BAOJ Nanotechnology

Joseph M. Rosen, et al., BAOJ Nanotech 2017, 3: 1
3: 014

Review

Diabetes Mellitus and Nanotechnology: Treatment in the 21st Century

Joseph M. Rosen[1*], Walter H Banfield[1] and Afton Chavez[1]

[1]Dartmouth-Hitchcock Medical Center, Lebanon

Abstract

Diabetes is a burden both nationally and internationally: it is the 7th leading cause of death in the United States; and afflicts 25.9% of U.S. seniors over 65, 9.3% of Americans overall, and8.5% of individuals, worldwide. This paper reviews current understandings of diabetes mellitus' causes, affects, and current conventional treatments. Specifically, we focus on Type 1 and Type 2 diabetes, as they make up the majority of the cases. We then examine recently developed nanotechnologies that offer new treatment options. Nanotechnology deals with dimensions of less than a hundred nanometers (nm), including manipulation of chemical and molecular structures. Recent technologies can create large quantities of stable distinct cell types, including pancreatic beta cells. Researchers have also synthesize danalginate hydrogel containing triazole, with a molecular structure that prevents aforeign-body immune response. The combination of these nanotechnologies can revolutionize diabetes treatments by restoring a patient's insulin production capacity, and in so doing, improve and potentially save millions of lives, thus beginning a new erain diabetes treatment.

Background: Diabetes Mellitus

Diabetes mellitus primarily affects the pancreas [1]. It is a group of metabolic disorders characterized by a chronic hyperglycemia resulting from defects in insulin use, insulin secretion, or both. This in turn can result in crippling or

fatal complications. In spite of effective treatment options and significant global research efforts, clinical outcomes remain sub-optimal with no reliable cure [2-6]. The World Health Organization (WHO) estimates that four hundred and twenty-two million people (eight and a half percent of the global population) were afflicted by diabetes mellitus as of 2014 [7]. By 2040 that figure is expected to increase to over six hundred and forty million. Also, diabetes mellitus is globally one of the leading causes of death, with a mortality rate equivalent to one person dying every six seconds, accounting for five million deaths in 2015 [8]. In the United States (U.S.) alone there were over two hundred thousand deaths from diabetes in 2015, and nearly one and a half million new cases are expected annually [9].

The complications associated with diabetes include: ketoacidosis, kidney failure, cardiovascular disease and blindness. These associated conditions can greatly reduce a patient's quality of life or be fatal [10]. Many of diabetes' associated complications are a result of vascular damage caused by long-term hyperglycemia [11-14]. For example, micro vascular damage from diabetes mellitus can result in retinopathy, with potential loss of vision due to impairment of retinal blood flow, increased inflammatory cell adhesion to blood vessels, and capillary blockage [15]. Through similar constrictions of blood flow, diabetes can also lead to kidney failure, foot ulcers, limb amputation, and significant nerve damage [13]. As a result, micro vascular damage from diabetes is currently the leading cause of kidney failure and lower limb amputations in the U.S. [16]. Additionally, diabetes can result in macro-vascular damage, with associated complications that are the main cause of diabetic mortality [13]. Although persistent hyperglycemia contributes to macro-vascular damage, hypertension and dyslipidemia are the main causes of macro-vascular complications in diabetic patients [12,15,17]. If not properly managed, these associated comorbidities can lead to complications including coronary heart disease, which is the leading cause of death for patients with diabetes [15]. All of these associated diabetic complications can be attributed to insulin dysfunctions involving the pancreas.

There are several different types of diabetes, each involving different pancreatic dysfunctions. The three most common forms of diabetes are type 1 diabetes (T1D), type 2 diabetes(T2D), and gestational diabetes [7,18]. T1D is an autoimmune disorder involving the destruction of pancreatic beta cells by one's own immune system. T2D is the most common form of the disease and

***Corresponding author:** Joseph M. Rosen, Department of Surgery, Section of Plastic Surgery, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03766, Fax: (603) 650-0911; Tel: (603) 650-5148; E-mail: Joseph.M.Rosen@Dartmouth.edu

Sub Date: March 10, 2017, **Acc Date:** April 7, 2017, **Pub Date:** April 7, 2017.

Citation: Joseph M. Rosen, Walter H Banfield and Afton Chavez (2017) Diabetes Mellitus and Nanotechnology: Treatment in the 21st Century. BAOJ Nanotech 3: 014.

is primarily characterized by progressive loss of pancreatic beta cells,and insulin resistance [12,17,19]. Gestational diabetes is much less common than T1D or T2D, and is a temporary condition that occurs during pregnancy and often dissipates after the mother gives birth. Of these, T1D and T2D account for nearly all cases of diabetes mellitus [2,7].

Pancreatic Anatomy and Physiology

The pancreas is a glandular organ located behind the stomach deep in the upper left abdomen. It extends across the body and is surrounded by other organs and sensitive structures including the small intestine, liver, spleen, and major arteries and veins. It is approximately fifteen centimeters long and is anatomically divided into four sections, the head, neck, body, and tail [21,22]. Importantly the pancreas has both exocrine and endocrine functions, and is often discussed in terms of these two functions as the exocrine pancreas and endocrine pancreas [18, 21].

Exocrine Pancreas

The exocrine pancreas constituents approximately ninety percent of the pancreatic mass. Also, it is devoted to secreting digestive enzymes into the duodenum through a series of ducts as part of the gastrointestinal system [18, 21,23]. Exocrine cells are arranged in clusters called acini. Within each individual cell are membrane-bound secretory granules filled with digestive enzymes which are secreted into the lumen of the acinus [24]. There is a wide variety of digestive enzymes that are crucial for digestion secreted by the exocrine pancreas. Yet, the main three types are pancreatic proteins, pancreatic lipase, and pancreatic amylase, responsible for breaking down dietary proteins, fat, and starches respectively [24]. However, enzymes alone do not comprise the pancreatic juices needed for proper digestive function. Once enzymes are secreted and pass through the lumen of the acinus, they flow through a series of pancreatic ducts. Epithelial cells line the walls of these small pancreatic ducts, and secrete bicarbonate and water. Bicarbonate is a base, critical to neutralizing acid, entering into the small intestine from the stomach. As it is secreted by epithelial cells lining the pancreatic ducts, the bicarbonate and digestive enzymes mix, forming pancreatic juice [23,24]. As this process occurs, the secretion flows through progressively larger ducts which eventually coalesce into the main pancreatic duct. From here the pancreatic juice drains directly into the duodenum where it aids in digestion [18,21,23,24].

