

**POTENTIAL USES OF NANOTECHNOLOGY
IN THE TREATMENT OF
COMPLICATIONS OF DIABETES**

BY

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PASS WITH MERIT

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Abstract

Diabetes affects millions of people worldwide and the complications of diabetes can be very severe. This paper considers three of the most common complications of diabetes, namely diabetic neuropathy, heart disease and stroke. Current treatments of these medical problems are only partially successful.

Here, possible alternative treatments using nanotechnology are explored, as well as the ethical implications of a relatively new and untested field of medicine. The side effects of nanomedicine are unknown, so it is difficult to come to a firm conclusion about its uses in treating the complications of diabetes and in the wider medical field. However, this paper concludes that nanomedicines could provide more effective treatments for diabetic neuropathy, heart disease and stroke in the future.

Introduction

Nanotechnology can be defined as a field of technology that researches into and manipulates matter on a molecular scale, between 1 and 100nm. One nanometer is one billionth (10^{-9}) of a metre. Nanoparticles often have different physical properties than the same elements when they are in bulk, also they can reach much smaller spaces and structures that other, larger substances cannot. This makes them very useful as they can perform tasks that larger materials cannot. ^[1] There are many uses of nanotechnology in medicine. Nanotechnology can potentially be used in drug delivery, where nanoparticles are used to transport drugs to specific cells, and to prevent the drugs from being damaged by extremes of pH (for example the low pH in the stomach). Also, the nanoparticles prevent the drug from damaging any tissue or organs en route to the target cells. ^[2] Nanotechnology could also be used in diagnostic and imaging techniques, for example in order to detect cancer cells. Scientists in Shanghai Jiaotong University have attached gold nanoparticles to antibodies that are specific for biomarkers of different cancer cells. These gold nanoparticles can be easily detected, which makes this method of detection highly sensitive. ^[3] Potential therapy techniques using nanotechnology include using titanium dioxide nanoparticles, covalently bonded with antibodies that are specific to brain tumour cells, to destroy brain tumours. These covalently bonded particles obtain their energy from light in order to produce reactive oxygen species, which have a cytotoxic effect, damaging the cell membrane of the tumour cells. A problem with this technique is that brain tumours cannot be exposed to light directly, so surgery is still needed. However, this method is less invasive than current surgical treatment, and brain tumours are often inaccessible for surgeons, so this method could reach tumours deep within the brain, and, as the antibody is specific to certain tumour cells, will not damage any healthy tissue on the way to the tumour. ^[4] Nanotechnology could potentially be used in cell replacement, where titanium oxide nanotubes could be used as a scaffold to support artificial cartilage, grown from chondrocytes in vitro. The aim is to use the scaffold to link the cartilage to the bone, restoring the tissue to its normal functioning environment. ^[5] Nanotechnology could also be used in antimicrobial techniques. Nanocrystalline silver particles could be used in wound dressing, acting as a physical barrier to microbes such as MRSA. As MRSA is a strain of bacterium that is resistant to methicillin, using nanotechnology would avoid this problem. ^[6] Nanotechnology is likely to influence the way all diseases are diagnosed and treated, however in this paper I have chosen to focus on the uses of nanotechnology in treating diabetic complications caused by blood vessel damage. These are diabetic neuropathy, heart disease and stroke. They are serious and present increasing problem for the NHS, and for the patients affected. The proposed treatment will demonstrate some of the different uses of nanotechnology. Also, the NHS spends approximately £9.6m every day treating diabetes and its complications, which equates to 5% of NHS expenditure and 9% of all hospital costs. ^[7] The number of people diagnosed with diabetes in the UK has increased from 1.4 million in 1996 to 2.6 million today. It is estimated that the number will increase further, with over 4 million people having diabetes in 2025. The number of new diagnoses is equivalent to 400 people every day. Our ageing population and growing number of overweight people are likely to cause most of the diabetes cases to be Type 2. ^[8]

