Nanotechnology and the future of diabetes management

Danny Meetoo, Mike Lappin

Article points

1. Nanotechnology has the potential to revolutionise diabetes care.
2. Nanotechnology has implications for people with diabetes and healthcare teams.
3. Nurses caring for people with diabetes need to be aware of the potential effects of nanomaterials.

Key words

- Diabetes
- Nanotechnology
- Nanotoxicology

Danny Meetoo and Mike Lappin are Lecturers in Adult Nursing, University of Salford, Greater Manchester.

Once considered the Cinderella of chronic conditions, diabetes is now fast emerging as one of the biggest health catastrophes the world has ever known (Meetoo et al, 2007). Cost, access and quality of care will continue to be the triumvirate guiding any healthcare system reconfiguration, including diabetes management. The advent of nanotechnology has the potential to improve health and decrease cost. The purpose of this article is to shed some light on the recent development of nanotechnology and its impact on diabetes care.

Contemporary diabetes management places heavy emphasis on individual responsibility (Meetoo, 2004). The lives of people with type 1 diabetes, for example, revolve around a temporal regularity in which insulin doses must be calculated and administered at precise times. Meals, exercise, rest and monitoring of blood glucose parameters must be planned and performed to match those times when insulin levels are expected to drop or peak.

The perceived complexity of the regimen often leads to lapses in adherence. Furthermore, non-adherence is often mistakenly attributed to inadequate knowledge of diabetes care by ignoring psychosocial factors that significantly contribute to this problem (Schlundt et al, 1994; Weissberg-Benchell et al, 1995; Boehm et al, 1997).

Irrespective of the cause, non-adherence is a major problem in diabetes, leading to complications and often to subsequent hospitalisations, poor clinical outcomes and increased healthcare costs (Lau and Nau, 2004; Ho et al, 2006). The concept of nanotechnology (NT), however, has the potential to eradicate non-adherence from diabetes care, and to enable millions of people with diabetes to lead a more normal life.

Nanotechnology – an overview

NT can be defined as the monitoring, repairing, construction and control of human biological systems at the cellular level by using materials and structures engineered at the molecular level (Kralj and Pavelic, 2003). When applied to medicine, NT is referred to as nanomedicine – a discipline where there are promises of revolutionary opportunities to fight against many diseases (Logothetidis, 2006).

NT is likely to have a significant impact on society, and is perceived as a human affair designed to serve human purposes (Schiemann, 2005). The prefix "nano" originates from the Greek word "nanos", implying 1 billionth of a metre (1 nm = $1x10^{-9}$ m). To gain a sense of proportion, 1 nanometre is about 100 000 times smaller than the diameter of a single human hair (see *Figure 1*). At the heart of NT's promise lies the concept of controlling matter at the atomic and molecular level.

It is not surprising that NT is not yet a household word, given that it has mainly been confined to research laboratories. While the term was coined in 1974 by Japanese researcher Norio Taniguchi to refer to engineering at length scales less than a micrometre, the futurist Eric

Page points

1. Passionate advocates of nanotechnology are keen to assert its promise of improved diagnostics and therapies with its progressive development in fields such as nanoscale surgery, tissue engineering and certain types of targeted drug therapy.
2. Although still in its experimental stage, nanomedicine holds the potential to revolutionise the management of diabetes, thereby contextualising the notion of non-adherence in history.
3. If taken orally, insulin is denatured by adverse pH levels, and undergoes proteolysis by enzymes of the gut where the intestinal epithelium has a low permeability for large molecules.
4. Chitosan nanoparticles have been found to enhance the intestinal absorption of protein molecules to a greater extent than aqueous solutions of chitosan in vivo.

Drexler is widely credited with popularising the term in the mainstream. In his book, *Engines of Creation*, Drexler envisioned a world in which tiny machines or "assemblers" will be able to build other structures with ultrafine precision by physically manipulating individual atoms (Drexler, 1986).