Endocrine Pancreas

The endocrine pancreas is the portion most associated with diabetes mellitus. It refers to those cells within the pancreas that secrete hormones directly into the blood stream. This portion of the pancreas accounts for approximately ten percent of the pancreatic mass, and is comprised of specialized clusters of cells called pancreatic islets of Langerhans, or simply islets [12,25]. These clusters vary greatly in size and are scattered throughout the pancreas. They are highly vascularized and consist of four distinct cell types, namely: alpha (α), beta (β), delta (**δ**), and gamma (F) or PP cells [26]. PP cells are mainly found in islets located in the posterior head of the pancreas. These islets have a unique microscopic anatomy with PP cells comprising approximately eighty percent of the islet and β-cells making up a lesser number with very few α or **δ-cells** [18]. However, islets of Langerhans in the rest of the pancreas have a different microscopic anatomy. Here α and β-cells make up approximately twenty and seventy-five percent of islet composition respectively, while delta and PP cells only account for approximately four and one percent [21,27]. Additionally, beta cells are found primarily in the interior of islets surrounded by a shell of alpha cells with PP and delta cells scattered throughout [18]. Each of these cell types secretes differentglucose-regulatoryhormones. The primary hormones in blood glucose regulation produced by islets are glucagon from α-cells and insulin from β-cells (figure 1.) [12,28,29]. In this bi-hormonal model, glucagon increases blood glucose, while insulin decreases it. Normal glucose levels in healthy individuals are between approximately3.9 and 6.1millimoles per liter (mmol/L). Maintaining blood glucose at normal levels affords the central nervous system the constant supply of energy needed to maintain cortical function [28].

Islet Cell Type	Product	Primary Function
Alpha (α)	Glucagon	Increase blood glucose
Beta (β)	Inulin Prainsulin C peptide Amylin	Decrease blood glucose
Delta (**δ**)	Somatostatin	Inhibit insulin and glucagon secretion
Gamma (F) or PP	Pancreatic Polypeptide	Regulate exocrine and endocrine pancreatic secretion

Table 1: List of cells within islets of Langerhans with the hormones they each produce. It is important to note that the functions also listed in this figure are only the primary functions in regard to diabetes and blood glucose regulation.

Glucagon

Glucagon is a key catabolic hormone consisting of twenty-nine amino acids, secreted from pancreatic α-cells. It serves to increase blood glucose when receptors on the pancreas sense a decline. Glucagon inhibits cellular uptake of circulatory glucose, thus contributing to blood increased glucose concentrations [30]. Additionally, glucagon secreted by pancreatic α-cells actively contributes to increasing blood glucose by regulating its hepatic production through several metabolic processes [28,30]. One

such process is converting glycogen (stored carbohydrates) into glucose. This process known as glycogenosis, occurs through the initiation of the phosphatidylinositol signaling pathway. A series of cascading intercellular events then occur, provoking the liver to convert its stores of glycogen back into glucose and release it into the circulatory system. Additionally, glucagon can increase blood glucose levels through gluconeogenesis. In this process, glucose is formed from precursors other than carbohydrates. Here glucagon promotes the liver to take up amino acids from the blood and convert them into glucose, thus increasing its concentration [12,30,31]. Another method by which gluconeogenesis occurs is through the breakdown of stored triglycerides into free fatty acids and glycerol, a process known as lipolysis. After triglycerides are broken down, the resulting freeglycerol travels to the liver where it is converted into glucose [32,33]. Through a combination of these mechanisms, glucagon produced by pancreatic α-cells helps to maintain optimal blood glucose levels by inhibiting glucose uptake and stimulating its production [30].

Insulin

Conversely, insulin secreted by pancreatic β-cells decreases blood glucose levels. Insulin is a small protein composed of two polypeptide chains containing fifty-one amino acids, and is a key anabolic hormone secreted in response to increased blood glucose levels [28]. Like many hormones, insulin exerts its effects by binding to specific receptors present on cell surfaces, specifically muscle cells, liver cells, and fat cells. Once bound to receptors on muscle and fat these cells increase glucose uptake. In muscle and adipose tissues, insulin stimulates tyrosine kinase receptors, triggering the phosphorylation of many substrates within the cell. These multiple biochemical reactions support the movement of facilitative glucose transporters (GLUT) to the cell membrane [34,35]. These transporters allow the rapid movement of glucose into the cells. As a result, muscle cells convert glucose into glycogen, thus removing it from the blood stream. Also, in the case of adipose tissue, glucose is converted to fatty acids for storage as triglyceride [12].

Another way in which insulin decreases blood glucose concentrations is by acting on the liver. Nearly all pancreatic insulin flows to the liver via the pancreatic and portal veins. During meal times insulin promotes glycogenesis. In this process insulin stimulates glycogensynthase enzymes and inhibits glycogen phosphorylase enzymes. These enzymes act synergistically to convert and store glucose as glycogen, thus removing it from circulation. Also, insulin inhibits pancreatic α-cells from producing glucagon, thereby preventing hepatic glucose production [36,37].

Type 1 Diabetes

Type 1 diabetes (T1D), previously known as insulin dependent diabetes or juvenile-onset diabetes, accounts for approximately ten present of all diabetes mellitus cases. It is achronic immune-mediated destruction of pancreatic β-cells. This loss of β-cells ultimately results in insulin deficiency and hyperglycemia [38]. T1D patients are also prone to other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease [39]. Yet, exact the cause ofT1D is not fully understood. Currently, it is believed to precipitate in genetically susceptible individuals as a result of environmental triggers [1,17,38,40].

