, foot ulcers, damage to the nerves, damage to the eyes and cognitive impairment and is among the top ten leading causes of death worldwide [26,27].

Regarding the everyday routine, insulin injections and glucose tests can be painful and time consuming for diabetic patients [28]. Many efforts are given to overcome the drawbacks of injection therapy [29]. Several technologies have been developed, such as continuous glucose monitors and insulin pumps to improve patient compliance [30]. But there is the need for new safe and cost-effective technologies for diagnosis and treatment, since there is still risk of patient's infection and scarring due to implanted sensors and cannulas [31]. All the widely used devices must be frequently replaced and maintained with a high cost for the patients and the health systems worldwide [32]. Nanotechnology has obtained increasing importance in the research of diabetes [33]. It can provide more accurate information for the diagnosis of diabetes mellitus [34]. Furthermore, several therapeutic methods have been proposed for non-invasive monitoring of blood glucose, based on nanotechnology [35]. Some representative achievements include the molecular diagnosis of diabetes, the oral delivery of insulin with the use of nanospheres as biodegradable polymeric carriers, the development of artificial beta cells and artificial pancreas [34,36]. Thus, this review outlines the role of nanotechnology in diabetes diagnosis and treatment, shedding light on the potential of nanotechnology in this field and discussing the future prospects.

Nanotechnology and Diabetes Diagnosis

Nanotechnology can provide sensing technologies for accurate and medical information, for diagnosis of diabetes [37]. Diabetes blood sugar level tests require autonomous periodical checks by the patients, to avoid the risk of blood glucose decrease to dangerous levels [38]. Sometimes this routine is difficult and painful to be held, particularly for the elderly people and the children [39]. Nanotechnology can offer the opportunity for the development of implantable and wearable sensing technologies, providing continuous and accurate medical information [40]. The most common ways of exploiting nanotechnology in the diagnosis of diabetes is by applying microphysiometer or by using implantable sensor [41]. The microphysiometer is built from multiwalled carbon nanotubes, which are electrically conductive [42]. The concentration of insulin in the chamber is directly related to the current at the electrode and thus, the nanotubes are absolutely functionable at pH levels which are characteristic of living cells [43]. The conventional detection methods typically measure insulin production at intervals, by collecting and measuring small samples, periodically [44]. The microphysiometer can detect insulin levels continuously and indirectly, by estimating the transfer of electrons which are produced when insulin molecules get oxidize, by the glucose [44]. Fundamentally, when the cells produce more insulin molecules, the current which is generated inside the sensor, increases and vice versa, allowing real time monitoring insulin concentrations in [45].

Nanostructured implantable sensors use polyethylene glycol beads, coated with fluorescent molecules in order to monitor diabetes blood sugar levels [46]. The beads are injected under the skin, staying in the interstitial fluid [47]. If the glucose in the interstitial fluid falls to dangerous levels, glucose displaces the fluorescent molecules and creates a glow, which is seen on a tattoo placed on the arm [48]. This method is considered as very effective. However, sensor microchip is another alternative, which is being developed to continuously monitor crucial body parameters such as pulse, blood glucose and temperature [40]. In these applications, the microchip is implanted under the skin, transmitting a signal that could be monitored continuously [40]. Recently a microchip-based test to distinguish between the two main forms of diabetes mellitus, allowing differential diagnosis has been developed [49]. Actually, this cheap, portable, microchip-based test can diagnose type-1 diabetes. Traditional methods for detecting diabetes are expensive, quite slow and they are available only in well-equipped health-care centers [50]. The proposed test applies fluorescence to detect the antibodies. The glass plates which are formed the base of each microchip are coated with gold nanoparticle-sized, allowing the amplification of the fluorescent signal in order to obtain reliable antibody detection [51]. The gold nanoparticles ensure the creation of nanogaps, supporting the enhanced electric field [52]. This technology is expected to improve patient care, assisting in a better understanding of the disease.

