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Nanomedicine in diabetes management

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Abstract
India has been declared as the diabetic capital of world. By 2030 there would be 366 million diabetics throughout the world and 79.44 million diabetics in India alone according to WHO, 2007. It is estimated that by the year 2030, diabetes is likely to be the seventh leading cause of death accounting 3.3% of total deaths in the world. Self-monitoring of glucose levels is major problem along with other conventional problems faced by patients, can be solved by use of nanotechnology. Nanotechnology offers accurate and timely medical information for diagnosing disease by administering miniature devices. Nanomedicine can assist elderly and children to perform regular tests like checking blood sugar levels without difficulty or pain as well give timely and accurate results. Nanotechnology can now offer new implantable and wearable sensing technologies like glucose nanosensors, layer-by layer (LBL) technique, carbon nanotubes, artificial pancreas and nanopumps which provide continuous and extremely precise medical information helping patients to maintain the quality life.

Keywords: Diabetes, Nanomedicine, self-monitoring, glucose Nanosensors

Introduction
Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago (Arora *et al.*, 2009) [1]. DM is the commonest endocrine disorder that affects more than 100 million people worldwide (6% of total population). The number of people with diabetes is increasing due to population growth, aging, urbanization increased prevalence of obesity and physical inactivity leading to increased morbidity and mortality in these patients because of its insidious onset and late recognition, especially in resource-poor developing countries like India (Olokoba *et al.*, 2012) [22]. It is caused by deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood leading to increased risk of complications like cardiovascular diseases, peripheral vascular diseases, stroke, neuropathy, renal failure, retinopathy, blindness, amputations, *etc.* (Ismail, 2009; Wild *et al.*, 2004 and Jothivel *et al.*, 2007) [16, 29, 17].

However, recent data from the International Diabetes Federation suggest that previous estimates have already been exceeded with a prevalence of 415 million by 2015 and estimated to reach 642 million by 2040 (IDF, 2015) [15].

Type I diabetes is an autoimmune disease characterized by a local inflammatory reaction in and around islets followed by selective destruction of insulin secreting cells whereas Type II diabetes is characterized by peripheral insulin resistance and impaired insulin secretion (Arora *et al.*, 2009) [1]. Type I diabetes accounts for 10-20% of diagnosed cases usually occurring in children and young adults. Type 2 diabetes accounts for 80- 90% of the cases and is usually diagnosed in middle age and older adults (Govindappa, 2015) [9]. Other specific type of DM are gestational diabetes, a temporary condition that appears during pregnancy usually develops during third trimester of pregnancy. After delivery, blood sugar levels generally return to normal (Deepthi *et al.*, 2017) [7]. Maturity-onset diabetes of the young (MODY) is linked with the defects in beta cell function and characterized by linkage of chromosome 7 to the glucokinase deficiency found in maturity-onset diabetes of the young MODY 2 where as in MODY 3 is linked to chromosome 12 and MODY 1 to chromosome 20. Although few patients have DM related to these other entities, the clinician interpreting blood glucose screening results must consider the patient's medical history (Harikumar *et al.*, 2015). Considering increase in number of diabetic patients, for ease and accuracy in treatment nano medicine gives a new hope.

Nano medicine offers a new line of solutions to manage and treat DM, by providing continuous and accurate information. Currently several researches with help of nanotechnology are conducting tests on potential of nano medicine for managing and treating diabetes. The various nanotechnologies used in managing and treating DM are discussed in this paper *viz.*, implantable glucose nano sensors, nano pump, nanotubes, artificial pancreas and oral insulin.

Nanotechnology in diagnosis and monitoring: Early detection and identification of DM is the key for management of disease. The advances in nanotechnology, molecular imaging and biomedical imaging are tools creating opportunities for the same. The β-cell mass along with insulin production and secretion is greatly reduced as diabetes progresses. The assessment of β-cell using imaging β-cell-targeting peptide dyes (Reiner *et al.,* 2011) [26] and antibody–dye conjugates (Moore *et al.,* 2001) [21] are tedious requiring invasive procedures for the detecting of these type of β-cell to develop successful therapies (Veiseh *et al.* 2015) [28]. The nano probes with β-cell specificity and high contrast to enable non-invasive quantification of *in-vivo* endogenous β-cell mass, survival of exogenous transplanted islets and the performance of islet cells in cell replacement therapy are being carried out (Veiseh *et al.* 2015) [28].

Implantable glucose nano sensors: Glucose monitoring is required for maintaining and control blood glucose levels within normal ranges, which is currently done but finger prick method, where an electronic device reads the blood placed on the sensor and reports the values. This method involves painful sampling and cannot be performed when the patient is preoccupied with some activities like driving or sleeping (Burge *et al.,* 2008; Pickup *et al*., 2008; Cash and Clark 2010) [3, 23, 4]. These drawbacks can be dealt with help of nanotechnology where implantable devices incorporated with glucose nano sensors provide accurate, patient-friendly and real-time tracking of blood glucose levels and using glucose-responsive nanoparticles mimicking the body's physiological needs for insulin (Veiseh *et al.* 2015) [28].

