How nanotechnology can help in the management of diabetes

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PASS

Abstract

Diabetes is a metabolic disease which affects an estimated 285 million people worldwide, with 2.8 million people of these in the UK alone. Although at the moment there isn't an easily available cure for this condition there are ways for people to manage it. This dissertation examines the possibility of nanotechnology being used in the management of diabetes. It will also examine the benefits and the problems that will arrive if this technology is used.

Introduction

In 2008 145,000 people in the UK were diagnosed with diabetes, this is equivalent to 400 people every day; almost 17 people every hour; three people every 10 minutes [1]. Diabetes is a group of metabolic diseases which as a result causes the person to have high blood sugar levels. This is either because their body does not produce enough insulin on its own, type-1 diabetes, or because their body has become resistant to the insulin that is being produced, type-2 diabetes. If diabetes continues without being managed it can lead to other health problems such as heart attacks, stroke, toe/foot/leg infections, which may lead to amputation, blindness, kidney failure and in women it may lead to pregnancy complications. An estimated 285 million people worldwide, corresponding to 6.4% of the world's adult population, will live with diabetes in 2010 [2]. 2.8 million of these will be living with diabetes in the UK [3]. This number is expected to increase significantly in years to come with 438 million worldwide projected to be diagnosed by 2030, corresponding to 7.8% of the adult population [2]. As a result diabetes is thought of as being one of the biggest health challenges in the 21st century. It is already an area of medicine in the UK that requires large amounts of money. Diabetes is reported to costs the NHS about one million pounds every hour [4], resulting in the NHS spending around nine billion pounds each year on diabetes [5]. Indeed statistics from 2008 state that about 700 million pounds was spent on blood sugar controlling drugs alone [6].

Currently there is no easily available cure for diabetes, short of having a pancreas transplant. Thus diabetes is a disease which requires management of the condition. This is usually done by having a given dose and type of insulin put into the body at the correct time that it is needed. There are several problems with this method of management. The first being the way that the insulin is taken into the body; as insulin is a protein it cannot, currently, be taken orally as it is simply broken down by enzymes in the stomach. This results in people, usually taking in insulin as a subcutaneous injection by single-use syringes, insulin pumps or through repeat-use insulin pens. There is also the problem selecting the correct dose, depending on many factors, and the timing of when that dose is taken. This poses a problem, as there are many factors which can affect the dose of insulin that is required, therefore causing the dose which is needed to be adjusted. The factors which can cause this adjustment to be necessary include exercise, the food intake timings, the amounts and the types of food which are eaten e.g. carbohydrates. Also, through this way of intake there is variability in the absorption of the insulin in the blood stream. There is also a very serious problem if one was to take an incorrect dosage of insulin. For example if the amount of insulin injected is in excess of the amount required to remove the carbohydrates, it can cause hypoglycemia. This can then lead to a hypoglycemic coma and death. It can also cause brain damage, paralysis and it is also thought that a long term risk can be the development of type-2 diabetes; however this has yet to be proven.

Even with all the money that is spent on managing diabetes, and the ways that people can manage diabetes, it is a serious issue due to the problems that may occur because of it.

