The management of type 1 diabetes in adults. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).

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Duality of Interest

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List of Abbreviations

BGM: Blood glucose monitoring
CGM: Continuous glucose monitoring
DKA: Diabetic ketoacidosis
DSMES: Diabetes self-management education and support
GMI: Glucose Management Indicator
HbA1c: Glycated haemoglobin A1c
NPH: Neutral protamine Hagedorn
TIR: Time in range
TBR: Time below range
Abstract

The American Diabetes Association and the European Association for the Study of Diabetes convened a writing group to develop a consensus statement on the management of type 1 diabetes in adults. The writing group has considered the rapid development of new treatments and technologies and addressed the following topics: diagnosis, aims of management, schedule of care, diabetes self-management education and support, monitoring, insulin therapy, hypoglycaemia, behavioural considerations, psychosocial care, diabetic ketoacidosis, pancreas and islet transplantation, adjunctive therapies, special populations, inpatient management and future perspectives. Although we discuss the schedule for follow-up examinations and testing, we have not included the evaluation and treatment of the chronic microvascular and macrovascular complications of diabetes as these are well-reviewed and discussed elsewhere. The writing group was aware of both national and international guidance on type 1 diabetes and did not seek to replicate this but rather aimed to highlight the major areas that healthcare professionals should consider when managing adults with type 1 diabetes. Though evidence-based, recommendations in the report represent the consensus opinion of the authors where the available evidence is incomplete.
Section 1: Introduction and rationale for the consensus report

Type 1 diabetes is a condition caused by autoimmune damage of the insulin-producing $\beta$ cells of the pancreatic islets, usually leading to severe endogenous insulin deficiency. Type 1 diabetes accounts for approximately 5-10% of all cases of diabetes. Although the incidence peaks in puberty and early adulthood, type 1 diabetes affects all age groups with a global prevalence of 5.9 per 10,000 population (1). The incidence has risen rapidly over the last 50 years and is currently estimated to be 15 per 100,000 per year.

Prior to the discovery of insulin a century ago, type 1 diabetes was associated with a life-expectancy as short as a few months. Beginning in 1922, relatively crude extracts of exogenous insulin, derived from animal pancreases, were used to treat people with type 1 diabetes. Over the ensuing decades, insulin concentrations were standardized, insulin solutions became more pure, and additives (zinc, protamine) were incorporated into insulin solutions to increase the duration of action. In the 1980’s, semi-synthetic and recombinant human insulins were developed, resulting in reduced immunogenicity (2). In the mid-1990’s, insulin analogues became available; basal insulin analogues were designed with prolonged duration of action and reduced pharmacodynamic variability compared to protamine-based (NPH) human insulin while rapid-acting analogues were introduced with quicker onset and shorter duration than regular human insulin, resulting in reduced early postprandial hyperglycaemia and less later post-meal hypoglycaemia (2).

The discovery of insulin transformed the lives of many people but it soon became apparent that type 1 diabetes is associated with the development of long-term complications and shortened life expectancy. Over the last 100 years, developments in insulin, its delivery, and technologies to measure glycaemic indices have markedly changed the management of type 1 diabetes. Despite these advances, many people with type 1 diabetes do not reach the glycaemic targets necessary to prevent or slow the progression of diabetes complications, which continue to exert a high clinical and emotional burden.

Recognizing the on-going challenge of type 1 diabetes and the rapid development of new treatments and technologies, the European Association for the Study of Diabetes (EASD) and the American Diabetes Association (ADA) convened a writing group to develop a consensus report on the management of type 1 diabetes in adults, aged 18 years and over. The writing group was aware of both national and international guidance on type 1 diabetes and did not seek to replicate this but rather aimed to highlight the major areas of care that healthcare professionals should consider when managing adults with type 1 diabetes. The consensus report has focused predominantly on current and future glycaemic management strategies and metabolic emergencies. Recent advances in the diagnosis of type 1 diabetes have been considered. Unlike many other chronic conditions, type 1 diabetes places a unique burden of management on the individual with the condition. In addition to complex medication regimens, other behavioural modification is also needed; all of this requires considerable knowledge and skill to navigate between hyper- and hypoglycaemia. The importance of diabetes self-management education and support (DSMES) and psychosocial care are rightly documented in the report. While acknowledging the significance of screening, diagnosing, and managing the chronic microvascular and macrovascular complications of diabetes, a detailed description of the management of these complications is beyond the scope of this report and where relevant the reader is directed to other publications.
Two members of the writing group, one from the ADA and one from EASD, were assigned to be the primary authors of each section. The chosen individuals had specific knowledge of the area and were tasked with reviewing and summarizing the available literature. Each section, in turn, was reviewed and approved by the entire working group. The draft consensus report was peer reviewed (see “Acknowledgments”), and suggestions were incorporated as deemed appropriate by the authors. Though evidence-based, the report represents the consensus opinion of the authors given that the available evidence is incomplete.

