Advances in the management of diabetes: new devices for type 1 diabetes

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ABSTRACT
Type 1 diabetes (T1D) is an autoimmune condition that affects a significant number of people worldwide, with higher prevalence in white European populations. The condition is responsible for a high burden of microvascular complications, especially when poorly controlled. The condition is also burdensome on the patient and has major psychosocial and occupational impacts. It requires lifelong frequent blood glucose monitoring and regular insulin injections. Important technological advances in the management of T1D have occurred in recent years. These include the advent of new glucose testing devices using interstitial glucose, and new insulin delivery devices. These technologies may improve quality of life, and glucose management in this condition. This review aims to outline the current advances in the management of T1D for the general physician, with a particular focus on new technologies.

INTRODUCTION
Type 1 diabetes (T1D) is a condition in which autoimmune pancreatic beta-cell destruction leads to absolute insulin deficiency.1 In 2017, it was estimated that 451 million people worldwide had diabetes, of whom around 10% have T1D.2

As the condition often occurs in childhood or young adulthood, the potential for complications due to chronic hyperglycaemia is high, including blindness, end-stage kidney disease, cardiovascular complications and foot disease.3-9 Patients with T1D also have a higher risk of other autoimmune conditions, including vitiligo, coeliac disease, pernicious anaemia, thyroid disease and Addison’s disease.1

Approximately 85% of cases of diabetes in people aged under 20 years is due to T1D.10 The disease is commoner among white European ethnic groups, especially in Northern Europe.11 Genetic factors appear important—the concordance rate for T1D in monozygotic twins is around 60%,12 and while T1D usually occurs in people without a family history of diabetes, there is a 1 in 20 lifetime risk of developing TID in individuals who have a first-degree relative with T1D (compared to 1 in 300 for the general population).13 Human leukocyte antigen (HLA) genes on chromosome 6 are shown to contribute to the development of T1D.14

There is also evidence of patterns in the seasonality of the diagnosis of T1D and the birth of individuals with T1D, with higher rates of T1D in children born in spring and lower rates in children born in autumn,15 and increased diagnosis in late autumn, winter and early spring.16 This has been suggested as evidence for an association with viral infections that might precipitate T1D.10 Viral respiratory tract infections in early life may lead to damage of beta-cells, autoimmunity and the development of T1D.17-19 This may be through molecular mimicry or bystander activation in genetically predisposed individuals.20 Systematic review suggests a strong link between enterovirus infection and T1D.21 Other viral aetiologies implicated include Epstein-Barr virus and cytomegalovirus.22 23 Early exposure to cow’s milk protein has been suggested as contributing to the aetiology of T1D,24 although the data are not consistent.25

DIAGNOSIS OF T1D
Most patients presenting with T1D will have osmotic symptoms and evidence of hyperglycaemia. At diagnosis, distinguishing between T1D and type 2 diabetes (T2D) is usually straightforward (table 1) but occasionally can be more difficult.26 Measurement of islet autoantibodies (glutamic acid decarboxylase, islet antigen 2, zinc transporter 8 ), may be helpful, as a significant positive titre suggests T1D. In addition, measurement of a non-fasting C peptide (with plasma glucose) may help, as the presence of high C peptide suggests a degree of pancreatic beta-cell function, which might suggest T2D.27 Distinguishing T1D from monogenic diabetes (also called maturity-onset diabetes in the young) can also be challenging. Presence of a very strong family history and lack of ketosis might be a reasonable reason to consider genetic tests for monogenic diabetes.28

GLYCAEMIC CONTROL IN T1D
The Diabetes Control and Complications Trial (DCCT) and The Epidemiology of Diabetes Interventions and Complications (EDIC) studies explored whether complications of TID could be

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<th>Table 1</th>
<th>Differences between type 1 and type 2 diabetes</th>
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<td>T1D</td>
<td>T2D</td>
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<tr>
<td>Ketoacidosis</td>
<td>Non-ketoacidosis</td>
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<tr>
<td>Insulin deficiency and absolute requirement for insulin</td>
<td>Variable degree of insulin resistance with insulin deficiency</td>
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<td>Acute onset</td>
<td>Insidious onset</td>
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<td>Non-obese</td>
<td>Often obesity associated</td>
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<td>Usually younger onset</td>
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<td>Often islet autoantibody positive (GAD)</td>
<td>Autoantibody negative</td>
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GAD, glutamic acid decarboxylase.
delayed. The DCCT study randomised 1441 people with T1D to intensive therapy (which aimed to get glycaemic levels as close as possible to the non-diabetic range) and conservative therapy (which aimed to keep participants asymptomatic). The EDIC study was an observational follow-up of the DCCT cohort.