However, once T1D is triggered the series of events leading to β-cell death is well documented. Initially, β-cells experience cellular turnover and damage causing the production of auto-antigens. Antigen-presenting cells then process and present the β-cell auto-antigens to T-helper cells [41,42]. Once stimulated these T-helper cells activate cytotoxic T-cells as well as B-lymphocytes, which secrete antibodies and macrophages [43]. Stimulated macrophages and dendritic cells enter the pancreatic islets, where they present the major histocompatibility complex and β-cell peptides to CD4+ T cells circulating in the blood and lymphoid organs [41]. These CD4+ T cells are also activated by cytokine interleukin-12 released from macrophages and dendritic cells. While this process takes place, CD4+ T cells produce interleukin-2 initiating CD8+ T cells to differentiate into cytotoxic T cells, which are then recruited into islets. These CD4+ T cells and CD8+ cytotoxic T cells are actively involved in the destruction of pancreatic β-cells. Additionally, β-cells can be damaged by soluble mediators such as cytokines, and reactive oxygen molecules released by macrophages in the islets. Thus, CD4+ T cells, β-cell cytotoxic CD8+ T cells, and activated macrophages act synergistically to destroy β-cells in pancreatic islets resulting in type 1 diabetes [1,17,41-43].

Genetic Factors

Several genes in specific loci have been identified as high risk factors for T1D [43].The Human Leukocyte Antigen (HLA) complex is thought to be the primary genetic risk site for T1D. Various studies types including genetic, functional, structural, and animal models have all indicated that the highly polymorphic HLA class II molecules, namely the DR and DQ α-β heterodimers, are central to susceptibility of T1D [38-46]. It is estimated that eighty-five to ninety percent of T1D patients carry one of these risk factors, while thirty to fifty percent carry both. The exact mechanism by which the HLA class II molecules confer susceptibility to immune-mediated destruction of pancreatic β-cells is not fully known [45]. However, it is likely that binding of key peptides from auto-antigens in the thalamus and periphery play an important role. Additionally, class I HLA alleles(HLA-A2, HLA-A24, and HLA-B39) are believed to contribute to the risk of developing T1D; as are forty additional loci outside of the HLA [17,45,46].

Environmental Factors

Several environmental factors have been implicated in the development of T1D. The most commonly noted are infectious

agents, particularly enteroviruses [45]. These are small non-enveloped RNA viruses which are responsible for most viral infections in humans. Although the exact mechanisms through which enteroviruses contributes to the onset of T1D are unclear, there is a large body of evidence supporting their association [47]. However, it is important to note that this evidence is highly controversial, as persons with an autoimmune condition may also be especially prone to enteroviral infections [14,38,48].

Second to viruses, nutritional factors are thought to influence T1D onset. Predominantly, an association between developing T1D and early exposure to complex dietary proteins, such as breast and cow milk, has been demonstrated [49]. To examine this association, a large study was conducted to test whether cow milk avoidance reduces T1D risk in infants. The researchers concluded that there is an association between complex dietary protein exposure in young children and T1D onset [49]. However, this association remains highly debated due to lack of study replication and supporting evidence. Another dietary risk factor may be the timing of exposure to dietary gluten. Several studies suggest that there is a window extending from birth to the age of three months in which exposure to dietary gluten can increase the risk of T1D in genetically predisposed children. However, further research is needed to substantiate this association [14,50].

Treatments

Diagnoses of this disease can be determined by detecting auto antibodies, including islet cell antibodies (ICA), glutamic acid decarboxylase antibodies (GAD-65), protein tyrosine phosphatase, and anti-insulin antibodies (IAAs) [13,42]. However, diagnosis of T1D does not usually occur until late stages of the disease when symptoms become clinically apparent [17]. Once diagnosed, administration of insulin is required for T1D patients either via subcutaneous injection or insulin pumps. Due to the T1D patients 'inability to produce insulin, careful monitoring of blood glucose levels and appropriate insulin injection is required. Additionally, dietary adjustment is important, with patients keeping track of carbohydrate intake [51]. According to the American Diabetes Association's standards of medical care, these treatments are focused on keeping blood glucose within the range of 4.4–7.8 m mol/L, there by delaying or avoiding sever complications [52].

Additionally, less conventional treatments for T1D exist. One such option is a pancreas transplant. This procedure is often performed as a double transplant with both a kidney and pancreas being replaced from a cadaveric donor [53]. Pancreas transplants can drastically improve the quality of life for patients with T1D, by eliminating or greatly reducing their need for blood glucose monitoring and insulin injections. However, putting aside the limiting factor of sever donor tissue shortages, the procedure itself is complex and has a relatively high surgical risk. The fact that the pancreas is situated deep in the abdomen, surrounded by various vital structures contributes to the risk and difficulty of the procedure. Also, as with other tissue grafts, the patient must be placed on a life-long immunosuppressant regimen. Such immunosuppressant therapies often have severe side effects such as, infection, a vascular necrosis, and susceptibility to neoplasms [54]. Considering the deterrents of this treatment option and the shortage of donor tissues, pancreatic transplant is only a viable option a small number severe T1D cases [53].

Another treatment is pancreatic islet transplantation. Currently this option is only suitable for patients with unstable glycemic control that cannot be corrected by standard intensive insulin therapies [55]. In this procedure islets are isolated from a deceased donor using collagenase, and implantation via injected into the liver with a catheter threaded though the portal vein. This procedure constitutes an evolving field with significant amounts of ongoing research. Recent studies have shown success rates, defined as not needing insulin injections three years' post-procedure, as high as forty-four percent. However, this treatment option faces significant challenges due to limited donor supply and immune rejection of the grafted cells [55,56]. Similar to pancreatic transplants, patients who undergo this islet transplantation need to adhere to a life-long immunosuppressant regime and endure its associated side effects [53,55].

