Research may find route to repairing the sick pancreas

Reducing pill: Metformin cuts the body's glucose production Alamy

Drugs Although insulin is still the primary tool to control blood sugar, new treatments may delay complications, says *Alan Rappeport*

Diabetes is approaching epidemic proportions in the US, afflicting nearly a tenth of the population at a cost of billions of dollars per year, but growing awareness has been a boon for new research.

Diabetes is an excess of blood sugar, that comes about either because the body does not produce insulin, type 1; or because the body does not respond to the insulin that is produced, type 2.

Researchers and drug companies are investing heavily in developing new treatments for both type 1 and type 2 diabetes, in the hope of slowing the disease's progression and delaying its debilitating complications.

Insulin, which reduces blood sugar levels, has been a backbone of treatment for both types of diabetes since Canadian researchers first discovered it in the pancreas in the 1920s.

The synthesised hormone is still central to treatment of type 1, but scientists are working on versions more responsive to sugar intake that can be administered less frequently.

Type 2 diabetes has been on the rise in the US as obesity has become a growing problem. Excess body weight and lack of exercise reduce the body's ability to produce insulin.

Novo Nordisk, the Danish drug company, is seeking regulatory approval for a long-acting insulin, which is intended to be effective for 24 hours, rather than the usual 12-hour half-life.

The company is awaiting a final approval from the US Food and Drug Administration but, if given the go-ahead, it is expected to be a blockbuster because of demand for an effective, long-acting insulin treatment.

"You can view insulin treatments as a form of hormone replacement treatment – a physician is creating a drug that the body cannot produce in a sufficient amount," says Alan Moses, chief medical officer at Novo Nordisk.

Generally, for patients with type 2 diabetes, doctors first prescribe lifestyle modifications such as diet and exercise to help reduce blood sugar levels, which spike after intake of carbohydrates or sugary foods. Secondary treatments include medications such as metformin or glyburide.

Metformin works by decreasing the amount of glucose the body produces and increasing its response to the insulin made by the pancreas, while glyburide boosts insulin production in the pancreas.

Drug companies are also studying the potential of medicines such as dapagliflozin, which lowers glucose levels by causing sugar to be excreted through urine. However, concerns exist about possible side-effects, such as bladder cancer.

Dr Moses says researchers are studying the relationship between obesity and diabetes, particularly looking at obese people who do not develop the disease to see what genetic characteristics they may have that protect them from its onset.

Because of the link between obesity and diabetes, doctors have been encouraged by the recent approval of Qsymia, a new diet drug that could be helpful for diabetics or pre-diabetics attempting to control their weight.

For patients with type 1 diabetes, insulin remains the primary treatment, because the pancreas is unable to produce it on its own.

However, Denise Faustman, director of the Immunobiology Laboratory at the Massachusetts General Hospital and an associate professor at Harvard, is working on a drug that could potentially reverse type 1 diabetes.

She is testing a generic vaccine that was used to prevent tuberculosis and has been shown in early trials to restore insulin production in type 1 diabetics by killing the cells that destroy the pancreas and increasing regulatory "T" cell levels.

"The goal is to get rid of bad white blood cells and see if the pancreas can kick in on its own accord," says Dr Faustman.

Diabetes experts lament that many of the treatments for the disease have negative side-effects such as weight gain – which can be counterproductive – or heart and liver problems.

In spite of those concerns, studies by the US Centers for Disease Control found this year that the incidence of heart disease, strokes and lower limb amputations related to diabetes have all declined in recent years as treatments for diabetes and its common side effects have improved.

Ann Albright, director of CDC's Division of Diabetes Translation, says: "Taking care of your heart through healthy lifestyle choices is making a difference, but Americans continue to die from a disease that can be prevented. Although the cardiovascular disease death rate for people with diabetes has dropped, it is still twice as high as for adults without diabetes."

Post-marketing trials Debate simmers on usefulness of research after approval has been granted

It used to be that when a regulator requested more studies after initially approving an experimental drug, companies were reluctant to comply. But when it comes to new types of insulin, some seem all too keen to go far beyond what is required.

In an article in the British Medical Journal over the summer, Edwin Gale, emeritus professor of diabetic medicine at the University of Bristol, identified nearly 400,000 people who had been recruited for "post-marketing" trials of insulin analogues around the world in recent years. "The scientific value of such data might be doubtful, but the commercial rationale is good," he wrote.

Most clinical trials take place before approval, designed to test safety and efficacy. But the trend today among regulators is to demand ever more "Phase 4" testing of medicines, and sometimes even to grant only a "conditional approval" with a requirement for subsequent data after launch to determine whether it should stay on the market.

When conducted well, such research can provide valuable additional information on safety and efficacy that extends far beyond the data derived from the small numbers of carefully selected patients in the idealised conditions of short-term closely-monitored trials.