Section 2: Diagnosis of type 1 diabetes

Adults with new-onset type 1 diabetes can present with a short duration of illness of 1–4 weeks or a more slowly evolving process that can be mistaken for type 2 diabetes. Additionally, monogenic diabetes can be misdiagnosed as type 1 diabetes. Most of the available data discussed below are derived from white European populations and may not be representative of other ethnic groups. The clinical presentation may differ, but the classical triad of thirst and polydipsia, polyuria, and weight loss are common symptoms of type 1 diabetes. Accurate classification of the type of diabetes has implications beyond the use of insulin treatment; education, insulin regimen, use of adjuvant therapies, access to newer technologies, need for psychosocial support to address the profound psychological impact of the diagnosis of diabetes and concurrent disease screening may all depend on the diagnosis an individual receives. Furthermore, accurate diagnosis allows an assessment of the risk of diabetes in first degree relatives and appropriate counselling. Although profound insulin deficiency is the hallmark of type 1 diabetes, some adults with type 1 diabetes maintain some insulin secretion for years after diagnosis and may not require insulin treatment at diagnosis (3), leading to diagnostic uncertainty about the type of diabetes and its management.

Differentiating type 1 diabetes from type 2 diabetes

Identifying whether an adult with newly diagnosed diabetes has type 1 diabetes may be challenging where the individual has features pointing towards both type 1 diabetes and 2 diabetes, for example an older adult with a low or normal body mass index (BMI) or young adult with an elevated BMI. Ketoacidosis, once considered pathognomonic of type 1 diabetes, may occur in ketosis-prone type 2 diabetes. Misclassification of type 1 diabetes in adults is common and over 40% of those developing type 1 diabetes after age 30 years are initially treated as having type 2 diabetes (4–6). A misdiagnosis of type 2 diabetes can bring with it stereotypes, biases and stigma, especially for those with type 1 diabetes who are overweight or obese. No single clinical feature confirms type 1 diabetes in isolation (7,8). The most discriminative feature is younger age at diagnosis (<35 years), with lower BMI (<25 kg/m²), unintentional weight loss, ketoacidosis, and glucose >360 mg/dL (20 mmol/L) at presentation also being informative. Other features classically associated with type 1 diabetes, such as ketosis without acidosis, osmotic symptoms, family history, or a history of autoimmune diseases are weak discriminators (6–8).

The very strong relationship between type 2 diabetes incidence and age means that even ‘classical’ features of type 1 diabetes may have a limited predictive value in older adults, as type 2 diabetes in this age group is so common (9). The majority of older adults with low BMI will have type 2 diabetes (7,10,11), even more so when a person’s ethnicity is associated with high type 2 diabetes risk (12). Rapid progression to insulin treatment (<3 years) is strongly suggestive of type 1 diabetes at any age (4,6,13). Controversy remains as to whether latent autoimmune diabetes of adulthood (LADA) is a discrete subtype, a milder form of type 1
diabetes, or a mixture of some individuals with type 1 diabetes and others with type 2 diabetes (14).

**Differentiating type 1 diabetes from monogenic diabetes**

Monogenic diabetes is found in approximately 4% of those diagnosed with diabetes before the age of 30 years; the likelihood of monogenic diabetes rises to 20% where islet antibodies are negative and C-peptide secretion is maintained (15). Monogenic diabetes is commonly mistaken for type 1 diabetes because of the young age at onset. A diagnosis of monogenic diabetes allows specific treatment with discontinuation of insulin in many cases and has implications for family members and screening for concurrent conditions (16,17).

**Investigation of an adult with suspected type 1 diabetes**

A suggested algorithm for the investigation of adults with suspected type 1 diabetes is shown in Figure 1.