The DCCT study showed a 35–76% decrease in microvascular complications of T1D in the intensive therapy group. The median haemoglobin A1c (HbA1c) in the intensive therapy group was 7% (53 mmol/mol) in comparison to 9% (75 mmol/mol) in the conservative treatment group. During the course of the EDIC study, differences in HbA1c disappeared between the two groups. Despite this, however, there was a durable effect on long-term complications in subjects in the intensive arm of the DCCT study. In both the DCCT and EDIC studies, intensive treatment resulted in long-term reductions in the risks of renal complications of diabetes, including microalbuminuria, macroalbuminuria, chronic kidney disease and cardiovascular disease.

These studies also suggested that intensive glucose treatment in T1D delayed the onset and progression of diabetic retinopathy and peripheral neuropathy. Those in the intensive arm of the study also had long-term delays in the development and progression of cardiovascular disease and atherosclerosis, including a lower incidence of stroke, myocardial infarction and myocardial death.

The main adverse effects of intensive treatment were hypoglycaemia and weight gain. Significantly more participants became overweight or obese in the intensive treatment arm. In addition, the frequency of severe hypoglycaemia was threefold higher in the intensive treatment group. There was no effect on quality of life (QoL) or cognitive function.

**MANAGEMENT OF T1D**

Multiple-dose insulin therapy is the mainstay of treatment for people with T1D. The most physiological method of insulin administration is the basal–bolus regimen, which involves prandial subcutaneous rapid-acting insulin injections given just before meals, and one or two times per day long-acting basal insulin injections given usually before bed and/or on waking. In this regimen, around 50% of the total daily dose of insulin is given as basal, with the remaining 50% as given as rapid-acting insulin divided into mealtime doses, although the actual dose may vary according to prevailing glucose levels and carbohydrate intake.

A crucial aspect to treatment of T1D is the use of structured diabetes education. These education programmes include aspects regarding diet, blood glucose monitoring, dose adjustments depending on prevailing glucose levels and carbohydrate intake (carb counting), rules on the management of acute illness (sick day rules), driving and occupation, pregnancy and family planning, long-term complications of diabetes and the importance of regular follow-up and monitoring. One widely used education programme with good evidence for improved glycaemic control is the Dose Adjustment for Normal Eating (DAFNE) programme, which is recommended for all people with T1D within 6–12 months of diagnosis. The programme is usually led by specialist diabetes nurses and dietitians, and is a prime example of multidisciplinary working.

T1D is associated with a high burden of distress, and the assistance of psychologists and psychiatrists is often beneficial in managing these aspects, especially in patients with possible eating disorders or recurrent hyperglycaemic emergencies.

Annual screening for microvascular and macrovascular complications is an important aspect in the management of people with T1D. All patients must have annual screening of the eyes (digital retinal screening), feet (for neuropathy and pulses) and kidneys (checking for elevated albumin creatinine ratio, or reducing estimated glomerular filtration rate). Timely management of early changes detected on screening can significantly reduce their progression.

In addition to this, the care should be individualised whenever it is possible—for example, giving appropriate support to patients with physical or mental disabilities, setting up individualised targets and care plans for different patients depending on their lifestyle and personal circumstances. Discussions with people with T1D should always be non-judgemental and aimed to support improved QoL and control of glucose and other factors. Extra support is required for women with T1D aiming to achieve pregnancy even before conception, as outcomes can be significantly improved with better glucose control preconception.

**NEW DEVICES FOR MANAGING T1D**

T1D is a lifelong condition associated with a poor QoL due to its high burden of care. Technological advances have the prospect of easing that burden for many patients.

**Glucose monitoring devices**

Self-monitoring of blood glucose (SMBG) is an integral part in the management of T1D. Since the development of the first glucometer in 1971, self-monitoring has been undertaken by obtaining finger-prick blood and using test strips inserted into a glucometer. In 1999, continuous glucose monitoring (CGM) devices were developed, which have been superior to the conventional SMBG devices in several ways. They provide frequent glucose monitoring, thus enabling more rapid treatment decisions. Their ability to alert the wearer to hypoglycaemia and hyperglycaemia leads to a reduction of acute diabetes-related complications.

