Emerging technologies for diabetes

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Abstract
The lives of people with diabetes may be revolutionised by an explosion of new product developments and launches. These emerging technologies include new continuous blood glucose monitoring, innovative insulin delivery techniques and novel data and decision support mechanisms that could improve HbA1c levels. In addition, to potentially decreasing the time spent either in hypoglycaemia or hyperglycaemia, these new technologies also have the potential to improve a patient's quality of life as well as to reduce the burden of self-management.
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Key words
technology; insulin; biosimilars; biochaperoned peptides; continuous glucose monitoring; data support; decision support

Introduction
Since the discovery of insulin in the early 1920s, many in the research community have pursued novel ways to deliver insulin in order to improve effective self-management and quality of life and to circumvent other issues like injection pain, needle phobia and lipodystrophy. These have involved developments in insulin pump delivery as well as a number of alternative delivery routes including transdermal, oral, buccal, ocular and rectal.

The Diabetes Control and Complications Trial demonstrated the importance of intensive insulin therapy in type 1 diabetes in the prevention of the micro- and macrovascular complications.[1] However, the increased risk of hypoglycaemia due to this intensive insulin therapy has highlighted the need to partner good glycaemic control with minimal hypoglycaemia. The goals, therefore, are to deliver insulin in a way that mimics endogenous insulin secretion by the pancreas in a method that is minimally invasive, is safe and accurate, and that reduces the burden of daily subcutaneous (SC) insulin injections.

This review focuses on some of these developments and explores not just the current or anticipated products on the market but also the efforts being made in the data and decision support tools available to patients.

Continuous and real-time continuous glucose monitoring
Continuous glucose monitoring (CGM) has been a welcome addition to the diabetes armamentarium in recent years. The current National Institute for Health and Care Excellence (NICE) guidelines state that there is insufficient evidence to support the widespread use of CGM in adults because it is not cost-effective.[2] The guidelines conclude that:

'In adults with type 1 diabetes who have high HbA1c values, there still may be some value in using continuous glucose monitoring systems, and further research is needed to determine whether newer technologies would prove to be cost-effective, particularly in this group.'

Real-time CGM (RT-CGM) should, in certain circumstances, be considered, however. These include in people with:
- More than one episode per year of severe hypoglycaemia with no obviously preventable precipitating cause.
- Complete loss of awareness of hypoglycaemia.
- Frequent (more than two episodes a week) asymptomatic hypoglycaemia that is causing problems with daily activities.
- Extreme fear of hypoglycaemia.
- Hyperglycaemia (HbA1c level of 75mmol/mol [9%] or higher) that persists despite testing at least 10 times a day.

In addition, adults with type 1 diabetes using CGM should:
- Be willing to commit to using it at least 70% of the time and to calibrate it as needed.
- Be using either a multiple daily injection insulin regimen or continuous SC insulin infusion.
- Be cared for by a health care team with expertise in providing CGM

use as part of strategies to optimise that person's HbA1c levels and reduce the frequency of hypoglycaemic episodes.

For children with type 1 diabetes, NICE's recommendations are that CGM with alarms should be offered to those with frequent severe hypoglycaemia, impaired awareness of hypoglycaemia associated with adverse consequences (for example, seizures or anxiety), or inability to recognise, or communicate about, symptoms of hypoglycaemia (for example, because of cognitive or neurological disabilities).[3]

Although not widely implemented in the UK, the technology is becoming more refined in an effort to ensure that the devices become more attractive. Their current drawback is undoubtedly that they measure glucose levels in the interstitial fluid rather than in the blood. There is a lag phase between blood glucose levels and the interstitial glucose levels meaning that, when levels are rising or falling rapidly, CGM accuracy may not be optimal.[4]

Recent research has indicated that CGM may result in better glycaemic control compared with conventional treatment. In the GOLD randomised clinical trial of 161 adults with type 1 diabetes, the mean difference in HbA1c between the two groups was 0.43% in favour of those on CGM (mean HbA1c 7.92%) and those on conventional treatment (mean HbA1c 8.35%).[5] In a second study, the DIAMOND randomised clinical trial, the difference was slightly greater at 0.6%. A total of 158 adults with type 1 diabetes were tested over a 24-week period. Those randomised to the CGM arm showed a significantly greater decrease in HbA1c level compared to those on conventional treatment (-1.0% vs -0.4%).[6]