Yet Prof Gale argues that the post-marketing "observational" trials he examined were of limited value, with no "control arm" of cheaper insulins against which to compare the costlier new products, and a "deficit of data" collected over relatively short periods using unnecessarily large numbers of diabetics, notably in developing countries.

What they did provide was a way for the companies concerned to potentially influence recommendations of doctors (who are paid a fee) and the treatments of patients, with the potential that those introduced to the products studied remained on them once the research came to an end.

Philip Home, professor of diabetes medicine at Newcastle University and head of the global advisory board for A1chieve, one such study in nearly 67,000 patients and funded by Novo Nordisk of Denmark, a diabetes specialist, defends the research.

"The findings were very useful," he says. "We found very good improvements in blood glucose control could be achieved everywhere. The quality of data in observational studies is undoubtedly below that in randomised clinical trials. It would be a very odd world if on occasion it didn't happen that a prescriber prescribed an inappropriate insulin.

"The world is not perfect. But we do have to do studies to decide whether agents are effective in different environments."

Jesper Høiland, Novo Nordisk's head of international operations, argues that the data were useful and that the study was approved by ethics committees in every country where it was conducted.

"It's interesting that white academics can sit in Europe and decide what's right or wrong for Brazil," he says. "Does the western world know much better?"

Nevertheless, some European politicians are now calling for tougher rules akin to US legislation designed to avoid so-called "seeding studies" viewed as linked more to commerce than science.

Post-marketing research may be on the rise, but it will also come under much more scrutiny ahead.

Andrew Jack

Testing times in race to identify sufferers

Diagnostics

The technology is improving but misconceptions are the big problem, says *Denise Roland*

Diagnosing a disease before serious symptoms become evident may sound a tall order. But health leaders are being asked to do just that, in a call to action from the International Diabetes Federation that says for every diabetic aware of their condition, another is undiagnosed.

Type two diabetes goes undetected for an average of 10 years in the UK. The disease's insidious progression means one or more of its serious complications – such as sight loss, heart disease and kidney disease – has already developed by the time of diagnosis.

Diabetes of all types is indicated by high blood sugar, a sign that the digestive hormone insulin is not working effectively.

But defining diabetes is not straightforward. Blood sugar levels vary on a sliding scale, leaving experts with the task of setting the cut-off point for diagnosis.

They face the challenge of including all those whose blood sugar is high enough to cause harm while not casting the net so wide that people suffer the stress and social stigma of a diagnosis when the benefits of treatment are not clear.

The World Health Organisation's blood sugar criteria are widely accepted, but no single test successfully identifies all cases, nor do any completely avoid false positives. Doctors minimise the risk of misdiagnosis by repeating tests or using two different methods.

The cheapest technique is measuring blood sugar after an eight-hour fast, but this approach alone is thought to miss around 30 per cent of people with diabetes.

An alternative is reading blood sugar two hours after a fixed intake of glucose. This may pick up cases of diabetes missed by the fasting test, but is less popular due to its higher cost and heavy time demands.

These two techniques were the standard approach for decades, but recently a newly approved method has become the procedure of choice. The HbA1c test, which uses the presence of an unusual form of the blood protein haemoglobin as an indicator of blood sugar levels, requires no preparation from patients, and allows doctors to test opportunistically.

Simon O'Neill, director of care, information and advocacy at charity Diabetes UK says: "Although HbA1c is not significantly better at diagnosing diabetes than the traditional blood tests, it is hugely more convenient, so the hope is that it will identify more cases because more people will be willing to be tested."

The HbA1c test's widespread adoption in the developed world cannot be emulated in many developing nations, however, due to its higher costs and unreliability in patients with conditions including malaria.

But misconceptions about diabetes, rather than the shortcomings of the tests, are largely the reason for such a high rate of underdiagnosis. A relaxed attitude towards the disease, even from within the medical profession, leaves people untested and unaware of their serious condition.

Mr O'Neill says: "There's a general belief about type two diabetes that it's a milder form than type one, fixed by simply not having sugar in your tea."

The challenge, he says, is both getting people at risk to approach a doctor, and convincing physicians that it is worth testing patients.

The potential to prevent millions of cases of diabetes when one in every 10 adults worldwide is predicted to have the disease by 2030 provides the drive for screening programmes such as the NHS Health Check initiative, which aims to identify all those at risk of lifestyle diseases.

And while the execution of this programme has been inconsistent, global discrepancies for diagnosis are starker still.

Eighty per cent of cases occur in low and middle-income countries, thanks to increasingly western lifestyles and a greater genetic propensity for the condition among some ethnicities.

Deaths due to diabetes compare to numbers killed by Aids, malaria and tuberculosis combined

While around a third of all diabetics in high-income countries are undiagnosed, this proportion reaches 90 per cent in parts of sub-Saharan Africa.

Jonathan Shaw, a member of the IDF's Diabetes Atlas Committee says: "For decades the focus has been on infectious disease, and health systems are set up for this purpose.

"Tackling lifestyle diseases like diabetes requires a change of structure towards proactive identification and long-term care."