Type 2 Diabetes

Type 2 diabetes, previously known as non-insulin dependent diabetes or adult onset diabetes, is characterized by insulin resistance and the loss of functioning β-cells [12]. T2D is the most common form of diabetes accounting for approximately ninety percent of all cases [7]. Initially, most T2D patients do not require insulin theory to survive, but it may become necessary if β-cells death and insulin resistance progress over time [57]. T2D insulin resistance is known to be an associated with free fatty acids, but its exact etiology is not fully defined. Currently it is believed that an increased intracellular concentration of fatty acid metabolites activates a serine kinase cascade, which leads to defects in insulin signaling to downstream receptors [54]. Additionally, the mechanisms by which β-cells are disabled in T2D are also not fully understood. However, it is thought that loss of functioning β-cell is linked to β-cell turn over and insulin secretory pathways. Postprandial hyperglycemic excursions are believed to induce β-cell proliferation in insulin-resistant individuals. Yet, this adaptive mechanism may fail in the long term and be overridden by β-cell apoptosis. Interactions between saturated fatty acids, lipoproteins, leptin, and circulating and pro-inflammatory cytokines may activate theimmunological responses leading to β-cell dysfunction [59].Currently, the predominate hypothesis is that a combination of genetic and life style factors initiate these pathological processes [60].

Genetic Factors

Although the specific genetic causes of T2D are not fully understood, it is widely accepted that a family history of T2D increases the likelihood of an individual developing the disease [61]. Currently there are thirty-six known gene loci that contain variants showing significant associations with T2D. The strongest genetic associations are identified at loci TCF7L2 and KCNQ. TCF7L2 encodes a transcription factor that has been implicated in β-cell development and function; whereas, KCNQ1 encodes for a pore-forming subunit of a K^+ channel expressed in several tissues, including pancreatic islets [61]. The prevalence of risk alleles at these loci is relatively high with an estimated frequency of twenty-five percent in a population [62]. However, eachallele by itself does not contribute significantly to the risk of T2D. The effects of most risk variants can be described with an additive model, where a greater number of risk alleles equates to a greater risk of developing T2D [12,61].

Lifestyle Factors

Like with T1D, genetic factors are believed to only be part ofT2D etiology. Major life style factors that are also associated with T2D onset. Such risk factors include diet, obesity, and lack of physical activity [14,63-65]. Dietary consumption of trans fatty acids and saturated fatty acids are associated with an increased risk of insulin resistance and, therefore, T2D. The mechanisms of this correlation are unclear, but it is believed that dietary fat quality affects cell membrane fatty acid composition and, consequently, cell membrane function. The fatty acid composition affects membrane fluidity, ion permeability, and insulin receptor binding and affinity. These are all cellular functions that influence translocation of glucose transporter interactions with second messengers. Thus, by altering the fatty acid composition of cell membranes, trans and saturated fatty acids act to diminish insulin sensitivity [11].

Obesity is another major lifestyle risk factor. It is estimated that fifty-five percent of people with T2D are obese [64]. Chronic obesity can lead to increased insulin resistance. It is believed that adipose tissue in the abdomen and around internal organs produces hormones and cytokines. In turn, inflammatory cytokines such as TNFamay activate the NFk-B pathway. This pathway then incites macrophages to enter fat cells eliciting an inflammatory response linked with insulin resistance [63]. Additionally, adipose tissue has been shown to play a role in regulating the body's response to insulin and glucose uptake [66]. Furthermore, obese individuals have an excess of fatty acids and glucose which adipocytes absorb, causing them to expand and become engorged. These obese fat cells create the circulating molecule RBP4. RBP4 induces insulin resistance by blocking the effects of insulin in the liver and muscle cells. Additionally, engorged adipocytes produce more RBP4 than non-engorged healthy adipocytes [66]. In tangent with this, fat cellsnormally produce adiponectin, which improves insulin sensitivity, yet rather than producing normal levels of adiponectin, engorged adipocytes secrete smaller amounts of adiponectin and greater amounts of RBP4 than healthy fat cells. This combination acts to exacerbate obesity elicited insulin resistance and contributes to the development of T2D [17,63,66].

Another lifestyle choice that can increase susceptibility to T2D is lack of physical activity. Exercise can increase sensitivity to insulin. Those who regularly engage in moderate physical activity are approximately thirty percent less likely to develop T2D than sedentary individuals. Exercise increases insulin-stimulated glycogen synthesis. This occurs through an increased rate of insulin-stimulated glucose transport by GLUT4,as well as increased glycogen synthase activity [67]. Also, elevated capillary proliferation in muscles, increased muscle mass, and a higher proportion of insulin-sensitive muscle fibers contribute to exercise induced insulin sensitivity. Furthermore, exercise can help reduce obesity, thus mitigating its associated risks with T2D. When individuals do not engage in physical exercise they lose the opportunity to improve insulin sensitivity, and thereby become more susceptible to insulin resistance and T2D [66-68].

Treatments

There is no cure for T2D. Instead, management of T2D aims to slow or prevent the disease and its debilitating complications [68]. Currently conventional treatment of T2D focuses on management of blood glucose through a mixture of lifestyle alterations and medications. Lifestyle alterations include a minimum of one hundred and fifty minutes of moderate physical activity a week, losing seven percent of baseline weight, and a low calorie, fat reduced diet [69]. These lifestyle adjustments are designed to counteract some of the negative effects of obesity and improve insulin functionality. Also, such behavioral changes aim to help lower blood pressure to less than a hundred and forty millimeters of mercury (mmHg), which is associated with improved clinical outcomes [70]. However, the majority of T2D patients are unable to normalize blood glucose levels with life style adjustments alone, and medications become needed [69].

Medications are prescribed to treat T2D often aim to normalize blood glucose and reduce cardiovascular risk factors such as hypertension, dyslipidemia, and micro-albuminuria. Typically, metformin is the first-line medication. Metformin is an oral medication that decreases hepatic glucose output and increases insulin sensitivity of surrounding tissues [69]. The goal of this medication is to normalize fasting glucose levels. However, this metformin is not for patients with chronic or acute renal insufficiency and should be discontinued when creatinine levels reach 1.4 mg per dL in women and 1.5 mg per dL in men [69-71]. Additional medication such as sulfonylureas, non-sulfonylurea

secretagogues, thiazolidinediones, and alpha-glucosidase inhibitors, can be combined with one another to normalize fasting glucose levels. Yet, progressive failure of β-cells often occurs even with proper diet, exercise, and oral medications [69]. As a result, many patients will eventually need insulin therapy. Insulin can be added to oral medication régimes or be used alone, depending on the specific case [72]. Most patients typically require one to two injections a day. For the majority of T2D patients, this is a life-long regime that may need to be intensified as the disease progresses [5,69,71].