When such a control becomes achievable, then atom-by-atom construction of larger objects will provide a whole new way of making materials, thereby ushering in a second Industrial Revolution with even more profound societal impacts than the first.

Passionate advocates of NT are keen to assert its promise of improved diagnostics and therapies with its progressive development in fields such as nanoscale surgery, tissue engineering and certain types of targeted drug therapy (Haberzettl 2002; Emerich and Thanos, 2003; Freitas, 2005). In so doing, NT will advance broad societal goals, such as better health care, increased productivity and improved comprehension of nature (Roco, 2003).

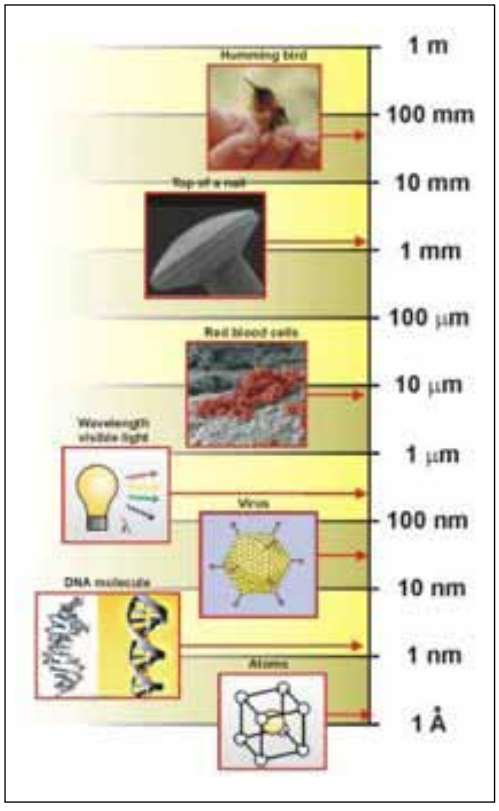

Figure 1. Examples of nanoscales. Reproduced with kind permission of Martin Bennink.

In extending this view, Stix (2001) adds that "there has emerged a cult now of futurists who foresee NT as a pathway to technological utopia: unparalleled prosperity, pollution-free industry and even something resembling eternal life". NT will inevitably have huge impacts on health care and nursing and yet there is sparse publication on the subject in the nursing literature.

The development of NT is occurring at an unprecedented rate. Although still in its experimental stage, nanomedicine holds the potential to revolutionise the management of diabetes, thereby contextualising the notion of non-adherence in history. It is useful, therefore, to review the potential that nanomedicine has in the field of nursing and diabetes care.

Oral insulin

Research into oral administration of insulin has been ongoing for several years, and such an agent is possibly very close at hand. According to Krauland et al (2004), the oral route is considered to be the least invasive, and a painless approach to diabetes management for individuals whose treatment plan depends entirely or partially on insulin, thus leading to higher levels of adherence.

Presently, if taken orally, insulin is denatured by adverse pH levels, and undergoes proteolysis by enzymes of the gut where the intestinal epithelium has a low permeability for large molecules (Carino and Mathiowitz, 1999; Owens, 2002). This major barrier to the absorption of hydrophilic drugs prevents their diffusion into the bloodstream (Borchard et al, 1996; Kotzé et al, 1998).

Consequently, a carrier system, such as chitosan, has been used to protect protein drugs from gastric enzymes (Ramadas et al, 2000) and facilitate the absorption of hydrophilic macromolecules (Ward et al, 2000). Furthermore, chitosan nanoparticles have been found to enhance the intestinal absorption of protein molecules to a greater extent than aqueous solutions of chitosan in vivo (Agnihotri et al, 2004). Chitosan is mucoadhesive, which may prolong its residency in the gut and enhance permeability by disrupting tight junctions between gut epithelial cells, thus allowing the drug to reach its ultimate bloodstream destination (Lin et al, 2007).