Discussion

Causes and symptoms of diabetic neuropathy, heart disease and stroke

If patients do not control their blood glucose level, it may become dangerously high. Prolonged high blood glucose levels can lead to atherosclerosis, where fatty deposits build up inside the blood vessel walls, narrowing the lumen of the blood vessel and causing the blood vessel to

harden.^[9] When the lumen of the blood vessel becomes narrower, blood flow may be obstructed. Nerves running alongside the blood vessel may then become starved of oxygen and nutrients, causing nerve damage and diabetic neuropathy (see Figure 1). Since diabetic neuropathy affects nerves throughout the body, symptoms occur throughout the body. Symptoms include pain, wasting of the muscles in the feet and hands, inability to regulate blood pressure and gastroparesis, a disorder that causes the stomach to empty too slowly, which in turn could cause persistent vomiting and weight loss.^[10]

Heart disease is associated with diabetes. When the lumens of the arteries supplying the heart narrow, blood flow to the heart is restricted, causing the heart muscle to be starved of oxygen and other nutrients. This could cause necrosis of the heart muscle tissue, possibly resulting in acute myocardial infarction.^[11] Diabetes is also associated with strokes. An atherosclerotic plaque carried by the blood can cause the blockage of an artery in the brain, and the resulting brain infarction may cause a stroke. Also, a blood clot, or thrombus, may form in the artery because of the narrowed lumen and cause brain infarction and subsequently a stroke. Increased blood pressure, also associated with diabetes, could cause a brain haemorrhage and consequently a stroke. Symptoms of stroke could include paralysis of one side of the body, sudden loss of vision and problems with communication, balance and coordination.^[11]

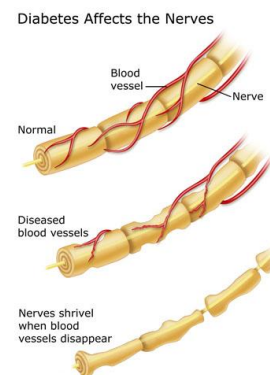


Figure 1: illustrates how damage to blood vessels leads to nerve damage^[i]

Current treatments of diabetic neuropathy, heart disease and stroke and their side effects

Rigorous control of blood glucose level can usually prevent diabetic neuropathy. However, since 60 – 70 per cent of all diabetic patients are affected by diabetic neuropathy, a direct treatment of symptoms is needed. The risk of neuropathy increases with time; the highest rates of neuropathy occur when patients have had diabetes for 25 years or more.^[10] According to NICE guidelines the current drug of choice for treating diabetic neuropathy is the antidepressant duloxetine.^[12] There are many side effects of duloxetine, most commonly gastrointestinal.^[13]

In more serious cases, nerve damage caused by diabetic neuropathy can be treated with autograft surgery, where a section of a healthy nerve is taken from a donor site and used as a bridge across the site of damage. There are many problems with this surgery, including loss of function at the donor site, no suitable nerves being found for the surgery, and multiple surgeries being needed.^[14] There are several different types of drug treatment for heart disease, including angiotensin-converting enzyme (ACE) inhibitors and beta-blockers.^[15] However there are side effects of both of these drugs; for example, 1 in 10 people develop kidney problems as a result of taking ACE inhibitors and beta blockers can cause tiredness, nausea, diarrhoea and slow heartbeat.^[16] Strokes can be treated with aspirin, which has side effects including bleeding in the stomach or gut, worsened breathing problems if the patient is asthmatic, and occasionally the patient may be allergic to aspirin.^[17]

How nanotechnology could treat diabetic neuropathy, heart disease and stroke

Detection of atherosclerosis is a critical step towards treating patients with complications of diabetes. Nanoparticles are being developed that enhance magnetic resonance imaging (MRI; now a very important technique for diagnosis), as the particles' size creates a brighter contrast than the conventional MRI techniques. Additionally, current MRI contrast agents such as gadolinium chelates can cause kidney failure in patients. To avoid this type of damage, nanoparticles are encased in a biocompatible shell.^[18] The clinical trial phase for some nanoparticle MRI contrast agents is just beginning,^[19] therefore it is likely that “nano contrast agents” will be used to diagnose a wide range of diseases in the future. Fibrin deposits, key components in atherosclerotic plaques (see Figure 2), could be targeted using a fibrin-specific antibody bound to a nanoparticle that enhances MRI. In this way, smaller atherosclerotic plaques could be detected.^[20] The advantage