Weight loss surgery is a less conventional treatment option for T2D. Such surgeries encompass a number of procedures designed to reduce patient obesity. Common weight loss surgeries performed in the U.S. include roux-en-Y gastric bypass surgery, gastric banding, and gastroplasty [73]. This treatment method can cause a loss of thirteen to twenty percent of a patient's initial body weight. Additionally, the weight loss is often sustained, which can greatly improve a T2D patient's condition by alimenting the detrimental metabolic process associated with obesity and T2D. Some studies suggest that blood glucose levels are maintained within the normal range in seventy-seven percent of T2D patients who undergo weight loss surgery [5,73]. Thus, this treatment can be effective for patients who are unable to achieve necessary weight loss through diet and exercise, but has far greater risks as it is a major surgical procedure.

Despite these treatments and the ability of patients to maintain normal glucose levels though a combination of lifestyle adjustment, approximately forty-four percent of the patients still fail to meet the American Diabetes Association target of hemoglobin A_{1c} levels of less than seven percent [5]. A major disadvantage of these treatments is the need for a life-long drug regime, with the exception of weight loss surgery. The requirement for patient adherence to continual lifestyle adjustments and drug regimes constitutes a major limiting factor in the effectiveness of current T2D treatments [74]. Additionally, weight loss surgeries are highly invasive procedures and may not be appropriate for many T2D patients. Also, as with all surgeries, there are associated risks [73]. What is needed is a treatment that does not require long term patient adherence and can overcome insulin insufficiency without severe adverse side effects.

Shifting the Treatment Paradigm: Nanotechnology

Transplantation of glucose-responsive insulin-producing β-cells can restore glycemic control in patients with both T1D and T2D [56,75]. Pancreas and islet transplants are performedclinically, yet are limited by a shortage of donor tissues, immune rejection, and the need for immunosuppressive therapy [55,75-78]. Emerging nanotechnologies have the potential to overcome these limitations. In so doing these nanotechnologies enable the replacement of β-cells that are capable of both producing appropriate amounts of insulin and avoiding an immune response. As the autoimmune destruction of β-cells is the primary deficiency in T1D patients, this novel treatment method constitutes a possible cure [75]. In the case of T2D, the implantation of functional β-cells offers a way to abolish insulin therapy dependence. Also, by implanting a sufficient number of insulin producing β-cells, a patient may overcome insensitivity to insulin [56,71]

Overcoming the Donor Shortage: Cell Production

Those involved in regenerative medicine place great emphasis on the use of stem cells. Stem cells are undifferentiated cells capable of giving rise to a diverse range of specialized cell types [79]. Through the use of nanotechnologies such as engineered molecules and hormones, it has become possible to create stem cell derived insulin-producing β-cell [56,80]. Both the genetic makeup and phenotype of cells must be considered because unique environmental factors (biofactors) influence cell expression and function [81]. Biofactors give cells a combined set of instructions that direct the cell to have specific functionality. Such biofactors engineered to produce desired cell differentiation are a key piece of nanotechnology that is giving rise to a potentially unlimited source of pancreatic β-cells [79,80,82]. Studies of pancreatic development have identified factors important to the formation of pancreatic cell lineages. These findings have been applied to differentiate human pluripotent stem cells (hPSCs) into β-cells in vitro. Specifically, researchers have utilized mTeSR1 media+10μM Y27632 serum to initiate differentiation of hPSCs into functional β-cell [80]. Other groups have developed similar protocols, utilizing various other serums developed through the use of nanotechnology [79,81,83]. Additionally, industrial software that integrates liquid handling robotics and Design-of Experiments mathematics has been developed to create "recipes" for fabricating distinct, stable cell linages [79,84]. The coalescence of these emerging medical nanotechnologies has the potential to create an unlimited supply of pancreatic β-cells which, in turn, could revolutionize the treatment of diabetes mellitus in the near future.

Making Immuno suppression Irrelevant

Immune rejection of foreign entities has been a major limitation to all implant based therapies [85, 86]. Implanted medical devises elicit a foreign body response consisting of inflammatory events and wound-healing processes that lead to fibrosis [87]. Often these detrimental immune responses are incited by macrophage and dendtric cell recognition of the foreign entity [56]. Currently, implantation of many cell based therapies requires immuno suppression regimes which have severe associated side effects [85,88,89]. Encapsulation could overcome the need for immunosuppression, but the biomaterials used often illicit an immune-mediated foreign body response [56].

However, alginate derivatives containing triazole have been developed that substantially mitigate foreign body response. More specifically, chemically modified alginates such as triazole-thiomorpholine dioxide (TMTD) have been found to resist implant fibrosis in both rodent and nonhuman primates [56,86]. Alginate is a versatile biomaterial that forms hydro-gels in di-cationic aqueous solutions and is used in many biomedical applications, often as a coating. Like many other biomaterials, alginate elicits a foreign body immune response. However, the modified alginate TMTD does not. This is due to the distribution of the triazole modification creating a unique hydrogel surface that inhibits recognition by macrophages and fibrosis deposition [87]. This new nanotechnology has been tested as microspheres encapsulating stem cell derived β-cells (SC-β cells) in both rodent and nonhuman primate models. When implanted into the intraperitoneal space of immune competent mice and nonhuman primates, the SC-β cells encapsulated in TMTD alginate microspheres did not elicit an immune response [56,87]. Furthermore, when implanted in immune competent mice with chemically induced T1D, these implants caused glycemic correction until their removal at day one hundred and seventy-four. Capsules retrieved after a hundred and seventy-four days showed minimal fibrosis, and staining revealed human insulin and β-cells markers. These results suggest that TMTD alginate can not only mitigate host foreign body responses, but that it can do so while maintaining the viability and differentiation of encapsulated cells [79].