**Islet autoantibodies**

An assessment of islet autoantibodies at diagnosis is recommended as the primary investigation of an adult with suspected type 1 diabetes. Glutamic Acid Decarboxylase (GAD) should be the primary antibody measured and, if negative, should be followed by islet tyrosine phosphatase 2 (IA2) and/or Zinc transporter 8 (ZNT8) where available. Islet cell antibody (ICA) measurement is no longer recommended because it is an imprecise biological assay that has been superseded by the direct measurement of single antibodies (18,19). In people with clinical features suggesting type 1 diabetes, the presence of one or more positive islet autoantibodies is highly predictive of rapid progression and severe insulin deficiency and these individuals should be considered to have type 1 diabetes, even if they were not insulin requiring at diagnosis (20,21).

The absence of autoantibodies does not exclude type 1 diabetes, as approximately 5-10% of white European people with new-onset type 1 diabetes have negative islet antibodies (6,7,22), and further consideration of the diagnosis is necessary. In those diagnosed below the age of 35 years, type 1 diabetes is still the most likely diagnosis, particularly if there are no clinical features of type 2 diabetes or monogenic diabetes. In those aged over 35 years, type 2 diabetes becomes increasingly likely with absent islet autoantibodies and older age. However, it can be hard to differentiate between type 1 diabetes and type 2 diabetes based on age and clinical features in non-white European populations.

It is important to make a clinical decision about how to treat the person with diabetes. Regardless of any features of type 2 diabetes or absence of islet antibodies, if there is a clinical suspicion of type 1 diabetes, the individual should be treated with insulin. However, in some individuals, where the clinical course is more suggestive of type 2 diabetes, a trial of non-insulin therapy may be appropriate. Those whose diabetes is treated without insulin will require careful monitoring and education, so that insulin can be rapidly initiated in the event of glycaemic deterioration. Type 2 diabetes and other types of diabetes should be considered
in all age groups but in those aged under 35 years, negative islet antibodies should raise the suspicion of monogenic diabetes.

C-peptide measurement

Beyond 3 years after diagnosis where there is uncertainty about diabetes type, a random C-peptide measurement (with concurrent glucose) within 5 hours of eating is recommended. Where a person is treated with insulin, this test should always be performed prior to insulin discontinuation, to exclude severe insulin deficiency.

Persistent C-peptide >600 pmol/L (non-fasting) is strongly suggestive of type 2 diabetes and people with C-peptide in this range are often able to replace insulin with other agents (23–26). Routine C-peptide testing in those with clinically diagnosed type 1 diabetes of at least 3 years duration has led to reclassification in 11% of those with adult-onset diabetes (27). By contrast, low or absent C-peptide confirms the diagnosis of type 1 diabetes.

Genetic testing

As monogenic diabetes was less likely to have been considered in the past, molecular genetic testing for neonatal diabetes should be considered for all people with type 1 diabetes, regardless of current age, who were diagnosed under 6 months of age as more than 80% have monogenic neonatal diabetes, and the 30–50% with K$_{ATP}$ channel mutations can replace insulin with sulfonylureas (28,29).

Monogenic diabetes should be considered in those with one or more of the following features: age at diagnosis of less than 35 years, HbA$_1c$ <58mmol/mol (7.5%) at diagnosis, one parent with diabetes, and features of specific monogenic cause (e.g. renal cysts, partial lipodystrophy, maternally inherited deafness, severe insulin resistance in the absence of obesity) (30). A monogenic diabetes prediction model risk calculator (https://www.diabetesgenes.org/mody-probability-calculator) (31) may also be used to identify which individuals diagnosed between 6 months and 35 years are at increased risk of monogenic diabetes. Those at increased risk should have islet autoantibody and C-peptide testing. Molecular genetic testing should only be considered if the antibodies are negative and non-fasting C-peptide is >200 pmol/l (32–34). Molecular genetic testing is not universally available.

Section 3: Aims and Goals of management of type 1 diabetes

The aim of diabetes care and management is to support people with type 1 diabetes to live a long and healthy life. The management strategies to achieve this aim broadly include:

- Effectively delivering exogenous insulin to maintain glucose levels as close to the individual’s target range as is safely possible to prevent the development and progression of diabetes complications while
- Minimizing episodes of hypoglycaemia, of all levels, but in particular Level 2 (moderate) and Level 3 (severe) hypoglycaemia and preventing episodes of diabetic ketoacidosis while treating these appropriately should they occur
- Effectively managing cardiovascular risk factors
- Providing approaches, treatments, and devices that minimize the psychosocial burden of living with type 1 diabetes, and consequently diabetes-related distress, while promoting psychological wellbeing.