Heart problems, such as heart disease or strokes, are one of the difficulties which may occur as a direct result of diabetes, with 80 per cent of people with diabetes dying of cardiovascular complications [7]. The kidneys are also affected when diabetes isn't managed properly; diabetes is now the leading cause of end stage renal failure [7]. Diabetes can also cause complications with eyesight, when not controlled. Diabetes is the leading cause of blindness of people of working age in the UK, with people with diabetes up to 20 times more likely to go blind than people who do not have diabetes [7]. Diabetes is also a reason that many people have amputations. This can be a result a small cut becoming a large infection. There are two reasons for why this easily happens in cases of people with diabetes. Firstly, through diabetic neuropathy where the nerves in the feet can become damaged resulting in it being difficult for one to feel the sensation of pain. This can then cause an inconvenience to develop into a much larger problem i.e. someone could get a blister without realizing, this could then develop into a serious infection. The second reason is that diabetes can cause the arteries to narrow. This reduces the flow of blood to the feet and other extremities, making it harder for sores to heal as there is less blood able to get to the tissues, to nourish them. It is then possible for this to develop into gangrene which may require toe, foot or even leg amputations. On average around 100 people a week in the UK have a limb amputated as a result of diabetes **[7].** The rate of lower limb amputation in people with diabetes is 15 times higher than in people who do not have diabetes [7]. 70 per cent of people die within five years of having an amputation as a result of diabetes [7]. Diabetes is a major reason of death in the UK, with more than one in ten (11.6 per cent) deaths among 20 to 79 year-olds in England being attributed to diabetes [7]. It is estimated that if current trends continue, one in eight (12.2 per cent) deaths among 20 to 79-year-olds will be attributable to the condition by 2010 [7]. Diabetes also causes more deaths than breast and prostate cancer combined [7]. On average one's life expectancy is reduced by 20 years in cases with tye-1 diabetes and by up to ten years in cases of type-2 diabetes [7]. However, more people die as a result of diabetes than the statistics show, as many death certificates fail to show that the underlying cause of death was diabetes [7]. Therefore diabetes is an extremely dangerous disease when it isn't managed correctly.

Diabetes when allowed to continue uncontrolled not only poses problems for the person with diabetes but it also causes problems for the hospitals which have to treat that person. One in ten people in hospital have diabetes and 60 per cent on inpatients who have diabetes have been admitted as emergencies [7]. People with diabetes are twice as likely to be admitted to hospital, than those without diabetes [7]. As well as there being many people who are admitted to hospital due to diabetes, it also causes inpatients to stay in hospital longer no matter what the cause of admission was [7] The hospital stay for a person with diabetes is likely to be up to twice as long as average, with the hospital stay of someone with diabetes usually being 11 days [7]. Diabetes UK estimates that, in total, patients with diabetes spend 1.1 million days a year in hospital [7]. People with diabetes are also in hospital more frequently, as well as staying in hospital longer, with 20 per cent of patients with diabetes in hospital who had already been hospitalised the year before [7]. In 2007, accident and emergency admissions of children with short-term complications of diabetes rose to 3,317, an increase of 8 per cent on the previous year [7], therefore showing that diabetes is becoming more of an issue for hospitals and that many people aren't managing their condition correctly, for whatever reason. All this time that these patients stay in hospitals cost the NHS vast amounts of their budget. On average a daily bed stay costs the NHS around £215 [7]. Emergency ambulance attendance costs around £220 and minor Accident and Emergency attendance costing around £55 [7]. All of these factors along with the costs of drugs and the payment of staff costs around £9 billion which equates to around 10 per cent of NHS spending [7].

Nanotechnology as a solution

Although nanotechnology has implications in many areas of medicine, the ability to cure diabetes may not be one of them. As diabetes is due to biological errors on a larger scale (particularly in type 2 diabetes) it may not be so easy to correct these errors, if at all possible. However, easier and more effective treatment of diabetes is a viable option. Many people with diabetes struggle with the control of their disease; although there are few issues with the effectiveness of injecting insulin into the blood stream at a cellular level, as insulin is a hormone found normally within the blood. There are dangers and other issues present within the control methods of diabetes. For those who inject insulin there is the risk of overdose, incorrectly injecting the insulin, missing an injection or rather taking too many injections and decreasing blood sugar levels too low.

With a more convenient and reliable method diabetes could be a more manageable disease, especially for groups who particularly find the control of it difficult. Part of the struggle with controlling diabetes is often knowing when to take the medication and maintaining blood sugar levels. Such concepts can be difficult to explain to children or hard to grasp for others. Although practice makes perfect, one would prefer to get it right first time. However, if blood sugar levels could be monitored for the patient they could be more easily balanced as well as monitored more regularly as it would not affect the patient's daily routine. It is possible a small microchip could be placed on a viable area of the patient's body (preferably near a vein or other blood supply) and through the use of carbon nanotubes , small quantities of blood could be taken or merely filtered through and used to monitor blood sugar and insulin levels. However, another solution for the application of insulin is needed to fit with this monitoring system. The chip could monitor blood sugar levels for the patient and alert them when they drop too low, or rise too high the patient would still have to go through the impracticality of applying the insulin. Although with modern technology there may be no current solution in nanotechnology, the chip could still function alongside an insulin "pack" that would be able to inject the insulin when used in conjunction with the chip. The patient would then only need to refill the pack when it runs out, by prescription, avoiding the inconvenience and often, the difficulty of monitoring blood sugar levels and injecting the insulin. Unfortunately this solution of an insulin "pack" may be cumbersome and an equal inconvenience. Often different types of insulin injections are needed too, adding another layer of complexity to the process. Even without the insulin pack the use a chip utilizing nanotechnology that can monitor blood sugar levels constantly for the diabetes patient could be invaluable; more so to patients with Brittle Diabetes or Type 2 Diabetes as careful dietary control is vital.