Glucose monitoring

It is generally accepted that conventional finger-prick capillary blood glucose self-monitoring is associated with major problems. For example, Pickup et al (2005) argue that this aspect of self-management is painful (leading to non-adherence), it cannot be performed when the person is asleep or driving a vehicle (times when the individual is particularly vulnerable to hypoglycaemia), and because it is intermittent, it can miss dangerous fluctuations in blood glucose concentration between tests. Ideally, therefore, it would be more acceptable for blood glucose monitoring to be continuous and non-invasive.

Several subcutaneously implanted needle-type enzyme electrodes or microdialysis probes for continuous glucose monitoring are close to marketing (Mastrototaro, 2000; Maran et al, 2002; Garg et al, 2006). However, these are limited by their short duration, impaired responses and unpredictable signal drift in vivo, which contributes to sensor inaccuracies. Furthermore, repeated insertion of the sensor probe becomes semi-invasive.

One vision likely to meet the need for improved non-invasive glucose monitoring in vivo is a "smart tattoo", which is composed of glucose responsive, fluorescence-based nanosensors implanted under the skin but manipulated from outside. Research is still being conducted to rectify the biocompatibility and behaviour of this non-invasive device.

Nanopore immunoisolation devices

In collaboration with Tejal Desai et al (Desai et al, 1998), Mauro Ferrari has created one of the earliest therapeutically useful nanomedical devices applicable to diabetes care. It comprises a nano, bio-compatible silicon box composed of micromachined nanopores measuring 20 nm in diameter. The internal structure has been designed to hold healthy pancreatic beta-cells to replace those not functioning in the host.

To overcome the rejection of foreign material by the body, Ferrari has constructed a nanotechnological membrane placed between the transplanting cells and the host organism (Desai et al, 1998). The nanopores are large enough to allow small molecules, such as oxygen, glucose and insulin to pass through, but are sufficiently small to impede the passage of larger molecules that trigger an immune response, thus rendering the device rejection-free in animal models that have been used.

By implanting the silicon box under the skin of the person with diabetes, it is envisioned that the surface biosensors will monitor and counteract any rise in the blood glucose level by releasing sufficient amounts of insulin, thus converting it into glycogen to be stored in the liver. This could restore the body's delicate glucose control feedback loop without the need for powerful immunosuppresants that can leave the person at severe risk of infection (Freitas, 2002).

Artificial nanopancreas

Another possible permanent solution for people with diabetes could be the artificial nanopancreas. First described in 1974, the idea was based on a simple principle: a sensor electrode would repeatedly measure blood glucose levels and any deviation would be fed back into a small computer that energises an infusion pump, which would release the required amount of insulin into the bloodstream (Hanazaki et al, 2001). The large size of this device, however, made it unacceptable for anyone to have such an artificial organ.

NT is now relentless in its attempts to solve this problem. Scientists at Metronic MiniMed have constructed a nanorobot known as the "Long Term Sensor System" (LTSS), which is designed to hold insulin in its inner chambers and a glucose-level sensor on its surface. In the presence of hyperglycaemia, the surface sensors are triggered and insulin is released into the bloodstream, thereby restoring normoglycaemia (Hanazaki et al, 2001; Freitas, 2002; Arya et al, 2008). Experiments suggest that LTSS has the potential to revolutionise diabetes management in the near future (Juvenile Diabetes Research Federation, 2006).

The outcome of a successful formula would enable both healthcare professionals and people with diabetes to review their approach to diabetes care. For example, the benefits of LTSS would range from the maintenance of continuous normal glycaemia, the elimination of blood glucose monitoring and the experience

Page points

1. Several subcutaneously implanted needle-type enzymes electrodes or microdialysis probes for continuous glucose monitoring are close to marketing.
2. One vision likely to meet the need for improved non-invasive glucose monitoring in vivo is a "smart tattoo", which is composed of glucose responsive, fluorescence-based nanosensors implanted under the skin but manipulated from outside.
3. Another possible permanent solution for people with diabetes could be the artificial nanopancreas.