Management strategies should adapt to new therapies and technologies as they become available according to the wishes and desires of the person with diabetes.

The importance of glycaemic management was demonstrated convincingly by the Diabetes Control and Complications Trial (35) and the Epidemiology of Diabetes Interventions and Complications follow-up study (36). With the use of intensive insulin therapy that aimed to achieve levels of glycaemia close to the non-diabetes range, HbA1c was lowered by ~2% (22 mmol/mol) to a mean HbA1c of ~7.0% (53 mmol/mol) over a mean of 6.5 years compared with standard care (mean HbA1c ~9.0% (75 mmol/mol)) (35). The risk of primary development of retinopathy was reduced by 75% and progression of retinopathy slowed by 54%. The development of microalbuminuria was reduced by 39% and clinical neuropathy by 60% in those assigned to intensive therapy. These benefits persisted beyond the end of the trial despite equivalent glucose levels (HbA1c ~8% (64 mmol/mol)) in the post-trial period, and reductions in cardiovascular disease and mortality emerged with time (36). This seminal study has been the basis for glycaemic target recommendations for type 1 diabetes worldwide. The cost of intensive management was, however, a two- to three-fold increase in the rates of severe hypoglycaemia as well as weight gain.

The main results of the DCCT were published in 1993 before any of the current insulin analogues and diabetes technologies, except for insulin pumps, were available. Increasingly, achieving and maintaining glucose levels in the target range have become possible with fewer episodes of hypoglycaemia (37–40). Although the evidence of HbA1c reduction remains the most robust and is the only measure that is prospectively validated, more recent studies have begun to examine the relationship between time in range (TIR) and long-term complications and have provided the basis for glycaemic targets with newer glucose monitoring technologies (41,42).

The glycaemic target should be individualized considering factors that include duration of diabetes, age and life expectancy, comorbid conditions, known cardiovascular disease or advanced microvascular complications, impaired awareness of hypoglycaemia, and individual considerations, and it may change over time. Goals should be achieved in conjunction with an understanding of the person’s psychosocial needs and a reduction in diabetes distress if elevated. An HbA1c goal for most adults of <7.0% (53 mmol/mol) without significant hypoglycaemia is appropriate. Achievement of lower HbA1c levels than the goal of 7% (53 mmol/mol) may be acceptable, and even beneficial, following discussion between the person with diabetes and their healthcare team if these can be achieved safely without adverse effects of treatment. Less-stringent HbA1c goals (such as <8.0% [64 mmol/mol]) may be appropriate for individuals with limited life expectancy or where the harms of treatment are greater than the benefits. It should be recognized that any reduction in HbA1c from high initial levels has significant benefit even if the “goal” is not reached.

Capillary blood glucose monitoring (BGM) can help people with type 1 diabetes achieve HbA1c goals. A pre-prandial capillary plasma glucose target of 80–130 mg/dL (4.4–7.2 mmol/L) is appropriate for many people. Postprandial glucose may be targeted if HbA1c goals are not met despite reaching pre-prandial glucose targets. Post-prandial glucose measurements should be made 1–2 h after the beginning of the meal, which generally corresponds to peak
levels in people with diabetes. A peak postprandial capillary plasma glucose of <180 mg/dL (10.0 mmol/L) is appropriate for most people with diabetes, with higher goals in those with limited life expectancy or where the harms of treatment are greater than the benefits (table 1).

Alternatives to the measurement of HbA1c and BGM are assessments of the glucose management indicator (GMI) and time in range (TIR) from continuous glucose monitoring (CGM) data. GMI is calculated based on the average sensor glucose over the last 14 days and provides an approximation of a laboratory-measured HbA1c in some individuals, but it may be higher or lower than actual HbA1c in others (41). In some circumstances these metrics can replace HbA1c measurements. A typical GMI goal is <7.0% (53 mmol/mol). “Time-in-range” (TIR) is defined as 70-180 mg/dL (3.9-10 mmol/l) in most adults and time below range (TBR) as below 70 mg/dL (3.9 mmol/l) (low) as well as less than 54 mg/dL (3.0 mmol/l) (very low). Other metrics are also defined (Figure 2). TIR is associated with microvascular complications (41,42) and a TIR of 70% roughly corresponds to an HbA1c of 7.0% (53 mmol/mol). An international consensus conference reported that for most adults with type 1 diabetes, a target TIR should be above 70% with TBR less than 4%. The primary target for older people with long duration of diabetes should be TBR less than 1% (43).