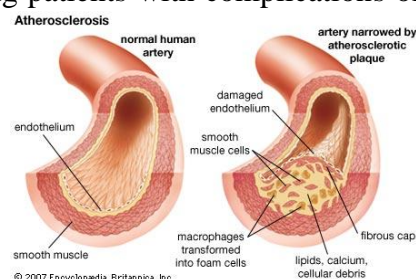


Figure 2: illustrates an atherosclerotic plaque narrowing the lumen of an artery (right panel). The nanoparticle MRI contrast agents will target the fibrous cap of the plaque. A normal artery is shown for comparison (left panel).^[iii]

of detecting smaller atherosclerotic plaques is that they may be detected earlier than with current treatments, and therefore may be treated before the patient suffers any consequences, such as nerve and blood vessel damage. Also, smaller plaques will usually be easier to treat, meaning that early detection could make treatment more effective.

New research suggests that functioning blood vessels could potentially be grown around biodegradable nano-“scaffolds” (see Figure 3). However, instead of letting the cells grow inside the scaffold, researchers at the San Diego Department of NanoEngineering are using projection bioprinting to encase the blood vessel cells within the walls of the scaffold. Projection bioprinting works by printing a pre-designed model of the scaffold and using light to solidify a solution of polymers and cells that will grow into the blood vessel tissue. Mirrors are used to achieve the exact shape of the 3D model. The solution of polymers contains nanoparticles of hyaluronic acid; a disaccharide that is derived from collagen and like collagen can play a structural role in the scaffold. Once the scaffold has solidified, the cells inside the walls of the scaffold are encouraged to grow in a uniform pattern, meaning that they can be manipulated depending on the shape of the nanostructure that has been designed. ^[21] Research into blood vessel regeneration is still in its infancy, however, since the body cannot regenerate blood vessels spontaneously, nanotechnology could be the best method of treating diseases whose consequence is blood vessel damage.

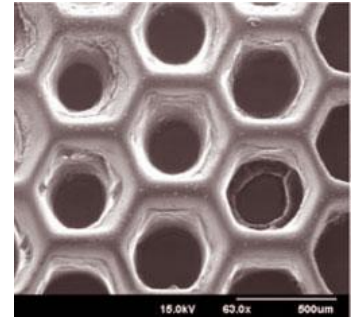


Figure 3: a scanning electron microscopy image of a nanoscaffold. ^[iii]

Research is underway to develop nanocoatings for stents used in surgical procedures such as opening arteries for treatment of heart disease and stroke. This new coating will potentially help to stop the build up of “sludge”, such as bacteria, proteins and glycoproteins, on the walls of the stent. Also, the nanocoatings could decrease the chance of the body rejecting the metal stent after surgery, as it is a foreign body. The Clear coat nanocoating is hydrophobic, meaning that it repels all polar molecules. ^[22] This means that the polar “sludge” molecules will not stick to the coating and therefore the lumen of the blood vessel will remain unobstructed.

Nanoscaffolds are also being developed for nerve regeneration. Unlike the scaffolds used in blood vessel repair, these structures do not contain cells. The purpose of the scaffolds is to provide a pathway for axons to grow along and ultimately to connect with targets below the site of the damage, for example muscle or other neurons. The nanofibres that form the scaffold are aligned to form a straight path, as the shortest distance across the site of damage is a straight line, so that the nerve can grow as quickly as possible in the desired direction. The scaffold contains one or more growth factors, creating a “bioactive matrix” to stimulate nerve growth in a particular direction. ^[14] This technology could be used to treat nerve damage caused by diabetic neuropathy. However, the nerve repair technology would have to be used in conjunction with the blood vessel repair technology, as the nerve damage is commonly caused by lack of oxygen and nutrients to the nerve as a result of blood vessel blockage or damage.