The field is moving rapidly and a number of new devices are currently either newly on the market or will be available shortly including devices with extended wear (10 to 14 days) with just one fingerstick calibration per day and others with a one-button insertion system for the sensor. These new systems, along with others, are being designed with the user in mind. They will improve on overall reliability and be more convenient.[7] Additionally, companies are striving to minimise the interference patterns observed in the presence of uric acid, paracetamol and vitamin C to improve their overall accuracy.[8–10]

Flash glucose monitoring

Flash glucose monitoring (flash GM) is a much newer technology where the patient has a small sensor implanted into the upper arm. This automatically measures and continuously stores glucose readings throughout the day. Using a separate touchscreen reader, people using this technology swipe the reader close to the sensor which then transmits two different sets of data – an instantaneous glucose reading and an 8-hour trend line.[11]

This potentially powerful addition to the CGM field has several advantages. Users will not need to fingerstick test unless driving and the trendline allows action to be taken earlier to prevent against high or low blood glucose levels. However, because the device does not have hypo- or hyperglycaemia alarms, it does not help the user to recognise a hypo.[12]

Other insulins

In addition to the existing insulins that are currently available, there are several strands of research looking at newer forms with altered pharmacodynamics or alternative delivery routes.

Glucose-responsive insulins

Glucose responsive insulins – or smart insulins – are being designed to allow active insulin to be released into the bloodstream as and when it is needed. By developing tuneable pharmacodynamics, this class of insulin derivatives would be long-lasting and demonstrate glucose-mediated activity so that the higher the blood sugar, the more insulin is released and *vice versa*.

Several groups have published on preparations of this kind of self-regulated insulin therapy using glycosylated insulins in combination with glucose-binding lectins. The most commonly used member of this group of natural carbohydrate-binding proteins has been concanavalin A.[13–15] However, these forms of modified insulin were administered in a capsule or device that was designed to release the glycosylated, lectin-bound insulin in response to increasing systemic glucose levels.

This technology has moved on and Merck's MK-2640 smart insulin, a glucose-responsive insulin, is currently in clinical trial.[16] Other companies are interested in similar technology including Lilly who has recently acquired technology from Glycostasis, a start-up company at the Pacific Northwest Diabetes Research Institute, with early-stage glucose-responsive insulin drug development.[17]

Biochaperoned peptides

Biochaperoned peptides are designed to be complexed with other proteins that can protect them from enzymatic degradation and enhance their actions in the body.[18] This patented technology also allows the complexed protein to be soluble at physiological pH levels and to be stable during storage. The aim of biochaperoned insulin is to modify the kinetics of insulin release into the bloodstream.

BioChaperone Lispro is an ultra-rapid formulation of insulin lispro. In 2015, Adocia and Lilly reported positive results from their phase 1b trial on the post-meal effect of ultra-rapid BioChaperone Lispro in patients with type 1 diabetes. In the crossover, randomised, double-blind meal study, 38 people with type 1 diabetes received a 0.2 U/kg dose of either BioChaperone Lispro or Humalog prior to a standardised meal.[19] BioChaperone Lispro was associated with a 61% reduction in the post-prandial glucose excursion over the first 2 hours compared to Humalog with comparable numbers of episodes of hypoglycaemia being reported during the study.

Despite these promising results, Lilly has terminated the partnership with Adocia who own the intellectual property rights on the BioChaperone technology.[20] The company has announced that, while still planning to launch phase 3 trials, it remains confident of finding a new partner.

Buccal insulin

Although plagued by a variable success rate, research into the development of oral insulin has been one of continuous innovation and inventiveness. In 1993, the late Professor Michael Berger published a review on the history of oral insulin noting:

'On August 7, 1922, Dr Joslin started SC insulin therapy on a 42-year-old nurse. Between October 25 and October 31, 1922, he conducted a formal study on the efficacy of an oral insulin preparation which had been prepared for him by the Eli Lilly Company. Despite a stepwise increase in the dosage of orally administered insulin, the metabolism of this nurse re-deteriorated, and after 1 week Dr Joslin discontinued the experiment. Similar results were obtained with another patient in early 1923.'[21]