Page points

1. Smart-cell technology represents yet another development in the management of diabetes.
2. In time, nanotechnology will increasingly become a diagnostic and therapeutic enabler to the diabetes healthcare team and other healthcare professionals, as well as to people with diabetes to help take more ownership of their condition.
3. The advent of NT will present new implications for clinicians.

of hypoglycaemia and hyperglycaemia, freedom from diabetes-related complications to the disappearance of chronic immunosuppression as in islet transplantation.

Smart cells

Smart-cell technology represents yet another development in the management of diabetes.

In the presence of hyperglycaemia, glucose will attack the Smart cell by eating away its insulin-containing structure. This damage to the cell membrane will break down the protein matrix to release insulin and normalise blood glucose levels (Aaron, 2003). Smart-cell technology implies that endless checking and re-checking of blood glucose level will become unnecessary, as will injecting insulin.

Implications for nursing

Nursing prides itself on being at the patient's side in times of need, whether in hospital or in the community, and the social contract is based on a relationship for providing holistic care throughout the care continuum.

Nanomedicine has the potential to redefine health and the approach to care delivery. For example, in advancing nanomedicine, NT promises a transition from treating diseases in populations to a more person-centred level, dubbed "personalised medicine" (Vlasses and Smeltzer, 2007). The implants of nanotransmitters and nanosensors would allow individuals to access data transmitted from biochips monitoring such familial diseases as hypercholesterolaemia. This is particularly important when a critical level is reached, thereby allowing affected individuals to take appropriate action. For people with diabetes, a rise in blood glucose level could send a signal to the care team to prompt initialisation of a customised treatment plan, or nanoparticles could be programmed to administer insulin without a clinician's direct intervention.

In time, NT will increasingly become a diagnostic and therapeutic enabler to the diabetes healthcare team and other healthcare professionals, as well as to people with diabetes to help take more ownership of their condition. The continued development of personalised medicine will not only need a time commitment from carers, but it will also require a paradigm shift from consumers as patients to consumers as partners in the decision-making process (Ullman-Cullere et al, 2007).

Arguably, such collaboration is only possible if consumers can keep pace with the scientific development of NT. In a 2007 survey, 80% of consumers had heard very little about nanotechnology (ConsumerReportsHealth.org, 2007). A UK study (Currall et al, 2006) found that people expressed a positive attitude towards NT when interpreting the term "safe" to mean that all risks have been eliminated. This erroneous perception suggests the need for more communication and public education and involvement.

Furthermore, other issues that currently require a debate relate to healthcare professionals and consumers who elect not to assume cognitive responsibility or are unable to assume this level of responsibility. Whether they will be offered alternative options or be subjected to any form of sanctions remain to be seen.

The implementation of NT will inevitably have ethical implications, although the need to develop new ethical guidelines (Thompson, 2007) due to sparse publications within this field (Mnyusiwalla et al, 2003) is contested by others. Given the unknown future design of NT, Ebbesen and colleagues (2006) are nevertheless confident that the open-ended nature of Beauchamp and Childress's (2001) principalist model (autonomy, beneficence, non-maleficence and justice) is sufficiently sensitive to address emerging ethical issues in NT.

The advent of NT will present new implications for clinicians. The concept of routine care could disappear in a world where everything is likely to be customised for individuals presenting with strange or unusual symptoms arising as a consequence of nanomaterials being infected with viruses in minute software or technology circuits. This kind of personalised medicine (Vlasses and Smeltzer, 2007) will mean that nurses will need to update their knowledge of nanotechnology not only for use in the hospital, but also in the community. Similarly, safety considerations to avoid accidental ingestion of nanomaterials

during the delivery of treatments will require serious consideration.

Over-reliance on NT devices could also lead healthcare professionals to assume that they are receiving all the data when in fact that may not be the case (Lewis, 2001). Technological dependence could reduce interprofessional communications, while education for students and trained practitioners through curricular design will be essential to ensure that staff are knowledgeable about the principles underpinning the safe use of nanomaterials. Furthermore, a model of care providing round-the-clock NT support for consumers and nurses will need to be devised and implemented.