However, where possible it would be much more effective to prevent the blood clots in the first place. Diabetic patients are likely to have lower high-density lipoprotein (HDL) levels than healthy individuals. ^[23] Research is being carried out to generate and test synthetic nanoparticles that mimic the activity of HDLs. Gold nanoparticles can be synthesised and their size and shape manipulated, in order to mimic the HDL. Biological molecules are then attached to the nanostructure to carry out the activity of the HDL. ^[24] HDLs can remove cholesterol from the sides of the blood vessel walls, therefore helping to prevent atherosclerosis.

Side effects of nanotechnology

Since research into the different medical applications of nanotechnology is still in its infancy, possible side effects of nanotechnology are unknown. Nanoparticles have different physical and biochemical properties to the same elements when they are in bulk, meaning that nanoparticles could have different side effects than the drugs used currently to treat disease. According to the FDA (Food and Drug Administration, US), ninety two per cent of potential drugs that pass pre-clinical and animal testing fail to pass the human clinical trial phase. ^[25] This suggests that medical applications

of nanotechnology could also have different consequences in vitro and in animals than in humans, making it more difficult to predict possible side effects. Additionally, because of the size of the nanoparticles, they may be able to gain access across barriers in the body that larger substances, such as current drugs, would not be able to cross. This may cause damage that we have no experience of, and therefore do not know how to ameliorate.

Another important concern is whether the medically relevant nanoparticles will be compatible in the body. Some patients will need to take drugs for several different medical conditions. At the moment doctors consider whether current drugs are contraindicated when used together, however we have very little experience of nanomedicines and hence do not know how nanomedicines will interact with each other or in combinations with existing drugs.

Side effects arising from manufacture are other important considerations. As nanoparticles are between 1 and 100 nm, they can easily become airborne and could conceivably be inhaled, causing side effects in the respiratory system.^[26] Research into the effectiveness of current barriers to airborne nanoparticles, as well as the consequences of their inhalation, is still in its infancy. Possible side effects include damage to cilia and goblet cells in the lungs, as they may become blocked by the nanoparticles.

There is very little known about the removal of nanoparticles from the body. An important safety consideration is whether nanoparticles can be removed from the body naturally, for example by excretion, whether they will biodegrade, or whether they will remain in the body, and if so, will they be dormant? Nanoparticles remaining in the body after treatment could cause serious damage to healthy tissue, and the particles may also accumulate in a tissue that was not originally targeted for treatment.

The ethics of nanotechnology

The principles of Beauchamp and Childress' theory are widely acknowledged and used to identify and resolve ethical dilemmas. These are respect for autonomy, beneficence, nonmaleficence and justice.^[27] Beneficence means that the good effects of an action should outweigh the bad. Nonmaleficence means that one should not inflict mental or physical harm on another person.^[27] Since we do not know the possible side effects of nanotechnology we cannot be certain that we are acting with beneficence and with nonmaleficence.

One of the biggest advantages to nanomedicine is its potential to target specific cells or tissues. However, targeting some areas in the brain, for example pleasure centres, could create a new line of incredibly powerful recreational drugs. Such new drugs could have repercussions on the whole of society in two main ways. Firstly, this could create a new branch of organised crime, as the ability of these drugs to target pleasure centres of the brain could make them much more effective in smaller doses and also far more addictive. This may mean that it would be easier for criminals to make a profit. Secondly, as we do not know how to eradicate nanoparticles from the body, these drugs could have unexpected and irreversible effects on health. In addition, the potential of nanoparticles to target areas in the brain could cause changes to individuals' personalities. The ethical question raised might be: would you rather be ill and be yourself, or be cured and then live as someone else? Society would have to debate as to where the ethical line would be drawn. For example if the side effect of a treatment for a degenerative brain disease such as Alzheimer's was an increase aptitude for speaking languages, then there is a possibility that people would pay for that nanomedicine as a brain enhancement drug.