Putting it all Together

Nanotechnology has now enabled the potential production of unlimited numbers of desired cell types. This has been demonstrated with pancreatic stem cell derived β-cells in a number of different studies. Culturing cells for implantation enables can eliminate the shortage of donor tissues [56,79-83]. By combining engineered pancreatic cells with TMTD alginate microcapsules, the replacement of endocrine pancreatic function is possible. These nanotechnologies enable the replacement of dysfunctional β-cells that are both capable of producing appropriate amounts of insulin, and avoiding an immune response. As the autoimmune destruction of β-cells is the primary deficiency in T1D patients, this novel treatment method poses a possible cure to clinically relevant T1D [75]. Additionally, in the case of T2D the implantation of functional β-cells offers a way to abolish dependence on insulin injections. Also, by implanting a sufficient number of insulin producing β-cells, a patient may be able mitigate the effects of insulin resistance by simply producing enough insulin to elicit normal metabolic function [56,75]. Thus, the combination of novel cell production nanotechnologies and TMTD alginate microspheres offers a potential cure to both T1D and T2D.

Conclusion

Diabetes mellitus constitutes a chronic epidemic throughout the world. Management of both T1D and T2D requires long-term lifestyle adjustments and often medical regimes. Although these treatments can be effective in managing the disease, they only serve to slowdown its progression, not to cure it [1,5,13,42,69,71]. Developments in cell cultivation and differentiation could create an unlimited source of pancreatic cells, including insulin producing β-cells. It is also feasible to fabricate other pancreatic cell types to restore other glucose-regulatory hormone secretions if necessary [76,79,81,83]. When combined with TMTD alginate microcapsules, manufactured β-cells can restore insulin sufficiently in T1D and T2D patients while avoiding an immune response. Though further investigation is needed, these technologies represent a potential cure for the most common forms of diabetes mellitus, T1D and T2D [56,87,90,91]. Thus, we are on the verge of a medical revolution, one in which diabetes mellitus is not treated or managed, but cured.

References

1. Ozougwu JC, Obimba KC, Belonwu CD, Unakalamba CB (2013) The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. Journal of Physiology and Pathophysiology 4(4): 46-57.
2. American Diabetes Association (2002) Standards of Medical Care for Patients With Diabetes Mellitus. Diabetes Care 25(Supplement 1): S33-S49.
3. Meece J (2007) Pancreatic islet dysfunction in type 2 diabetes: a rational target for insulin-based therapies. Current Medical Research and Opinion 23(4): 933-944.
4. Stolar MW (2010) Defining and Achieving Treatment Success in Patients With Type 2 Diabetes Mellitus. Mayo Clinic Proceedings 85(12): S50-S59.
5. Edelman S, Philip-Tsimikus A, Burnton S, Kruger DF, Spollett G, et al. (2009) Current Issues in the Management of Type 2 Diabetes. Consultant 49(7): S1-S32.
6. Hoerger TJ, Segel JE, Gregg EW, Saaddine JB (2007) Is Glycemic Control Improving in U.S. Adults?. Diabetes Care 31(1): 81-86.
7. Roglic G (2016) Global report on diabetes. Geneva Switzerland: World Health Organization.
8. (2015) International Diabetes Federation. IDF Diabetes Atlas, 7th edn. Brussels, Belgium: International Diabetes Federation.
9. (2016) American Diabetes Association. Statistics About Diabetes.
10. (2017) American Diabetes Association Complications.
11. Risérus U, Willett WC, Hu FB (2009) Dietary fats and prevention of type 2 diabetes. Progress in Lipid Research, 48(1): 44–51.
12. Nussey S, Whitehead S (2001) Endocrinology: An Integrated Approach. Oxford: BIOS Scientific Publishers. Chapter 2, The endocrine pancreas.
13. Pittas, AG, Greenberg AS (2003) Contemporary Diagnosis and Management of Diabetes. Handbooks in Health Care Co Newtown PA.

14. Atkinson M, Eisenbarth GS, Michels AW (2014) Type 1 diabetes. The Lancet 383(9911): 69-82.

15. Cade WT (2008) Diabetes-Related Microvascular and Macrovascular Diseases in the Physical Therapy Setting. Physical Therapy 88(11): 1322-1335.

16. (2014) Centers for Disease Control and Prevention. National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States, 2014. Atlanta GA: U.S. Department of Health and Human Services.

17. Atkinson MA (2012) The Pathogenesis and Natural History of Type 1Diabetes. Cold Spring Harbor Perspectives in Medicine 2(11): a007641.

18. Lott JA (1997) Clinical pathology of pancreatic disorders. Totowa NJ: Humana Press.

19. Hussain A, Claussen B, Ramachandran A, Williams R (2007) Prevention of type 2 diabetes: A Review. Diabetes Research and Clinical Practice 76(3): 317-326.

20. Perkins JM, Dunn JP, Jagasia SM (2007) Perspectives in Gestational Diabetes Mellitus: A Review of Screening, Diagnosis, and Treatment. Clinical Diabetes 25(2): 57-62.

21. Betts JG, DeSaix P, Johnson E, Johnson J, Korol O, et al. (2013) Anatomy & physiology. Houston TX: OpenStax College.

22. Pansky B (1990) Anatomy of the pancreas. Int J Pancreatol 7(1): 101-108. doi:10.1007/BF02924225

23. Longnecker D (2014) Anatomy and Histology of the Pancreas. The Pancreapedia: Exocrine Pancreas Knowledge Base 1: 1-26.

24. Pandol SJ (2010) The Exocrine Pancreas. San Rafael (CA): Morgan & Claypool Life Sciences.

25. Barrett EJ (2017) The Endocrine System. In WF Boron (Author) Boulpaep E (Author). Medical Physiology 3: 973-1168.

26. Rorsman P, Braun M (2013) Regulation of Insulin Secretion in Human Pancreatic Islets. Annual Review of Physiology 75(1): 155-179.