The cornerstone of type 1 diabetes therapy is insulin replacement. This is challenging because of the low therapeutic window of insulin and insulin demands that vary widely according to meals, exercise, and many other factors. People with type 1 diabetes have to walk a tightrope between high and low glucose levels. Insulin management must be supported by adequate monitoring of glucose and education and training to allow the individual with type 1 diabetes to make the most of their treatment regimen. Type 1 diabetes is a demanding condition and requires on-going professional medical, educational, and psychosocial support. Care may differ at particular times of life, such as at the point of diagnosis, during concomitant illness or pregnancy, and later in life. These issues are discussed in greater detail in the sections that follow. Overall approaches for people with newly diagnosed or established type 1 diabetes are shown in figures 3 and 4.

Section 4: Schedule of Care

A detailed evaluation should be obtained at the initial consultation, and more targeted interval care at follow-up visits with a focus on person-centered care (Table 2) (44,45). A personalized approach for visit frequency is recommended. For adults whose glycaemic profile is stable and at goal, a visit once a year should be sufficient, providing that earlier and more frequent appointments can be scheduled if problems arise. In contrast, more frequent contact is preferred for adults who are not meeting their diabetes goals and who would benefit from additional self-management education and support. More frequent contact will allow additional review of glucose data and support. Additional visits can also be useful when the therapeutic regimen changes, for example, when the insulin regimen is modified or when a new device is started.

In the past, initial and follow-up visits were primarily conducted face-to-face and telemedicine only used sporadically. With the onset of the COVID-19 pandemic, the use of telemedicine became a necessity and there was an abrupt widespread adoption of remote visits (video/audio) to deliver diabetes care. Pre-COVID-19, results from a limited number of studies using telemedicine in different subgroups of people with type 1 diabetes suggested that
remote monitoring, education, and provider visits have the potential to improve outcomes, quality of life, and self-management; increase access to care and reduce costs; and are well-accepted with improved treatment satisfaction (46–49).

The use of telemedicine, however, should be individualized and will vary depending upon individual needs, computer literacy, and access to care (50). The healthcare professional and person with diabetes should be in a private space. In advance of the visit, people with diabetes should receive clear instructions on the expectations for the tele-visit, including how to connect to the consultation and how to upload data from their diabetes devices (glucose meters, data collecting apps, CGM devices, and insulin pumps) prior to the appointment (51). When clinically indicated and appropriate, people with diabetes should be asked to weigh themselves and perform home blood pressure measurements where possible. A list of all medications and relevant medical reports should be available.

Section 5: Diabetes self-management education and support

Diabetes self-management education and support (DSMES) is an essential component of type 1 diabetes care. The objective of DSMES is to provide those living with type 1 diabetes with the knowledge, skills, and confidence to successfully self-manage their diabetes on a daily basis and thereby reduce the risks of acute and long-term complications while maintaining quality of life (52). DSMES aims to empower people with type 1 diabetes, with an emphasis on shared decision-making and active collaboration with the health care team.

Levels and content of diabetes self-management education and support

Three levels of DSMES can be distinguished. Level 3 DSMES refers to structured education that meets nationally-agreed criteria, including an evidence-based curriculum, quality assurance of teaching standards and regular audit. These programs are guided by learning and behaviour change theories. Level 2 refers to ongoing learning that may be informal, perhaps through a peer group, while level 1 comprises information and one-to-one advice.

Several level 3 programs have been developed for adults with type 1 diabetes and have proven to be effective both in terms of improved glycaemic and psychosocial outcomes (53). Most programs use a group format, increasingly supplemented with digital support, including text messaging and cloud-based solutions and telemedicine (54). Structured DSMES programs most often include multiple components and cover a broad range of topics from pathophysiology to medical technology and healthy coping (Table 3).