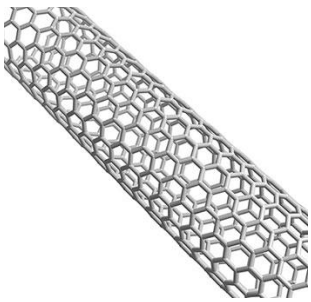

Figure 1 Carbon nanotube

Figure 2 Carbon nanobud

A proposed use of nanotechnology within this chip is the use of carbon nanotubes as a way of extracting blood for analyse. Due to the width of a single carbon nanotube many would have to be used. The amount of glucose would be measured on a molecular scale, as the nanotubes are only wide enough for a few molecules. But the measurement of a small sample could easily give an idea of glucose levels on a larger scale. The extracted samples could then be filtered back into the blood stream, through the nanotubes, to keep the chip clean and efficient with the ability

for repeated use. These nanotubes could either sit within the blood stream constantly, being used when necessary, or they could be protruded and retracted when needed. This movement could be facilitated by the use of carbon nanobuds along the nanotubes to act as "teeth" within a working mechanism. Whole molecules could act as controllable gears [8] or other nanotubes with protruding nanobuds could be used to move the essential nanotubes in and out of the blood stream. Due to the size of the carbon nanotubes they can slip between or through cell walls and capillary walls without causing any damage, although a prolonged presence could cause the body to react unfavourably. A more radical concept for the use of nanotechnology within the treatment of diabetes could be the manipulation of individual cells, either within the pancreas or within fat, muscle or liver tissues. On an extreme scale a cure for diabetes could be synthesized, based around nanotechnology. Within the pancreas the beta-cells responsible for insulin production could be replaced by working synthetic cells, although this idea is likely to be more fiction than reality. On the other hand, existing dysfunctional cells (in the case of Diabetes Type 1) could be augmented to revive their efficiency and production; although with the case manipulating pancreatic cells a pancreas transplant is still more viable, albeit more risky. A more likely solution (particularly for patients with Diabetes Type 2) is the augmentation of fat, muscle or liver cells responsible for taking up glucose in the blood and storing it as glycogen. Cells could be specifically targeted and augmented with added receptor sites or improved receptor sites to reduce insulin resistance (Artificial Receptor Sites) [9] . The delivery method for this treatment could involve buckminsterfullerene to contain the receptor and through the enhancement of pre-existing biological cell-specific molecules [10]. Charged gold nanoparticles have also been found to be capable of targeting specific organs due to varying charges. [11] . Other devices which can be used in the management of diabetes are the nanopump and the implantable sensor. The nanopump is a powerful device and essentially performs the job its name describes. The first application of the pump, introduced by Debiotech, is Insulin delivery. The pump injects Insulin to the patient's body at a constant rate, balancing the amount of sugars in the patient's blood. The pump can also administer small drug doses over a long period of time [12]. The implantable sensor however is more of a detection device to alert the patient to take their insulin. The use of polyethylene glycol beads coated with fluorescent molecules to monitor diabetes blood sugar levels is very effective. 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 [13]. Another, more creative way nanotechnology has been used to combat diabetes is by creating an 'artificial pancreas', At UCSF Professor of bioengineering, Tejal Desai, implants millions of pancreatic cells that secrete insulin into tiny capsules that can be implanted into the body in an effort to create an artificial pancreas. When blood sugar flows inside the capsule, it stimulates the cells to produce insulin to control sugar levels. The device has nano pores, pores so small that the body's antibodies cannot get in to attack the cells, but large enough that the insulin can flow out and into the body [14].

