Particle Progress

Nanotechnology can help revolutionise the fight against diabetes, particularly in investment-starved developing regions. From microchip tests and nano-tattoos to a new gel system, diagnosis, monitoring and treatment of the disease could soon take a leap forward

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Diabetes is a big problem and one that is growing larger every day. Current estimates put the number of people diagnosed with diabetes types 1 (T1DM) and 2 (T2DM) in the UK alone at 3.9 million, with a 10/90% split between type 1, the autoimmune disease, and type 2, the diet and lifestyle related condition. That figure is projected to rise to over 5 million by 2025. And it is believed that a further 630,000 people are currently undiagnosed (1).

Globally, the figures are even more sobering, with the WHO counting diabetes as one of the top 10 causes of death in 2012 (2). In that same year, the estimated figure for adults between the ages of 20 and 79 diagnosed with the disease was 382 million, with another 175 million going undiagnosed. It is also an ageing problem, with 70% of those diagnosed in the age bracket 50-79 (1). That said, children are affected massively too. In the UK, 29,000 under-18s were diagnosed.

A Global Burden

New and interesting symptoms of the disease are being discovered: an example is the effect on cognitive functions. A recent Harvard study showed that elderly patients diagnosed with T2DM suffered diminished global and regional cerebral vasoreactivity, which leads to a decline in their ability to perform cognitive tasks: "Inflammation may further impair cerebral vasoregulation, which consequently accelerates decline in executive function and daily activities performance in older people with T2DM" (3).

These new symptoms are only adding to the plethora of health issues already endured by diabetic patients, such as eye, kidney and cardiovascular diseases, depression, neuropathy, sexual dysfunction, dementia, and complications in pregnancy and amputation (1). While some of these can be relatively easy to treat, others are major factors in the death rates of those with the condition. For example, cardiovascular disease was implicated in the deaths of 44% of T1DM and 52% of T2DM patients worldwide (4). In addition, it was reported that the number of diabetes-related amputations in the period 2011-2014 totalled 21,125 – equating to 135 per week, ranging from toe to foot or part-leg amputations (1).

The financial burden is considerable, too. Figures from 2014 indicate that the cost for diabetes, globally, was 11% of the total healthcare spend around the world. As with many other health conditions, the countries with the least money available for the effective diagnosis and management of diabetes are dealing with the highest levels of incidence – a situation that clearly needs addressing (5).

To add to the issue, researchers at Imperial College London have now discovered a third type of diabetes, inherited via recessive-genes (6). This new form of the disease is caused by the patient inheriting two copies of a harmful gene, which then prevents the production of the protein, carboxypeptidase-E, that helps control appetite regulation and insulin generation.

In looking for solutions, reliable, transportable and reusable diagnostic methods need to be adopted, and more effective monitoring and delivery systems developed. There is a lot of promising research in the pipeline, and the emerging field of nanotechnology could provide some of the answers.

Nanotech Response

Current diagnostic and treatment processes are essentially too expensive and difficult to administer, especially for the developing world. The way most patients are diagnosed, and a distinction between T1DM and T2DM established, requires a complicated radioimmunoassay (RIA) blood test. This is slow, labour intensive, expensive, potentially harmful to human health due to the radioactive element involved, and only available in sophisticated healthcare settings (7).

Obviously, this presents an immediately limiting cost factor for those countries with low to medium economic development. State-of-the-art medical facilities, with adequately trained staff, may not be a realistic prospect, meaning many people go undiagnosed.

The nanotech response from Dr Brian Feldman at Stanford University Medical School was to create an inexpensive, portable, microchip-based test that is capable of detecting between T1DM and T2DM (8). Making the distinction between the two forms of the disease is becoming ever-more relevant, as the conventional view that T1DM mainly affects children and T2DM is an adult condition no longer holds true.

This test, described as "a plasmonic gold chip for near-infrared fluorescence-enhanced detection of islet cell-targeting autoantibodies", has succeeded where others have failed due to its ability to chemically preserve the structure of the antigens.

As well as accurately detecting T1DM or T2DM, the test offers the following benefits (9):

- Capable of checking for all four of the known auto-antibody markers for T1DM – unlike RIA, which can only test for one at a time
- Economical with blood: only a single drop is needed, whereas RIA requires millilitres at least
- The test can be completed quickly in 1 to 1.5 hours: speedy treatment can be vital for T1DM, as research has shown that delay can lead to severe illness or death
- Simple to use, requiring fluidics that can be automated, if need be

Monitoring and Management

This nano-based technology could revolutionise the diagnosis of the disease, but two later obstacles must also be addressed – monitoring and management.