Additionally, nanotechnology could have unexpected adverse effects on the environment. If nanoparticles become widely used in medicine, there is a possibility that they will be inadvertently released into the environment during their manufacture. They could also reach the environment through patients' excretion. There are already examples of medicines affecting the environment; a particularly startling one is the effect of oestrogen on fish. In rivers in the US it has been observed that male fish are carrying eggs in their testes due to exposure to oestrogen.^[28] These "intersex" characteristics could possibly have a detrimental effect on breeding in these populations of fish. Also, exposure to oestrogen is inhibiting productions of hepcidins, a protein that has antifungal and possibly antibacterial activity, in the fish. This means they are more susceptible to disease, which could potentially reduce the numbers of fish in these rivers.^[28] Nanoparticles could be more difficult

to contain due to their size, hence the environmental repercussions could be even greater, and, as with oestrogen exposure in fish, have the potential to affect the whole food chain, including humans. More research into both the possible good and bad effects is needed before nanoparticles are widely used in medical applications.

Applications of nanotechnology in medicine could be very expensive. If this is the case, medical care using nanotechnology could be offered only to those able to pay for it. This contradicts the principle of justice, as this kind of medical care would only be available to a few individuals.

Regulation and control of nanomedicine is another important area that raises ethical questions. As further research is carried out, more possibilities and applications of nanotechnology in medicine will become feasible. It is important that all research results on nanomedicines should be shared in order that doctors can provide the best possible care for their patients. Since nanomedicine is a new and rapidly developing field, it would be easy for pharmaceutical companies to withhold information about their developments. Furthermore, there is a danger that pharmaceutical companies could charge excessively for nanomedicines that the NHS could provide more cheaply. This is an example of injustice, as companies should not profiteer at the expense of patients' health.

Another important ethical consideration is the need for informed consent, in the first instance for clinical trials. When a normal drug trial is carried out, researchers can predict possible dangers and side effects, as similar drug trials have been performed previously. Subjects can be informed appropriately, and so have a basis upon which to form a decision about taking part in the trial. Nanomedicine is an area that we are not familiar with, and therefore the risks involved are difficult to identify. Hence truly informed consent is impossible at this time.

Conclusion

Nanomedicine is often described as a medical "revolution", but the term revolution implies that the changes are going to happen relatively quickly and on a grand scale. It is likely that nanotechnology and its applications will have major and lasting effects on medical care, however it may take some time before these changes become apparent. The human genome project and stem cell research are two other fields that have attracted a lot of media attention, and have been labelled medical revolutions, but, like nanomedicine, it may be many years before these research areas are widely applied in medicine.

Richard Feynman first used the term nanotechnology in 1959, when he said "There's plenty of room at the bottom" ^[29], meaning that the possibilities of using very small molecules and structures are both unexplored and extensive. If nanomedicines could be successfully and safely applied then there would be many advantages. Firstly, nanoparticles are able to target specific cells and tissues, making them more effective and faster than current drugs and avoid effects on healthy tissue. Secondly, nanoparticles can be manipulated to make particular structures that are specific to the needs of the treatment, and can be introduced into the body without rejection, as they are biocompatible and biomimetic, making them very versatile.

However, there may never be away to mass-produce medically relevant nanoparticles safely, thus it may be too expensive to use nanotechnology in all areas of medicine. Also, nanotechnology may not be appropriate to be used in some areas of medicine.

In conclusion, nanomedicine shows great potential for the future and the knowledge that we have at the moment suggests that their advantages will outweigh the possible dangers. Nanomedicine represents a new system of treating patients: repair and regeneration rather than treatment of symptoms, as nanomedicines could get to the root of the problem where current treatments often cannot. Nevertheless, more research should be done to minimise the possible side effects.

Drawing overall conclusions about the applications of nanotechnology in medicine is only the first step in treating a specific medical problem, in this case the complications of diabetes. To date, nanotechnological research has been carried out in a wide variety of fields, but has not yet been applied to treating diabetic neuropathy at all, and only to a limited extent in heart disease and stroke. Hence more research directly in the area of diabetes and its complications will need to be undertaken.