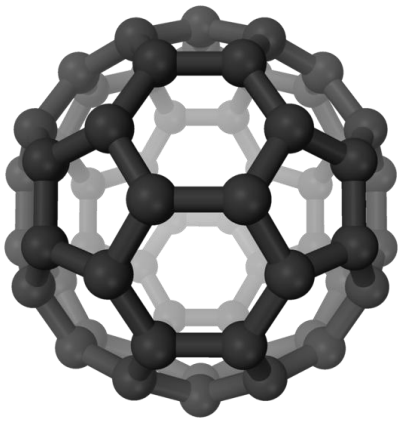

Figure 3 Buckminsterfullerene

Ethics

As with most areas of medicine and especially with new drug and drug administration development there are prominent ethics involved in the process. In particular nanotechnology in general, there is concern over how in the future to regulate what is 'treatment' and what is 'enhancement'. For instance, there is a fine line between medical and non-medical uses of nanotechnology for diagnostic and therapeutic purposes (e.g. condition regulating such as in Diabetes) and preventive purposes (e.g. non-medical implants in soldiers). The question of whether nanotechnology should be used to make intentional changes in or to the body when the change is not medically necessary is just one hot topic in a long list of concerns [15].

However, when focusing solely on the regulating of insulin and treatment of Diabetes, there are much less ethical concerns and many more advantages to the patient. A primary motivator in investing in alternative solutions such as nanotechnology is because of the sheer scale of diabetics, the money needed to finance the NHS to cope with the insulin demands is high. Studies have shown the increase in the amount of money spent on insulin has outstripped the increase in amount of insulin used. Whereas many drugs become cheaper over time - as similar drugs or generics enter the market - the unit cost of insulin used has actually increased. Put simply, the insulin we're using is more expensive [16]. By turning to nanotechnology, money would be saved in the long run as the exact amount of insulin needed at exactly the right time can be injected, therefore saving resources and money. In turn, if Diabetics are managing their condition better, this relieves pressure of the hospitals of people mismanagement of their medication which opens up time, resources and the expertise of medical professionals for other patients. The uniqueness of how the blood levels are monitored by a chip or a nanoparticle inside the body as opposed to regular fingertip-prick glucose blood tests, and also the uniqueness of specific drug administration would greatly benefit certain types of Diabetes sufferers. For example young children and the elderly may find it difficult and more distressing to self inject insulin and a major inconvenience in day to day life as they are more likely to require assistance ensuring they've taken the correct dosage at the right time. Another important factor to consider in young diabetic children is that things like the finger-prick blood glucose tests can be painful and obtrusive in a child's life [17] and if they experience inconsistent treatment or develop severe negative feelings towards their treatment, they are more likely to grow up to mismanage their medication, resulting in the same problems the health care industry is experiencing now. So considering the young is very important for future attitudes and advancements in treatment. Children and the elderly are also higher risk groups of mismanaging their medication as they are more likely to forget or just dismiss their condition entirely. Nanotechnology could benefit these ages of patients in particular as there would be no need for as regular testing like the finger-prick test; the particle or chip under the skin would inform the patient regularly and would not often need replacing. Then the insulin would be released as and when needed, in exact doses needed. This would remove the inconvenience of remembering to self inject and also the issue of correctly self injecting the medication, this would not only let the patient lead a less stressful life, but also a less painful one.

Of course, nanotechnology is far from replacing the tried and tested procedure of self testing blood glucose levels and self injection of insulin, and there is still a great deal of research to be done into the long term health risks associated with nanoparticles staying in the human body for a great length of time. As Peter Singer wrote in his 2003 tutorial Mind the gap: science and ethics in Nanotechnology: *"The science leaps ahead, the ethics lags behind."* Nanomedicine, and nanotechnology in general, is new and little experimental data about unintended and adverse effects exists. The lack of knowledge about how nanoparticles might affect or interfere with the biochemical pathways and processes of the human body is particularly troublesome. Scientists are primarily concerned with toxicity, characterization

and exposure pathways. There are also valid concerns over the disposal of nanowaste and environmental contamination from the manufacture of nanomedical devices[12]. There is also ,perhaps more importantly, the attitude of the patient to be concerned about. Offering nanotechnology as an aid to treatment should not encourage them to take less responsibility of their condition. There is the risk with nanotechnology's quality to self regulate blood glucose, that the patient could become more reckless with their eating habits and just dismiss their behaviour in the belief that the nanoparticles can fix it all. To ensure that this innovating technology is properly incorporated into the patients' lives and management of diabetes, there must be adequate understanding by Doctors and patients of nanotechnology's limitations and how best to use them.