Traditionally, monitoring has taken the form of a pin-prick blood test for measuring glucose levels. There are some obvious drawbacks with this approach, the major one being pain. Pin-pricks can become sore very quickly, especially when multiple tests are required daily to find the correct levels of insulin. Another hurdle is the fact that this test cannot be conducted when the patient is sleeping, but the significant disruption to sleep patterns required to ensure accurate monitoring can cause health issues such as depression. However, the most limiting factor is the test's inability to detect dangerous and sudden spikes and troughs in blood glucose (10,11).

Addressing this, nanotechnology offers three promising new ways to remove the daily, painful burden of pin-prick blood testing:

Breathalyser
Research into non-invasive tests which detect acetone in the breath – commonly believed to be an accurate marker of glucose levels in the blood – are in full swing. A breathalyser has been developed by Western New England University that utilises a one-use test strip coated with a nanometer-thick layer, made up of two polymers that are reactive only to acetone. The data is gathered and fed back to the patient quickly and easily (9). However, this method does not address the issue of testing when the patient is sleeping, the detection of spike and troughs, or the need for the regular purchase of testing strips.

Nano-Tattoo
Another method being developed is a glucose monitoring nano-tattoo, developed by Heather Clark at Northeastern University's Bouve College of Health Sciences in Boston. This device uses invisible nanoparticle based ink to implant 120 bio-compatible nano-metre-sized particles that react to the presence of glucose in the blood by fluorescing into the upper epidermis, which is less deep: this method is not as painful as normal tattoos. When ultraviolet light is passed over the nano-tattoo, the particles fluoresce; the brighter the shine, the greater the concentration of biomarkers in the blood (12).

While this is definitely a step forward, the issue is access to the technology and having trained staff to use it. In countries of low to middle economic status, this kind of economic investment may be beyond their reach.

Urine Testing Strips
Yet another emerging technology creates sensors using laser-light to organise metal nanoparticles into alternating layers of thin gel films that can detect glucose levels in urine. When the concentrations are high, the sensor changes colour, accurately determining the levels of glucose present in the body. Sample comparison can be done either visually or by the use of an image via a smartphone application (13).

These nano-based strips are particularly interesting because they can be produced at a fraction of the cost of most other commercially available testing strips. They can be reused too – up to 400 times – and, with a manufacturing cost of only 20p, the benefits of this technology for the developing world are clear. However, this kind of testing still does not address the issues of monitoring when asleep, and the spikes and troughs in levels.

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Insulin Delivery Methods

Once the glucose level has been accurately detected, a delivery method for the required dose of insulin is needed. Subcutaneous injection is the current method employed; but, as with pin-prick blood tests, the pain endured in this process is a likely factor in non-compliance with treatment protocols. This is understandable when patients may require frequent multi-dose injections every day. There have also been incidents of patients suffering from bouts of hypoglycaemia when using multiple insulin injections. Other issues, such as infection and irritation at the injection sites, remain unsolved with this method of delivery (14).

Nano-based systems offer the opportunity of delivery via the oral route, with specially engineered insulin nanoparticles. These are designed to encapsulate insulin within a core consisting of alginate and dextran sulfate nucleating around calcium and binding to poloxamer, stabilised by chitosan and subsequently coated with albumin. Using nanoparticle insulin allows for greater bioavailability due to the increased surface area; the multilayer construction lets the insulin reach the intestinal tract and permeate the intestinal wall, before being broken down by proteolytic degredation (15). While this can effectively remove the need for injections, issues still remain. For instance, it does not typically address concerns of cost-effectiveness or accessibility of the drug, or the need for the patient to be awake for the insulin to be administered.

Nano-Gel System

What is required is a monitoring and insulin delivery system that is cheap, easy-to-use and enables continuous monitoring and administration of accurate doses of insulin at any time of the night or day. Nanotechnology might just be able to deliver on two of those requirements in the short-term, with the third being a long-term goal.

A nanoparticle gel, developed by Dr Zheng Gu, uses insulin nanoparticles that are filled with a modified polysaccharide, dextran, which has been engineered with an enzyme that turns glucose into gluconic acid. As the gel allows glucose to easily transverse it, the enzymatic action produces a localised acidic environment, which degrades the dextran coating and releases the insulin encapsulated inside (11).

Testing is only at the animal experimental stage, but results so far are very promising. In laboratory tests with T1DM, the gel successfully regulated blood glucose levels for 10 days. If researchers are able to develop this technology for effective use in humans, it would be a major leap forward in the daily management of the diabetes. It essentially frees patients from the routine of pin-prick tests, and subsequent injections of insulin – reducing disruption to their everyday lives. Furthermore, being a simple injection, it should not require specially trained staff to administer, making it more accessible for poorer communities.

The only question remaining is how much it will cost. At this stage, it is too early to tell. But, even if the expense is large to begin with, the continual and increased use of nanotechnology will inevitably bring down the cost, enabling the effective management of diabetes for vast numbers of people.

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