Despite these early failures, oral insulin remains a very attractive route for the drug's administration, particularly for patients. The possibility of this development leading to improved compliance rates and thus improved metabolic control and perhaps an improved quality of life is appealing. However, there is an additional benefit to this administration route. If insulin was delivered directly to the gut in a form that was not rapidly broken down by the acids in the stomach or by proteolytic enzymes into smaller peptides with no biological activity, the peptide could be absorbed and transferred directly to the liver. This would allow patients to control their hepatic glucose production to the same extent as that in people without diabetes. Therefore, the outcome for oral insulin is more physiologically effective and it would also be associated with a reduction in peripheral hyperinsulinaemia as seen with the SC administration of insulin.[22]

Generex has developed an insulin formulation for the treatment of type 1 and type 2 diabetes which relies on delivery of insulin not to the stomach but directly via the mouth.[23] This relies on the company's patented RapidMist technology which administers insulin directly into the mouth as a metered-dose spray.[24] The buccal mucosa allows for rapid adsorption. Oral-Lyn, the company's oral formulation of insulin, has been trialled successfully and, launched in Ecuador in December 2005, it is now available in a number of other countries including the United Arab Emirates and India.[25]

Inhaled insulin

Thanks to the very high surface areas of the lungs and the potentially very rapid absorption of molecules like insulin via the highly vascularised alveoli, inhaled insulin has been the subject of much research over the years. Indeed, insulin delivery via the lungs was the first alternative route of administration.[26,27] In 2001, Skyler *et al.* published a proof-of-concept report on the effects of pre-prandial inhaled insulin in 73 patients with type 1 diabetes.[28] The results demonstrated that inhaled insulin was well tolerated having no effect on pulmonary function and that there was no change in the HbA_{1c} levels between the groups. Over a 12-week period, there were also no significant differences between the groups in fasting and post-prandial glucose concentrations or in the occurrence and severity of hypoglycaemia.

Despite this, the very high profile withdrawal of Pfizer's Exubera, an inhaled insulin product, within a year of launch has set this field back. The company cited lower than expected sales. Indeed, worldwide sales amounted to just $12m. A number of reasons were quoted including cost, restrictive labelling and national guidance, and confusing dose equivalence.[29] Side effects were also an issue, including a persistent cough. In addition, patients on the Exubera trial did develop lung cancer at a greater rate than those in the comparison arm and the long-term risk of cancer formation remained an issue.[30,31]

Mannkind has launched Afrezza, an inhaled insulin product marketed as a rapid-acting, mealtime insulin for both type 1 and type 2 diabetes. It is designed to work quickly, reaching its maximum effect in around 50 minutes but staying active for up to 3 hours.[32] Acute bronchospasms are listed as a side effect of the drug and it is contraindicated in patients with chronic lung disease such as chronic obstructive pulmonary disease and asthma. In clinical trials of Afrezza, there were two reported cases of lung cancer but no cases reported in the comparator arm of the study. After the trial had completed, two additional cases of squamous cell lung cancer were reported in non-smokers who had been taking Afrezza.[33]

Afrezza's technosphere insulin technology means that the median diameter of the microparticles inhaled are 2–2.5µm making it suitable for deposition in distal lungs.[34] According to research, only about 60% of the inhaled insulin dose reaches the lungs, with the other 40% being swallowed and entering the gastrointestinal tract.[34]

Its popularity remains in question, however. In January 2016, Sanofi terminated its $925 million marketing agreement with Mannkind citing poorer than expected sales. In the first nine months of 2015 following its launch, Sanofi recorded sales of just $5 million.[35] Since their active marketing stopped, Afrezza prescriptions have tumbled.[36]

Biosimilars

Biosimilars are essentially copies of drugs or biopharmaceuticals that are no longer under patent protection. From a cost point of view, these are often cheaper alternatives and generic versions are commonly used by health care systems including the NHS. However, with insulin, it is much more difficult to make an exact copy. As a biological drug, there may be small alterations in the manufacturing process – for example, that change the way that it acts. Because of the complexities of the insulin molecule and the obvious implications that manufacturing differences could have on the drug's safety and efficacy profiles, regulatory bodies in Europe and America have published a raft of guidelines on biosimilars, including insulin biosimilars.[37–39]

In a market that is perhaps overdue biosimilars, only Lilly's biosimilar glargine insulin, Abasaglar, is currently available.[40] A new insulin lispro biosimilar to Lilly's Humalog is in phase 3 clinical trials. The interim results, presented at the

76th Scientific Sessions of the American Diabetes Association in 2016, demonstrated that this biosimilar from Sanofi is as effective and well-tolerated as insulin lispro in patients with type 1 diabetes.[41]

Data and decision support

While the diabetes community waits for different insulins to come to market, many are looking towards data and decision support for answers. Diabetes self-management is data driven. Connected health enables collation of data on glucose insulin, macronutrients, activity and health events. Using mobile telephone technology, a number of new apps are available which help with education, lifestyle coaching and behaviour change.