How they work

CGM measures interstitial fluid glucose levels, which, whilst reflecting prevailing blood glucose levels, show a delay of 10–15 min against blood glucose levels, which may be important particularly in the setting of hypoglycaemia. CGM devices comprise a sensor inserted beneath the skin, and a transmitter that transmits the data from the sensor to the receiver (meter, mobile phone application or insulin pump device). There are three different types: real-time CGM in which the blood glucose level can be checked at any time via the receiver, retrospective CGM in which the data can be downloaded for retrospective analysis and Flash CGM in which the individual patient has to scan the sensor to get a reading.

Types of devices

The first CGM was released by Medtronic in 1999. A measure of accuracy of CGM is the mean absolute relative difference (MARD) between the actual blood glucose and the CGM reading. The first Medtronic CGM had a MARD of 19.7%, indicating that there could be a significant difference between the CGM reading and the prevailing actual blood glucose reading. In addition, users noted that there was some discomfort during the insertion and wearing of the device. Since then, however, the number of CGM devices has burgeoned, with much improved accuracy (MARD reduced to around 10%) and comfort.

The most widely used device currently in use is the flash glucose monitor, Freestyle Libre, developed in 2016 (figure 1).

It requires scanning of the sensor in order to obtain a reading, but it does actually measure glucose readings continuously. The MARD is 10%, and although there is currently no alarm system for
low glucose levels, it is the most affordable system available, is water resistant and each sensor lasts for 14 days. A recent meta-analysis of studies of flash glucose monitoring suggests a mean of 0.4% reduction in HbA1c in wearers compared to SMBG. 46

Newer sensors, such as the Dexcom G6, can last for about 10 days and do not require calibration with blood glucose levels (figure 2). The Medtronic Guardian Sensor 3 was released in 2017 and integrated in the Medtronic MiniMed 670G insulin pump as a part of first hybrid insulin delivery and glucose monitoring system (see later). It requires calibration every 12 hours and has approximately 9.1% MARD, and the sensor lasts for about 7 days. Medtronic Connect CGM was released in 2018. It uses Guardian Sensor 3 and can alert up to 60 min in advance of hypoglycaemic and hyperglycaemic events.

Evidence
Randomised controlled trials (RCTs) have shown that real-time CGM can improve glucose control as evidenced by HbA1c reduction, without increasing the risk of hypoglycaemia. 47 In the Multiple Daily Injections and Continuous Glucose Monitoring in Diabetes (DIAMOND) RCT, an improvement in diabetes-related QoL (distress related to hyperglycaemia, hypoglycaemic confidence) was seen. 48 In the Sensing with insulin pump therapy to control Hba1c(SWITCH) crossover study, CGM reduced HbA1c and time spent in hypoglycaemia. 49 Similarly, reduction of time spent in hypoglycaemia has been shown in a study which compared real-time flash glucose monitoring to traditional SMBG. 50 There is also evidence that the use of CGM in pregnant women with T1D can improve glucose control and reduce adverse neonatal outcomes. 51

Use of CGM in patients with T2D is limited. One study has suggested a greater reduction in HbA1c in patients with T2D using CGM compared SMBG. 50

Eligibility in the UK
According to National Institute for Health and Care Excellence (NICE) guidance, CGM can be offered to adults with T1D who are willing to use it at least 70% of the time and to calibrate it as necessary, and who have the following problems despite optimal use of multiple daily injections (MDI) and conventional SMBG: 37
1. More than one episode a year of severe hypoglycaemia without any obvious precipitating cause.
2. Complete loss of awareness of hypoglycaemia
3. Frequent (more than two episodes) of asymptomatic hypoglycaemia that is causing problems with daily activities.
4. Extreme fear of hypoglycaemia.
5. Hyperglycaemia (HbA1c more than 70 mmol/mol (9%)) despite SMBG testing more than 10 times a day.

The guidance also suggests continuing real-time CGM only if HbA1c can be sustained at, or below 53 mmol/mol (7%) and/or there is a fall in HbA1c of 27 mmol/mol (2.3%) or more.