Large-scale screening is unfeasible for most of the developing world, not least because of lack of capacity to treat all identified cases.

Nonetheless, efforts in countries such as Cameroon – where traditional healers were trained to identify people at risk from diabetes and refer them to clinics for testing – have shown how limited resources can be stretched further in the quest to detect the disease.

But with the yearly number of deaths due to diabetes comparable to the numbers killed as a result of Aids, malaria and tuberculosis combined, a globally co-ordinated approach to find, and inform, the undiagnosed 50 per cent will be needed if world leaders are to meet their ambitious pledge to cut premature deaths from lifestyle diseases by a quarter by 2025.

Apps hold promise to improve care and cut costs

Remote monitoring

The ubiquity of mobile phones can be used for health, says *Sarah Murray*

For diabetes sufferers, mobile apps and electronic monitoring devices can help control the disease and manage lifestyle changes that create improvements in their condition. But while mobile devices are ubiquitous, the question is how to get more people to use them to manage diabetes and prevent pre-diabetes from developing into the full-blown disease.

The technology available for monitoring blood sugar levels has moved far ahead from the days when the system was to use finger sticks, a test strip, a pad of paper and a pen.

"The tools are much better," says Harry Greenspun, senior adviser for healthcare transformation and technology at the Deloitte Centre for Health Solutions. "The technology has improved progressively."

Diabetes monitoring technology is increasingly available via mobile phones. For example, the iBGStar connects to iPhones and iPods. Designed and developed by AgaMatrix, a diabetes product maker, and commercialised by Sanofi, a healthcare company, the device displays results, analyses glucose patterns and offers graphs and statistics to help users track their disease.

The benefit of combining monitoring with mobile phones and apps is that it uses familiar and increasingly ubiquitous technology. In the US, 85 per cent of adults now have a cell phone, of which half are smart phones, according to new data from the Pew Research Centre's Internet & American Life Project.

Susannah Fox, an associate director of the project, says: "Those smart phones are capable of going online and running sophisticated apps. Which is just the sort of thing people are developing in the hope that patients will use them."

Devices also allow data to be transferred to healthcare professionals. Wireless-enabled glucose meters automatically upload blood glucose levels to a database that can be accessed online.

Even so, the new research from the Pew Research Centre suggests technology is not playing a huge role in helping people track their health. While 60 per cent of those polled said they kept track of their weight, diet and exercise, few were using technology to do so.

When asked about the most important indicator they tracked, half said they did it in their heads, a third said they used paper and a smaller group used software, a website, an app or a medical device such as a glucose meter.

Mobile monitor: the iBGStar connected to an iPhone

Ms Fox says: "Technology still plays only a small supporting role when it comes to self-tracking health indicators."

This could change as more apps and devices come on to the market, and as diabetes sufferers are increasingly individuals for whom technology is an integral part of daily life. The challenge then will be what to do with patient-reported information. As the volume of data reaching healthcare professionals increases, so will the room for error.

"For any test, there are 50 ways you can have erroneous data," says Mr Greenspun. "It can be done improperly, it can be done at the wrong time or it can be miscalibrated. And there are examples of people having other people take their tests for them."

Nevertheless, if doctors can manage their patients' conditions remotely, substantial cost savings can be made.

Shifts in the economics of healthcare delivery will support these savings, since payments to providers increasingly reward improved patient health, rather than numbers of hospital visits or medical interventions.

For policy makers, technology and remote monitoring offers broader benefits. With greater volumes of patient-reported data gathered, analytics tools could be used on diabetes levels across national populations, allowing for more informed policy decisions.

Technology can also support individuals in making the kinds of lifestyle changes needed to improve their condition.

In a 2011 trial, patients with type 2 received coaching via a mobile app developed by WellDoc, a technology-focused healthcare provider. Meanwhile, patients and their primary care providers had access to web portals.

The trial – the Mobile Diabetes Intervention Study, conducted by the University of Maryland School of Medicine – found the tech-enabled group lowered average glycated haemoglobin (a marker for blood glucose levels) by almost 2 per cent – more than double the fall in the control group.

Of course, apps can only facilitate lifestyle changes, not impose them on the unwilling. Mr Greenspun says: "Having a fitness app on a phone does not make you an athlete. A fundamental question is whether the added capability mobile gives you translates into improved outcomes – and the jury is still out."

Even so, given the ubiquity of mobile phones, Ms Fox believes technology holds great promise. She points out the data from Pew Research Centre show high numbers of people are tracking health indicators such as diet and exercise – but mostly offline.

"The question is what's going to tempt them to use the devices they use for their social life, communications and shopping for health," she says.

"It's currently only a small number of people – so there's big potential."

On FT.com »

Complications

Foot ulcers, eye problems and worse

A look at progress on treatments for side-effects

Feet first

Prospects for a Cuban breakthrough

The pros and cons of a revolutionary foot ulcer drug