Conclusion

Overall, the ethics and nanotechnology itself need their crinkles smoothed out before any major new treatment can be widely offered. Though the small clinical trials involving investigating the effectiveness of invasive and non-invasive nanotechnology like the nanopump, the implantable sensor and the 'artificial pancreas' have been largely successful, there is much more research needed into the long term effects before any nanotechnology drug delivery will be marketed. The possibility for easier management and ultimately, completely controlled Diabetes is hopeful, with nanotechnology rapidly developing and with many avenues on how it can be used in the human body; nanoparticles being just one of them. Also, even if any of these larger scale treatments became viable their availability at the time of manufacture would be limited and costly, similar to new drugs being produced. As well as this, due to the higher interest for treatment of other diseases through the use of nanotechnology, such as cancer, diabetes may not reach the top of the list anytime soon. Due to the physiological-scale complexity of diabetes these options may not prove to be viable in the future, although further research within this field is needed as well as in the field of nanomedicine.

There may also be easier and more cost-effective solutions to the problems with the treatment of diabetes; perhaps arising for nanotechnology or from other methods. Although nanotechnology is progressing at varying rates in different fields, each advancement is a leap in the right direction, bringing us nearer to more theoretical ideas in the field.

Currently the healthcare is under immense pressure with Diabetics mismanaging their medication; putting more strain on financial, medical and professional resources. We predict with certainty that nanotechnology will play a useful and dynamic role for the treatment of Diabetes in the future and are following eagerly the development of nanotechnology's role within medicine.

References

[1]www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf

[2]http://www.worlddiabetesfoundation.org/composite-35.htm

[3]http://www.diabetes.org.uk/Professionals/Publications-reports-and-resources/Reports-statistics-and-case-studies/Reports/Diabetes-prevalence-2010/

[4]http://www.diabetes.co.uk/news/2010/Oct/diabetes-costs-the-nhs-one-million-pounds-an-hour-93645072.html

[5]http://www.diabetes.co.uk/news/2010/Oct/diabetes-costs-the-nhs-one-million-pounds-an-hour-93645072.html

[6]http://www.nursinginpractice.com/article/22388/Too_much_spent_on_diabetes_drugs?category.id=10

[7]http://www.diabetes.org.uk/Documents/Reports/Silent_assassin_press_report.pdf

[8]http://www.understandingnano.com/medicine.html

[9]http://www.sciencedaily.com/releases/2009/06/090615102036.htm

[8] http://www.acceleratingfuture.com/wiki/Artificial_dopamine_receptor

[10] http://www.news-medical.net/news/2008/01/16/34405.aspx

[11] http://en.wikipedia.org/wiki/Nanomedicine#Nanoparticle_targeting

[12]http://thefutureofthings.com/news/1286/insulin-nanopump-for-accuratedrug-delivery.html

[13] Neil Gordon , Uri Sagman . Nanomedicine Taxonomy; Canadian NanoBusiness Alliance 1-28(2003

[14]http://www.smartplanet.com/people/video/nanotechnology-to-end-insulin-injections-for-diabetics/370926/

[15]http://www.bioethicsinternational.org/blog/2008/01/10/ethical-aspects-of-nanotechnology-in-medicine/

[16] http://www.channel4.com/news/why-diabetes-is-big-business-for-drug-companies

[17] http://www.ssdg.org.uk/info/child5

Figure 1: http://www.nanoid.co.uk/nanotube_filter.html

Figure 2: http://en.wikipedia.org/wiki/Carbon_nanotubes

Figure 3: http://en.wikipedia.org/wiki/Buckminsterfullerene