Continuous subcutaneous insulin infusion
Continuous subcutaneous insulin infusion (CSII), also known as insulin pumps, was developed in 1963, and were worn as a large backpack. The first compact wearable pump was developed 10 years later, and insulin pump therapy began in earnest in the late 1970s. 51, 52 Technology has improved such that it is now an important and effective treatment option in adults and children with T1D.
The insulin pump contains an insulin reservoir which can store from 175 units to 300 units of rapid-acting insulin (such as insulin aspart (novorapid), insulin lispro (humalog)). There are three different forms of insulin pumps. In tethered pumps, the reservoir is attached to tubing with a needle or cannula at the other end to insert into the skin (eg, MiniMed 670G—figure 3). In patch pumps, the pump is directly attached to the skin and there is no risk of kinking or blocking of the tube (eg, Omnipod—figure 4). Finally, there is the implanted insulin pump, which is sited inside the body and delivers the insulin into the peritoneal cavity. This is rarely used currently, and refills of insulin currently can only be done in a hospital facility in Montpellier, France.

Insulin pumps deliver insulin as a ‘basal rate’ throughout the day, and specific rates of delivery can be set up for specific needs, depending on the activities of the individual. Some users prefer to have low basal rates at night-time in order to reduce the risk of hypoglycaemia. Importantly, the user still needs to manually administer boluses of insulin at times when eating, by programming the pump to give an extra dose of insulin as per the individual’s requirements.

**Types of insulin pumps**

There are a growing number of insulin pump devices and companies. Most pumps can directly link to CGM systems, and when linked with a CGM, are known as sensor-augmented pump therapy (SAPT). Some insulin pumps have an advanced feature that can switch off insulin delivery when blood glucose level is low (low glucose suspend), and indeed some pumps linked with CGM can predict the possibility of hypoglycaemia earlier and cut off the insulin delivery reducing the occurrence of hypoglycaemia significantly.53

**Evidence**

Many studies have been carried out to review the differences between insulin pump therapy and MDI, as well as between SAPT and MDI with SMBG. Meta-analysis of such studies suggests a reduction in severe hypoglycaemic episodes and HbA1c with pump therapy.55 Studies in specific groups such as pregnant women with T1D, adults or children with T1D have also shown benefits even though in the case of pregnant women the benefits of SAPT are similar to those of MDI.55

SAPT is superior to MDI with SMBG without increasing the risk of hypoglycaemia.54 In terms of reduction in complications, RCTs in patients with T1D show that SAPT reduced albuminuria compared to MDI.56 A significant impact on QoL has also been noted in users of SAPT therapy, with major reduction in fear of hypoglycaemia and improvement in treatment satisfaction in adults.57

Not all studies, however, have shown improvements in outcomes with pump therapy. Restoration of hypoglycaemia awareness and prevention of severe hypoglycaemia without worsening overall metabolic control may be achieved with MDI as well.58 In addition, there has been no demonstrable difference in weight gain and number of diabetic ketoacidosis (DKA) episodes in SAPT compared to MDI.55 Some studies also suggest that there may be no difference in time spent in hyperglycaemia between insulin pump and MDI, although it may be shorter in patients on SAPT.54

While pump therapy is expensive, the cost-effectiveness of pump therapy has been demonstrated in certain patient groups.59

**Eligibility in the UK**

According to the current NICE guidance, insulin pump therapy is recommended for adults and children older than 12 years of age with T1D in the following circumstances60.

1. Attempts to achieve the target HbA1c level with MDI result in disabling hypoglycaemia (repeated and unpredictable hypoglycaemia resulting in persistent anxiety about recurrence and reducing the quality of life significantly).
2. Failure to achieve the target HbA1c level (8.5% or 69 mmol/mol) on MDI therapy despite the high level of care.
3. CSII is also recommended in children of younger than 12 years of age with T1D if the MDI therapy is impractical or inappropriate and provided that they would be expected to undergo trial of MDI therapy between 12 years and 18 years of age.

**Hybrid insulin pump (closed-loop systems) and the artificial pancreas**

The advent of newer technology linking an insulin pump with CGM sensor and artificial intelligence technology, which can
adjust the rate of delivery depending on the patient’s prevailing glucose level detected by CGM, has been achieved. Proof-of-concept studies have been published, and small studies of individuals living freely with such devices have also been undertaken.61

Medtronic released the first-ever hybrid insulin pump (closed-loop system)—the MiniMed 670G with Guardian Sensor 3 in 2017, and it has been available in the UK from March 2019. In ‘auto mode’, this hybrid closed-loop insulin system adjusts the insulin basal rates every 5 min based on the glucose levels sensed by the CGM, in order to achieve the target blood glucose level. Early studies show that there is an improvement in HbA1c and there is no occurrence of DKA or hypoglycaemia in initial safety trials.62 Eligibility is currently very limited in the UK.