27. Wierup N, Sundler F, Heller RS (2013) The islet ghrelin cell. Journal of Molecular Endocrinology 52(1): R35-R49.

28. Aronoff SL, Berkowitz K, Shreiner B, Want L (2004) Glucose Metabolism and Regulation: Beyond Insulin and Glucagon. Diabetes Spectrum 17(3): 183-190.

29. Steiner DJ, Kim A, Miller K, Hara M (2010) Pancreatic islet plasticity: Interspecies comparison of islet architecture and composition. Islets 2(3): 135-145.

30. Quesada I, Tudor E, Ripoll C, Nadal A (2008) Physiology of the pancreatic a-cell and glucagon secretion: role in glucose homeostasis and diabetes. Journal of Endocrinology 199(1); 5-19.

31. Noguchi R, Kubota H, Yugi K, Toyoshima Y, Komori Y, et al. (2014) The selective control of glycolysis, gluconeogenesis and glycogenesis by temporal insulin patterns. Molecular Systems Biology 9(1): 664-664.

32. Cabrera O, Berman DM, Kenyon NS, Ricordi C, Berggren P, et al. (2006) The unique cytoarchitecture of human pancreatic islets has implications for islet cell function. Proceedings of the National Academy of Sciences 103(7): 2334-2339.

33. Habegger KM, Heppner KM, Geary N, Bartness TJ, Dimarchi R, et al. (2010) The metabolic actions of glucagon revisited. Nature Reviews Endocrinology 6(12): 689-697.

34. Mayer JP, Zhang F, Dimarchi RD (2007) Insulin structure and function. Biopolymers 88(5): 687-713.

35. Sonksen P (2000) Insulin: understanding its action in health and disease. British Journal of Anaesthesia 85(1): 69-79.

36. Girard J (2006) Insulin's effect on the liver: "Direct or indirect?" continues to be the question. Journal of Clinical Investigation 116(2): 302-304.

37. Lin H, Accili D (2011) Hormonal Regulation of Hepatic Glucose Production in Health and Disease. Cell Metabolism 14(1): 9-19.

38. van Belle TL, Coppieters KT, Herrath MG (2011) Type 1 Diabetes: Etiology, Immunology, and Therapeutic Strategies. Physiological Reviews 91(1): 79-118.

39. Alves C, Santos L, Toralles MP (2016) Association of type 1 diabetes mellitus and autoimmune disorders in Brazilian children and adolescents. Indian Journal of Endocrinology and Metabolism 20(3): 381-386.

40. Gillespie KM (2006) Type 1 diabetes: pathogenesis and prevention. Canadian Medical Association Journal 175(2): 165-170.

41. Yoon J, Jun H (2005) Autoimmune Destruction of Pancreatic cells. American Journal of Therapeutics 12(6): 580-591.

42. Taplin CE, Barker JM (2008) Autoantibodies in type 1 diabetes. Autoimmunity 41(1): 11-18.

43. Cnop M, Welsh N, Jonas J, Jorns A, Lenzen S, et al. (2005) Mechanisms of Pancreatic -Cell Death in Type 1 and Type 2 Diabetes: Many Differences, Few Similarities. Diabetes 54(2): S97-S107.

44. Noble JA, Erlich HA (2012) Genetics of Type 1 Diabetes. Cold Spring Harbor Perspectives in Medicine 2(1): a007732.

45. Pugliese A (2001) Genetic Factors in Type 1 Diabetes. Endocrinology and Metabolism Clinics of North America 33(1): 1-16.

46. Pociot F, Akolkar B, Concannon P, Erlich HA, Julier C, et al. (2010) Genetics of Type 1 Diabetes: What's Next? Diabetes 59(7): 1561–1571.

47. Tauriainen S, Oikarinen S, Oikarinen M, Hyöty H (2010) Enteroviruses in the pathogenesis of type 1 diabetes. Seminars in Immunopathology 33(1): 45-55.

48. Jaïdane H, Sauter P, Sane F, Goffard A, Gharbi J, et al. (2010) Enteroviruses and type 1 diabetes: towards a better understanding of the relationship. Reviews in Medical Virology 20(5): 265-280.

49. Knip M, Virtanen SM, Seppä K, Ilonen J, Savilahti E, et al. (2010) Dietary Intervention in Infancy and Later Signs of Beta-Cell Autoimmunity. New England Journal of Medicine 363(20): 1900-1908.

50. Norris JM (2003) Timing of Initial Cereal Exposure in Infancy and Risk of Islet Autoimmunity. Jama 290(13): 1713-1720.

51. Shrivastava S, Shrivastava P, Ramasamy J (2013) Role of self-care in management of diabetes mellitus. Journal of Diabetes & Metabolic Disorders 12(1): 12-14.

52. (2013) Standards of Medical Care in Diabetes--2014. Diabetes Care 37(1): S14-S80.

53. Larsen JL (2004) Pancreas Transplantation: Indications and Consequences. Endocrine Reviews 25(6): 919-946.

54. Saidi R, HejaziiKenari S (2014) Challenges of Organ Shortage for Transplantation: Solutions and Opportunities. International Journal of Organ Transplantation Medicine 5(3): 87-96.

55. Shapiro J, Bruni A, Pepper AR, Gala-Lopez B, Abualhassan NS (2014) Islet cell transplantation for the treatment of type 1 diabetes: recent advances and future challenges. Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy 7: 211-223.

56. Vegas AJ, Veiseh O, Gürtler M, Millman JR, Pagliuca FW, et al. (2016) Long-term glycemic control using polymer-encapsulated human stem cell–derived beta cells in immune-competent mice. Nature Medicine 22(3): 306-311.

57. (2014) American Diabetes Association . Diagnosis and Classification of diabetes mellitus. Diabetes Care 33(1): 262-S69.

58. Saini V (2010) Molecular mechanisms of insulin resistance in type 2 diabetes mellitus. World Journal of Diabetes 1(3): 68-75.

59. Donath MY, Ehses JA, Maedler K, Schumann DM, Ellingsgaard H, et al. (2005) Mechanisms of -Cell Death in Type 2 Diabetes. Diabetes 54(2): S108-S113.