Nanomaterials and Diabetes Treatment

Various types of nanomaterials are currently studied for insulin delivery in diabetes treatment [53]. Ceramic nanoparticles, liposomes, dendrimers, polymeric biodegradable nanoparticles and polymeric micelles are the most promising among the proposed ones [54], (Figure 1). Depending on the type of administration each and every one of these categories of nanomaterials gathers some advantages [4].

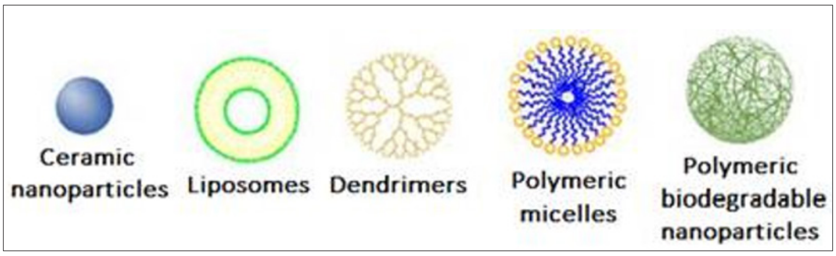

Figure 1: Nanomaterials suitable for diabetes treatment.

Oral administration

Oral insulin administration is considered as the most convenient method for diabetes mellitus maintenance [29]. However, the intestinal epithelium is considered as a major barrier to the absorption of hydrophilic drugs, like insulin, as lipid-bilayer cell membranes don't allow the diffusion of these drugs to the bloodstream [55]. Drug delivery systems based on gastric enzymes ensure the transfer and the degradation of the insulin in the stomach [7]. A protective matrix is necessary to embed the active substance, protecting it from the harsh environment inside the stomach [56]. A combination of calcium phosphate-polyethylene glycol-insulin with casein is indicated as an effective choice [57]. Mansoor et al. [58] present polymer-based nanoparticle strategies for insulin delivery, in various forms [58]. Polymeric nanoparticles are considered quite efficient compared to conventional oral and intravenous administration methods which are widely used [59]. In order to form insulin delivery systems, biodegradable, pH-sensitive polymers surrounded by nanoporous membrane are used, allowing controlled release of insulin [58]. In animal studies, the oral delivery of insulin polymeric nanoparticles is achieved through the use of nano-pellets loaded with insulin [58]. N-isopropylacrylamide, polyethylenimine and polymethacrylic acid are some of the polymer-based nanoparticles which are used for oral insulin administration [60]. Also, co-polymers like N, N-dimethylaminoethyl methacrylatem, polyurethanes, polyacrylic acids, polyanhydrides and polyacrylamide are being under investigation in order to be used as insulin carriers [61]. Hydrogels and microspheres can play a double role, acting both as protease inhibitors by protecting the encapsulated insulin from enzymatic degradation within its matrix as well as permeation enhancers by effectively crossing the epithelial layer post oral administration [62,63]. Thus, they can effectively carry insulin, providing a promising strategy for oral insulin administration [58].

Additionally, chitosan nanoparticles are proven to enhance the intestinal absorption of insulin to a greater extent than aqueous solutions of chitosan [55]. In particular, insulin loaded chitosan nanoparticles which are coated with mucoadhesive chitosan seem to prolong their residence in the small intestine [64]. These composite nanomaterials can efficiently infiltrate into the mucus layer, mediating transient opening within the tight junctions between epithelial cells, becoming unstable and finally degrading due to their pH sensitivity [65]. Thus, the insulin which is released from the broken-apart nanocomposites can permeate through the paracellular pathway into the bloodstream [66].