More recently, studies of a bi-hormonal pump which releases insulin and glucagon, respectively, and can achieve near-normoglycaemia, improved time in glucose range and reduction in hypoglycaemia.63

CONCLUSIONS

T1D carries a heavy personal burden and adversely affects quality and quantity of life. New technologies may have a considerable benefit in managing this burden. Ease of testing glucose has been a major goal of therapy for many years, and is finally fulfilling its potential. Delivery of insulin using CSII is a well-established therapy in many patients and has particular benefits for reducing hypoglycaemia and improving glucose control.

The management of T1D is, however, on the cusp of a major paradigm shift with the advent of closed-loop systems, which may have the benefit of managing glucose with lower burdens of care for the patient, and lower risk of adverse events. While the cost of these technologies is currently high, costs are likely to reduce as the technology becomes more easily available. The evidence for these technologies in reducing complications of T1D is, as yet, not available. If their efficacy can be demonstrated, then the cost-effectiveness of these technologies is likely to be high, and their uptake is likely to grow.

Main messages
► Type 1 diabetes (T1D) is a lifelong condition, which is burdensome to manage and has adverse effects on quality and quantity of life.
► Standard management requires frequent injections of insulin and frequent blood glucose monitoring.
► Technological advances in testing of glucose can reduce the burden of testing for people with T1D. The Freestyle Libre device is now widely available and evidence of its benefit in the management of T1D is growing.
► Continuous subcutaneous insulin infusion (CSII) is a well-established treatment that can reduce the risk of hypoglycaemia and improve glucose control in people with T1D.
► Closed-loop systems linking continuous glucose monitoring with CSII have been developed and appear to improve glucose management and quality of life in people with T1D.

Current research questions
► Do CGM, CSII or closed-loop systems reduce risk of microvascular and macrovascular complications and mortality in T1D?
► Can a closed-loop system manage T1D with minimal input from the patient?

Key references

Self-assessment questions
1. A 27-year-old woman was admitted with a first episode of diabetic ketoacidosis as a presenting feature of new-onset type diabetes. On recovery, she was commenced insulin therapy. Which of the following is the most appropriate insulin regimen?
   b. Insulin pump therapy.
   c. Once-daily basal insulin.
   d. Three times a day 50/50 mixed insulin.
   e. Two times per day 30/70 mixed insulin.

2. A 37-year-old woman with type 1 diabetes was admitted with hypoglycaemia. She noted that her awareness of hypoglycaemia had worsened recently. She was on a multiple-dose insulin regimen, and routine investigations were normal. She had appropriately reduced insulin doses, was carbohydrate counting and was rotating injection sites. Which of the following is the most appropriate course of action?
   a. Change all insulins to alternative preparations.
   b. Change of glucose metre.
   c. Continuous subcutaneous insulin infusion (insulin pump).
   d. Hybrid closed-loop system.
   e. Reduction in insulin doses by 50%.

3. A 25-year-old man with type 1 diabetes was keen to undertake flash glucose monitoring using a Freestyle Libre. Which of the following statement(s) concerning flash glucose monitoring are correct?
   a. It alarms if the glucose goes below 3 mmol/L.
   b. The glucose sensor needs to be changed daily.
   c. The sensors can never be used in water.
   d. There is good evidence for improvement in quality of life.
   e. There is good evidence of reduction in microvascular disease.

4. A 24-year-old woman with type 1 diabetes was keen on managing her diabetes with a closed-loop system. Which of the following is currently correct?
   a. Closed-looped loop systems are likely to be widely available in the next one year.
   b. Closed-loop systems can be used with a Freestyle Libre.
Review

5. A 23-year-old man with type 1 diabetes developed problems with hypoglycaemia and was keen to undertake some form of continuous glucose monitoring (CGM). Which of the following statement(s) concerning CGM are correct?
   a. CGM can only be used in conjunction with an insulin pump.
   b. CGM is available for all people with T1D.
   c. CGM is cheaper than flash glucose monitoring (Freestyle Libre).
   d. CGM is proven to reduce microvascular complications of diabetes.
   e. Glucose readings from the CGM can be used to assess ability to drive.

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