60. Wu Y, Ding Y, Tanaka Y, Zhang W (2014) Risk Factors Contributing to Type 2 Diabetes and Recent Advances in the Treatment and Prevention. International Journal of Medical Sciences 11(11): 1185-1200.

61. Herder C, Roden M (2010) Genetics of type 2 diabetes: pathophysiologic and clinical relevance. European Journal of Clinical Investigation 41(6): 679-692.

62. Kumar Das S, Elbein SC (2006) The Genetic Basis of Type 2 Diabetes. Cell Science 2(4): 100-131.

63. Shoelson SE (2006) Inflammation and insulin resistance. Journal of Clinical Investigation 116(7): 1793-1801.

64. Abdullah A, Peeters A, Courten MD, Stoelwinder J (2010) The magnitude of association between overweight and obesity and the risk of diabetes: A meta-analysis of prospective cohort studies. Diabetes Research and Clinical Practice 89(3): 309-319.

65. Franks PW (2012) The Complex Interplay of Genetic and Lifestyle Risk Factors in Type 2 Diabetes: An Overview. Scientifica 1-11.

66. Powell K (2007) Obesity: The two faces of fat. Nature. 447(7144): 525-527.

67. Jeon CY, Lokken RP, Hu FB, Dam RM (2007) Physical Activity of Moderate Intensity and Risk of Type 2 Diabetes: A systematic review. Diabetes Care 30(3): 744-752.

68. Defronzo RA (2010) Overview of Newer Agents: Where Treatment Is Going. The American Journal of Medicine 123(3): S38-S48.

69. Ripsin CM, Kang H, Urban RJ (2009) Management of Blood Glucose in Type 2 Diabetes Mellitus. American Family Physician 79(1): 29-36.

70. Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, et al. (2015) Blood Pressure Lowering in Type 2 Diabetes. Jama 313(6): 603-615.

71. Vija S (2015) Type 2 Diabetes. Annals of Internal Medicine 162(5): IT1C.

72. Swinnen SG, Hoekstra JB, Devries JH (2009) Insulin Therapy for Type 2 Diabetes. Diabetes Care 32(2): S253-S259.

73. Farchetti K, Goldfine A (2009) Bariatric surgery for diabetes management. Current Opinion in Endocrinology Diabetes & Obesity 16(2): 119-124.

74. García-Pérez L, Álvarez M, Dilla T, Gil-Guillén V, Orozco-Beltrán D (2013) Adherence to Therapies in Patients with Type 2 Diabetes. Diabetes Therapy 4(2): 175-194.

75. Potter KJ, Westwell-Roper CY, Klimek-Abercrombie AM, Warnock GL, Verchere CB (2013) Death and Dysfunction of Transplanted -Cells: Lessons Learned From Type 2 Diabetes? Diabetes 63(1): 12-19.

76. Berthiaume F, Maguire TJ, Yarmush ML (2011) Tissue Engineering and Regenerative Medicine: History, Progress, and Challenges. Annual Review of Chemical and Biomolecular Engineering 2(1): 403-430.

77. Naftanel MA, Harlan DM (2004) Pancreatic Islet Transplantation. PLoS Medicine 1(3): E58.

78. Benedini S, Caumo A, Terruzzi L, Luzi L (2013) Immunosuppressive therapy in pancreas and islet transplant: Need for simultaneous assessment of insulin sensitivity and secretion. Journal of Diabetes Mellitus 03(03): 156-160.

79. Atala A (2012) Regenerative medicine strategies. Journal of Pediatric Surgery 47(1): 17-28.

80. Pagliuca F, Millman J, Gürtler M, Segel M, Van Dervort A, et al. (2014) Generation of Functional Human Pancreatic **β** Cells In Vitro. Cell 159(2): 428-439.

81. Ohba, Shinsuke, Fumiko Yano, Ung-il Chung (2009) Tissue Engineering of Bone and Cartilage. Nature BoneKEy Reports 6: 405-19.

82. Shastri VP, Altankov G, Lendlein A (2010) Advances in regenerative medicine: role of nanotechnology and engineering principles. Dordrecht: Springer.

83. Atala A (2009) Engineering organs. Current Opinion in Biotechnology 20(5): 575-592.

84. Bajaj, Piyush, Ryan M, Schweller, Ali Khademhosseini, et al. (2014) 3D Biofabrication Strategies for Tissue Engineering and Regenerative Medicine. Annual Review of Biomedical Engineering 16(1): 247-76.

85. Lanza RP, Langer RS, Vacanti J (2007) Principles of tissue engineering (3rd ed.) Amsterdam: Elsevier / Academic Press.

86. Vishwakarma A, Bhise NS, Evangelista MB, Rouwkema J, Dokmeci MR, et al. (2016) Engineering Immunomodulatory Biomaterials To Tune the Inflammatory Response. Trends in Biotechnology 34(6): 470-482.

87. Vegas Arturo J, Veiseh O, Doloff JC, Ma M, Tam HH, et al. (2016) Combinatorial hydrogel library enables identification of materials that mitigate the foreign body response in primates. Nature Biotechnology 34(3): 345-352.

88. Anderson JM, Rodriguez A, Chang DT (2008) Foreign body reaction to biomaterials. Seminars in Immunology 20(2): 86-100.

89. Ward WK (2008) A Review of the Foreign-body Response to Subcutaneously-implanted Devices: The Role of Macrophages and Cytokines in Biofouling and Fibrosis. Journal of Diabetes Science and Technology 2(5): 768-777.

90. Stem J, Buksy MA, Jensen J, Bio T (2016) Xeno-Transplantation of macro-encapsulated islets and Pluripotent Stem Cell-Derived Pancreatic Progenitors without Immunosuppression. Journal of Stem Cell and Transplantation Biology 2(1): 768-777.

91. Ricordi C, Goldstein JS, Balamurugan A, Szot GL, Kin T, et al. (2016) National Institutes of Health–Sponsored Clinical Islet Transplantation Consortium Phase 3 Trial: Manufacture of a Complex Cellular Product at Eight Processing Facilities. Diabetes 65(11): 3418-3428.