'Smart tattoo' is one such non-invasive improved nano technique for *in-vivo* glucose monitoring consisting of glucose-responsive, fluorescence-based nanosensors implanted into the skin (Meetoo and Lappin, 2009; Rahiman and Tantry, 2012) [20, 25]. To monitor blood sugar levels effectively the researchers used polyethylene glycol beads coated with fluorescent molecules were injected under skin to stay in interstitial fluid. A tattoo placed on the arm glows when interstitial glucose levels drop (Gordon and Sagman 2003 and Arya *et al*. 2008) [8, 2].

Glucose oxidase, glucose-binding proteins and glucose-binding small molecules are the three main classes of glucose sensing molecules that can be used to engineer nanoparticle-based glucose sensors. Glucose nano sensors are at early stage of development and testing with *in vivo* studies being carried out only in animal models (Veiseh *et al.* 2015) [28]. Encapsulated glucose sensors such as glucose oxidase (Trau and Rennenberg 2003) [27] can be implanted in body in electrostatic layer-by-layer (LBL) technique which is a nano assembly of capsules composed of alternating layers of positively and negatively charged polymers with thin film and tunable permeability and controlled biocompatibility (Rahiman and Tantry 2012; Chinnayelka and McShane 2006; Pickup *et al*. 2008) [25, 5, 23].

In glucose monitoring it is most essential to maintain the normoglycemic levels, thus insulin replacement therapy helps to maintain is suggested to imitate the natural insulin levels the throughout the day for Type 1 diabetes (Veiseh *et al.*, 2015) [28]. Traditional insulin therapy might be painful for the patients, as they may have fear of injections, training needs to be given to the patients for self-assessment etc. (Grunberger G. 2013; Veiseh *et al.* 2015) [10, 28]. Thus, to overcome these problems with the injection therapy, many technologies are being developed for ease of the patients. These include glucose monitors and insulin pumps. An example is Pager-Sized Insulin Pumps worn externally having replaceable depot of insulin attached to a subcutaneously implanted canula. The pager is programmed to maintain insulin levels throughout the day. The continuous glucose monitors (CGMs) provide real time data for blood glucose with help of the sensors inserted subcutaneously which measure the glucose of interstitial fluid (Keenan, *et al.* 2008; Veiseh *et al.* 2015) [28]. Another such example is nanopump introduced by Debiotech for insulin delivery, the pump injects insulin balancing the amount of patients' blood sugar (Rahiman and Tantry 2012; Piveteau, 2013) [25, 24].

Nanotubes: Carbon nanotubes (CNT) discovered in 1991 are excellent medium keeping drug intact during effective delivery and transport in the body (Iijima 1991) [14]. The demonstrating semiconducting single-wall carbon nanotubes were versatile biosensors acting as sensitive PH sensors that can control GOx (glucose oxidase). The carbon nanotubes along with glucose-oxidase biosensors have been used for accurately detecting and controlling blood sugar in diabetic patients (Besteman, *et al*. (2003); He *et al.* 2013) [13].

Artificial Pancreas: Vascular problems associated with the long-term DMcannot be solved by traditional medication, thus one of the solutions could be pancreatic transplanting using artificial endocrine pancreas (electromechanical artificial pancreas) that consists of a glucose sensor, a computer and a pumping device (Rahiman and Tantry 2012) [25]. Artificial pancreas is tiny silicon box that can be implanted under the skin of diabetic patients, surrounded by specific nanopore size which allow glucose and insulin to pass through them, containing pancreatic beta cells taken from animals (Arya *et al*. 2008) [2].

Oral insulin: Oral consumption route is the most convenient and suitable way to manage diabetes as compared to the insulin injections thus developing oral insulin is beneficial (Arya *et al*. 2008) [2]. The only drawback of oral insulin is getting degraded in stomach; thus, it should be encapsulated in a membrane. A combination of calcium phosphate-polyethylene glycol-insulin with casein can provide the protective matrix (Gupta, 2017) [11]. Cui *et al.* (2009) [6] reported that insulin loaded carboxylated chitosan grafted poly (methylmethacrylated) nanoparticles (CCGN) increased the efficiency. CCGN also showed desirable tissue and blood compatibility. Krauland *et al.* (2004) [19] represent a promising strategy for the oral application of insulin. A combination of chitosan-TBA, chitosan-enzyme-inhibitor conjugates and reduced glutathione was found effective. Significant decrease in the blood glucose levels was observed in diabetic rat after oral administration of the tablets. It was found that chitosan–TBA–insulin formulation featured excellent mucoadhesive properties, combined with the enzyme inhibiting properties of two covalently linked enzyme inhibitors and the permeation mediating properties of reduced glutathione (Krauland *et al*. 2004) [19].

Conclusions

Nanomedicine can improve the treatment of diabetes and increase the quality of life of the persons with diabetes in future but it requires rigorous testing before using nanotechnology for diabetes management.

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