The Insulia app is now both US Food and Drug Administration (FDA)- and European Union-approved.[42] It provides patients with insulin dose recommendations and educational coaching messages based on blood glucose values and other diabetes-related data.

Another innovation, known as Glucommander, is a therapy management cloud-based software solution that calculates individualised insulin dose recommendations. Its use has been FDA cleared and is associated with impressive improvements in glucose control and HbA_{1c} measurements.[43,44]

Challenges of regulation, monitoring and implementation remain for apps and other software solutions, so people with insulin-treated diabetes are also taking matters into their own hands. The hashtag #wearenotwaiting is used by an international group of people developing their own platforms and apps in order to provide solutions to the challenges of type 1 diabetes self-management. Championing open-access data and data sharing, solutions are being designed to help people to utilise technology and devices more effectively, including through data sharing and artificial pancreas configurations using existing available devices.

The Nightscout project is an example of this.[45] It was developed by the parents of children with type 1 diabetes and is maintained and supported by volunteers. It is an open-source platform that allows real-time access to CGM data via personal website, smartwatch viewers, or apps and widgets available for smartphones.

Key points

- Continuous glucose monitoring is now a mature technology with an evidence base and support from NICE for implementation into routine clinical practice for adults and children with type 1 diabetes
- Novel insulins with faster actions, and potentially delivered by other routes, will become available in the near future, enabling greater flexibility and choice to optimise glucose
- The use of data other than glucose to support self-management and diabetes decision making, and the integration with smartphone and consumer technologies, will support people with diabetes on a daily basis

Conclusion

It is clear that, with the number of new products and technologies that are either now available or that are in development, the number of options available to people with diabetes to manage their condition is becoming much wider. A wider range of insulins is in development which offers differing pharmacodynamics and administration routes. These may have significant advantages to pump users and in closed-loop systems too. Importantly, these technologies are benefitting from public involvement and from 'patient power' which will ultimately ensure that the new devices and systems come to market tailored much more effectively to need.

Declaration of interests

Dr Eleanor D Kennedy has no conflicts of interest to declare.

Professor Nick Oliver has received honoraria for speaking and advisory board participation from Roche Diabetes Care, Medtronic Diabetes, and Dexcom. He has received research funding from Roche Diabetes Care, and Dexcom.

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Tribute

John Wales

It is with sadness that we report that John Wales has died suddenly aged 79. As a senior, founding member of the *Practical Diabetes* Editorial Board, John's contribution to the journal's success was considerable. Through his characteristic personal perspective, derived from substantial clinical experience, John provided a common sense and pragmatic wisdom, that very much shaped the special philosophy of the journal as seen today. Of particular popularity, his 'Consult the Experts' series, involving a number of case histories, served as an invaluable educational guide to clinical problem solving for all of the multidisciplinary diabetes team.

For 30 years John Wales was Senior Lecturer in Medicine at the University of Leeds and Honorary Consultant Physician at the General Infirmary at Leeds. At various times he also held prestigious appointments abroad, including at the George Washington University School of Medicine, USA and at the United Arabs Emirates University, as the Foundation Professor and Chairman of the newly established School of Medicine. Latterly, as Visiting Consultant Diabetologist to the Beijing Chaoyang Diabetes Hospital, John was instrumental in making recommendations in China for a modern and more western provision of high-quality diabetes care.

Although this testimony is primarily written to express our enormous gratitude to John for all that he contributed to *Practical Diabetes* over many years, he will also be much remembered as the driving force behind the launch of the Association of British Clinical Diabetologists (ABCD). As the Association's Founding Chairman, John was of great inspiration to his peers, charismatic and with a determination to ensure that people with diabetes should expect to receive the highest standard of diabetes care from their professional advisors.

We were all captured by his challenges to do better, and will very much miss him, but he leaves a wonderful legacy for us to follow.

Professor Ken Shaw,
MA, MD, FRCP

The 'Consult the Experts' series, of which John Wales was Series Editor, is available to view on the *Practical Diabetes* website, url: www.practicaldiabetes.com/article/obituary-john-wales/.