References:

Text references:

1. What is nanotechnology? <http://www.nano.org.uk/what-is-nanotechnology>
2. Uses of nanotechnology in medicine <http://www.understandingnano.com/medicine.html>
3. Gold nanoparticles detect cancer
<http://www.rsc.org/chemistryworld/News/2009/August/19080901.asp>
4. Nanotechnology therapy for brain cancer
<http://www.nanowerk.com/spotlight/spotid=12962.php>
5. Nanotube surface triggers increased chondrocyte extracellular matrix production <http://www-bioeng.ucsd.edu/faculty/area/biosel/publications/pub31.pdf>
6. Nanocrystalline silver dressings as an efficient anti-MRSA barrier
<http://www.ncbi.nlm.nih.gov/pubmed/15896880>
7. Diabetes in the NHS www.diabetes.nhs.uk/document.php?o=318
8. Key statistics on diabetes
http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf
9. Diabetes, Heart Disease, and Stroke <http://diabetes.niddk.nih.gov/dm/pubs/stroke/index.htm>
10. Diabetic Neuropathies: The Nerve Damage of Diabetes
<http://diabetes.niddk.nih.gov/dm/pubs/neuropathies/>
11. Overview of Diabetes, Heart Disease and Stroke
Kumar P & Clark M (2004) Clinical Medicine, 5th Edition, Elsevier Limited
12. Neuropathic pain <http://www.nice.org.uk/nicemedia/live/12948/47949/47949.pdf>
13. Cymbalta (duloxetine) <http://www.netdoctor.co.uk/medicines/100005102.html>
14. Regenerating nerve cells with nanotechnology
<http://www.nanowerk.com/news/newsid=1959.php>
15. Management of chronic heart failure
<http://www.nice.org.uk/nicemedia/live/13099/50517/50517.pdf>
16. Treating Heart Disease <http://www.nhs.uk/Conditions/Coronary-heart-disease/Pages/Treatment.aspx>
17. Aspirin and Other Antiplatelet Drugs <http://www.patient.co.uk/health/Aspirin-to-Prevent-Blood-Clots.htm>
18. Nanoparticles make better MRI images
<http://www.rsc.org/chemistryworld/News/2007/April/06040701.asp>
19. Clinical trial phase for nanoparticle MRI contrast agents
<http://www.nature.com/nrurol/journal/v7/n2/abs/nrurol.2009.254.html>
20. Applications of Nanotechnology to Atherosclerosis, Thrombosis, and Vascular Biology
<http://atvb.ahajournals.org/cgi/reprint/26/3/435>
21. Growing heart tissue with functional blood vessels <http://www.nano.org.uk/news/1130/>
22. Biliary stent clogging solved by nanotechnology?
Seitz U, Block A, Schaefer AC, Wienhold U, Bohnacker S, Siebert K, Seewald S, Thonke F, Wulff H, De Weerth A, Soehendra N. (2007) Biliary stent clogging solved by nanotechnology? In vitro study of inorganic-organic sol-gel coatings for Teflon stents. Gastroenterology. 133(1):65-71.
23. Raising HDL Cholesterol in Patients With Diabetes
<http://docnews.diabetesjournals.org/content/4/8/4.full>
24. Nanotechnology for synthetic high-density lipoproteins
<http://download.cell.com/trends/molecular-medicine/pdf/PIIS1471491410001528.pdf?intermediate=true>
25. A significant number of drugs are rejected during human clinical trials
<http://www.peta.org/issues/animals-used-for-experimentation/food-drug-administration.aspx>
26. Nanoparticles: Health Effects—Pros and Cons
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1764161/>

27. Nanoethics http://www.inano.dk/fileadmin/inano/iNANO-system/research/research%20areas/nanoethics/Ebbesen_Jens.pdf
28. Oestrogen in Waterways Worse Than Thought
<http://www.scientificamerican.com/article.cfm?id=estrogen-in-waterways>
29. History of Nanotechnology <http://cnx.org/content/m14504/latest/>

Image references:

- i. Diabetes affects the nerves <http://www.deo.ucsf.edu/type1/diabetes-treatment/complications/nerve-complications.html>
- ii. What is cardiovascular disease? <http://www.ichaonline.org/site/cardiovascular-disease/what-is-cardiovascular-disease/>
- iii. Illustration of nanoscaffold <http://www.nano.org.uk/news/1130/>