The advent of NT means that to reach and maintain excellence, healthcare professionals will need to be consistent in pursuing the required courses in advanced technology to deliver care (Vlasses and Smeltzer, 2007). NT nurses would be actively involved in contributing to policy-making decisions as well as assisting patients' understanding and consent to use their data, protecting privacy and ensuring that mechanisms exist that allow them to withdraw from any participation. Ultimately, however, everyone is likely to require an advocate for the safe and ethical use of nanomaterials in such areas as medical care, the environment, industrial health and the fiscal allocation of research (Traynor, 2006). NT, therefore, has the potential to drive down the costs of care and to create healthy communities that need to use less, rather than more, healthcare.

Nanotoxicology

Nanotoxicology is defined as the "science of engineered nanodevices and nanostructures that deals with their effects in living organisms" (Oberdörster et al, 2005). The sparse literature available regarding nanotoxicology indicates that biodegradable substances are normally decomposed and their waste products are excreted by the kidneys and intestines (Yih and Wei, 2005).

Evidence, however, suggests that non-biodegradable nanoparticles accumulate particularly in the liver, and the potential harm they may trigger, or at what dosage, is unclear, thus requiring further investigation (Hett, 2004). The finding that nanoparticles can provoke increased inflammatory responses and potentiate the effects of medications is another ground for concern (Hampton, 2005). Others have found that nanoparticles placed near rodents' nares travelled up the olfactory nerves in to the brain, thereby crossing the blood–brain barrier (Oberdörster et al 2004).

In the context of protective equipment, Gelperina et al (2005) argue that surgical gloves, masks and gowns may not provide adequate protection, thus creating an urgent need for new evaluative research before such a technology is widely implemented.

Conclusion

There is no doubt that while many of these technologies will require rigorous testing before being marketed, it is not hard to foresee the revolutionary approach that is likely to be adopted in the management of diabetes and in particular type 1 diabetes.

The discovery of insulin by Banting and Best has saved million of lives all over the world – diabetes care is due a revolution. This important leap to embracing NT needs to be taken so that progress can continue to be made and people with diabetes will be relieved of their burden of their condition. NT has the potential to revolutionise medicine, and hopefully it is just a matter of time before the treatment of diabetes is overhauled, reversing the current concept of non-adherence as an exception rather than the norm. ■

Aaron K (2003) *Outsmarting diabetes*. Cornell Engineering Magazine. Available at: http://tinyurl.com/nfzocr

Agnihotri SA, Mallikarjuna NN, Aminabhavi TM (2004) *J Control Release* **100**: 5–28

Arya AK, Kumar L, Pokharia D, Tripathi K (2008) *Digest Journal of Nanomaterials and Biostructures* **3**: 221–225

Beauchamp T, Childress J (2001) *Principles of Biomedical Ethics*. 5th Edition. Oxford University Press, New York

Boehm S, Schlenk EA, Funnell MM et al (1997) *Diabetes Educ* **23**: 157–65

Borchard G, Lueben HL, de Boer AG et al (1996) *J Control Release* **39**: 131–8

Carino GP, Mathiowitz E (1999) *Adv Drug Deliv Rev* **35**: 249–57

ConsumerReportsHealth.org (2007) *Nanotechnology: Untold promise, unknown risk*. ConsumerReportsHealth.org. Available at: http://tiny.cc/GSYgu

Currall SC, King EB, Lane N et al (2006) *Nat Nanotechnol* **1**: 153–5

Desai TA, Chu WH, Tu JK et al (1998) *Biotechnol Bioeng* **57**: 118–20

Drexler KE (1986) *Engines of Creation*. Anchor, New York

Ebbesen M, Andersen S, Besenbacher F (2006) *Bull Sci, Technol Soc* **26**: 451–62