Inhalation

The new nanotechnology-based insulin system is focusing on inhaling the insulin, instead of injecting it, allowing its controlled release into the bloodstream [29]. Compared to the gastrointestinal route, inhaler systems provide the pros of mild environment, including low enzyme concentrations and neutral pH [67]. Various types of inhaler systems can be used to deliver the active products [68]. Dry powder formulations and solutions are among the most common [69]. The encapsulation of insulin within the nanoparticles, allows the inhalation of the dry powder formulation of insulin into the lungs [70]. Insulin degradation is avoided, ensuring the delivery of insulin to the bloodstream. In order to maximize the efficacy, regular lung function tests are required to be applied to the patients, before the treatment, increasing the cost of this approach [29]. Di J et al. [71] proposed a controlled insulin delivery system, based on injectable polymeric nanoparticle-crosslinked network, able to be noninvasively triggered by a Focused Ultrasound System (FUS) [71]. As a matrix material biodegradable poly(lactic-co-glycolic acid) (PLGA) was used [71]. They demonstrated that the resulting FUS-activated insulin encapsulated nano-network could regulate blood glucose levels of type 1 diabetic mice in a long-term [71]. For the treatment of type 2-diabetes, chitosan nanoparticles are considered to be suitable for the development of an inhalation delivery system [53]. Since, insulin is a hydrophilic drug, it is difficult to be diffused through intestinal epithelium [72]. Chitosan can enhance the absorption of insulin [73]. Advanced composite nanomaterials, produced by carboxylated chitosan grafted with poly(methylmethacrylate) seem to increase the efficiency of the controlled release of insulin [65].

Nanopump

The nanopump is a powerful device with many medical applications. It is a tiny volumetric pump with a pair of check valves that is integrated into a Micro-Electromechanical Systems (MEMS) or a Nano Electromechanical Systems (NEMS) chip [74]. From as structural point of view, the chip is a stack of three layers bonded together. The first one is a Silicon-on- Insulator (SOI) layer with micromachined pump-structures, and the two others are Pyrex cover plates. Insulin delivery is the main application of the pump, introduced by Debiotech [75]. The pump can inject insulin to the patient's body in a constant rate, balancing the amount of glucose in the blood. It can also administer small drug doses over a long period of time [76].

Artificial pancreas

The development of an artificial pancreas system, comprising of a continuous glucose monitor, glucose meter and an insulin infusion pump for the monitor calibration could be the permanent solution for the patients who suffer from diabetes mellitus [77]. The original initial idea was first demonstrated in 1974 [78]. The fundamental of this concept includes a sensor electrode which can repeatedly measure the level of blood glucose, with the data feeding into a tiny computer [44]. This process can trigger an infusion pump, and the appropriate units of insulin can enter the bloodstream from a small reservoir [79]. The utilization of a tiny silicon box, containing pancreatic beta cells obtained from animals is an alternative approach [80]. This application is used to protect transplanted cells from the immune system. It also allows the sufficient diffusion of glucose, insulin and oxygen [81]. It can be implanted under the skin of diabetes patients. This box is encapsulated in a material with a specific nanopore size. These pores allow glucose and insulin to pass through them, while impede the passage of much larger immune system molecules [82]. A smart insulin patch is the promising achievement for insulin delivery [83]. This device can release depending on the body's needs and therefore it is called "smart" [84]. It contains a pack of more than 100 microneedles, which are packed with insulin and glucose-sensing enzymes [85]. The current scientific attempt includes the development of a nanorobot with glucose level sensors on the surface and insulin departed in inner chambers. The sensors on the surface can record any increase in blood glucose levels, triggering selective insulin release [86].

Conclusion

The impact of nanotechnology on medicine is uncontested. In this manuscript the use of nanotechnology in diabetes diagnosis and treatment was discussed. It was demonstrated that it is very promising in detection of insulin and blood glucose but also in insulin efficient administration and delivery. Nanotechnology-based techniques are being helpful in the development of new strategy for the treatment of diabetes, including glucose-responsive insulin therapy. Continuous glucose monitoring devices as well as insulin delivery systems like artificial pancreas will be invaluable for diabetic patients. Nanotechnology promised a total absence of lag time between glucose detection and insulin delivery, avoiding dangerous situations, such as hypoglycemia. The next generation nanocomposites-mediated insulin in parallel with advanced nano-devices are expected to improve everyday life of diabetic patients in the future.

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