Emerich DF, Thanos CG (2003) *Expert Opin Biol Ther* **3**: 655–63

Freitas Jr RA (2002) *Stud Health Technol Inform* **80**: 45–59

Freitas Jr RA (2005) *Int J Surg* **3**: 243–6

Garg S, Zisser H, Schwarz S et al (2006) *Diabetes Care* **29**: 44–50

Gelperina S, Kisich K, Iseman MD, Heifets L (2005) *Am J Respir Crit Care Med* **172**: 1487–90

Haberzettl CA (2002) *Nanotechnology* **13**: R9–R13

Hampton T (2005) *JAMA* **294**: 1881–3

Hanazaki K, Nosé Y, Brunicardi FCh (2001) *J Am Coll Surg* **193**: 310–22

Hett A (2004) *Nanotechnology: Small Matter, Many Unknowns*. Swiss RE Publications, Zurich

Ho MM, Rumsfeld JS, Masoudi FA et al (2006) *Arch Intern Med* **166**: 1836–41

Juvenile Diabetes Research Federation (2006) *The Next Five Years*. JDRF, New York. Available at http://tiny.cc/CXJNO (accessed: 16.04.09)

King H, Aubert R, Herman W (1998) *Diabetes Care* **21**: 1414–31

Kotzé AF, Luben HL, de Boer AG et al (1998) *J Control Release* **51**: 35–46

Kralj M, Pavelic K (2003) *EMBO Rep* **4**: 1008–12

Krauland, AH, Guggi D, Bernkop-Schnurch A (2004) *J Control Release* **95**: 547–55

Lau DT, Nau DP (2004) *Diabetes Care* **27**: 2149–53

Lewis C (2001) *FDA Consum* **35**: 10–15

Lin Y-H, Chen C-T, Liang H-F et al (2007) *Nanotechnology* **18**: 1–11

Logothetidis S (2006) *Hoppokratia* **10**: 7–21

Maran A, Crepaldi C, Tiengo A et al (2002) *Diabetes Care* **25**: 347–52

Mastrototaro JJ (2000) *Diabetes Technol Ther* **2**(Suppl 1): S13–188

Meetoo D (2004) *Br J Nurs* **13**: 1074–8

Meetoo D, McGovern P, Safadi R (2007) *Br J Nurs* **16**: 1002–7

Mnyusiwalla A, Daar AS, Singer PA (2003) *Nanotechnology* **14**: R9–R13

Oberdörster G, Atudorei V, Elder A et al (2004) *Inhal Toxicol* **16**: 437–45

Oberdörster G, Oberdörster E, Oberdörster J (2005) *Environ Health Perspect* **113**: 823–39

Owens DR (2002) *Nat Rev Drug Discov* **1**: 529–40

Pickup JC, Hussain F Evans ND, Sachedina N (2005) *Biosens Bioelectron* **20**: 1897–902

Ramadas M, Paul W, Dileep KJ et al (2000) *J Microencapsul* **17**: 405–11

Roco MC (2003) *J Nanopart Res* **5**: 181–9

Schiemann G (2005) *International Journal for Philosophy of Chemistry* **11**: 77–96

Schlundt DG, Rea MR, Kline SS, Pichert JW (1994) *J Am Diet Assoc* **94**: 874–6

Stix G (2001) *Sci Am* **285**: 32–7

Yih TC, Wei C (2005) *Nanomedicine* **1**: 191–2

Thompson RE (2007) *Physician Exec* **33**: 64–6

Traynor K (2006) *Am J Health Syst Pharm* **63**: 2175–7

Ullman-Cullere M, Clark E, Aronson S (2007) *Implications of genomics for clinical information*. Partners Healthcare Center for Personalized Genetic Medicine, Harvard Medical School, Boston, MA. Available at: http://tiny.cc/hpp11 (accessed 18.09.09)

Vlasses FR, Smeltzer CH (2007) *J Nurs Adm* **37**: 375–80

Ward PD, Tippin TK, Thakker DR (2000) *Pharm Sci Technolo Today* **3**: 346–58

Weissberg-Benchell J, Glasgow AM, Tynan WD (1995) *Diabetes Care* **18**: 77–82