Specific DSMES should not be confined to one particular moment but offered on a continuous basis and tailored to the ever-evolving individual’s educational needs. People with type 1 diabetes may be diagnosed at a young age or during adulthood, and many live with type 1 diabetes throughout different life stages. In this context four critical times can be distinguished: at diagnosis, when not meeting targets, when transitions occur, and when complications develop (Figure 5) (55). DSMES should be tailored towards individuals’ needs, taking into account literacy, ethnic, socio-cultural, cognitive, financial and geographical factors (56). A structured, periodic assessment of educational needs and barriers should be an integral part of ongoing diabetes care (Table 4).
Section 6: Monitoring of glycaemia

People with type 1 diabetes should have an assessment of their glycaemia with their healthcare professional as often as is clinically indicated but at least annually. Glycaemic status should be assessed at least every three months in those whose therapy has changed or who are not meeting glycaemic goals.

Glycated haemoglobin (HbA1c)

Monitoring of glycaemia has traditionally been by HbA1c, which has been used in most studies demonstrating the effects of lowering glucose on the development and progression of diabetes complications (35). A strong correlation (r>0.9) between HbA1c and average blood glucose during the preceding 3 months has been demonstrated where glucose levels are stable (57). In several conditions, however, HbA1c does not reflect mean glucose; these are mainly situations where red blood cell turnover is altered or in the presence of haemoglobinopathies (Table 5) (58). Variability exists between individuals, but the HbA1c and blood glucose within an individual correlate over time (59). Although HbA1c is an indicator of mean glucose, it does not inform glycaemic variability and hypoglycaemia and therefore is inappropriate as the only method of glucose evaluation in type 1 diabetes (59,60).

Other biomarkers, such as fructosamine, 1,5 anhydroglucitol, and glycated albumin provide measures of mean glucose albeit with shorter durations than HbA1c. None of these are as well associated with diabetes complications as HbA1c (61).

Capillary blood glucose monitoring

Capillary blood glucose monitoring (BGM) involves the use of a handheld meter and the measurement of capillary blood glucose. Frequent BGM measurements are important as an integrated part of diabetes management to guide insulin dosage, food intake, and prevention of hypoglycaemia with exercise. BGM is needed before meals for decisions about the meal insulin dose. Additionally, BGM is needed to prevent and detect hypoglycaemia in several situations such as before bedtime; before driving; before, during, and after exercise; and when hypoglycaemic symptoms occur. The evidence for the optimal number of daily BGM is lacking and may depend on variation in the person’s lifestyle. In registry studies, increased testing frequency is associated with lower HbA1c (62). However, even with frequent BGM, most people with type 1 diabetes will have undetected and an unacceptable high frequency of hyper- and hypoglycaemia (63). Frequent measurements are often not feasible and can be distressing. Seeing high or low glucose values can evoke feelings of frustration, anxiety and guilt, leading many people with type 1 diabetes to measure less often than needed (64).

Downloading memory-capable glucose meters can be helpful in observing patterns of hyper- or hypoglycaemia (65). Most meters meet the accuracy standards established by the International Organization for Standardization although there is still variability with many meters not meeting accuracy standards when tested independently (66).

Continuous Glucose Monitoring

Continuous glucose monitoring (CGM) devices measure interstitial glucose and have been available commercially since 2006. CGM devices have evolved and improved enough in accuracy to the point where most currently available sensors are “non-adjunctive” meaning that a check with capillary BGM before a treatment decision is taken is not required.
Currently there are two types of CGM devices. One provides a continuous value of current glucose and trends to a receiver, mobile app, smartwatch, or pump (designated as real-time [rt] CGM) while the other requires the glucose level to be determined by scanning a small reader or smartphone across the transmitter (intermittently scanned [is]CGM). Historically, rt-CGM has offered a variety of alerts, both in terms of indicating when a specific glucose level is reached as well as for trends in glucose levels. IS-CGM did not have these alerts but increasingly includes them. In the near future, these sensors and others in development will increasingly connect to other devices, including “smart pens.” All currently available devices can be uploaded to an internet cloud to allow people with diabetes and healthcare professionals to easily view the data at or between clinic visits. CGMs report a reading every 1 to 15 minutes.

Based on RCT data, rt-CGM is effective for adults with type 1 diabetes in improving HbA1c (particularly when high) and reducing hypoglycaemia for both those using insulin pumps or multiple daily injections (38–40,67); RCTs of the original isCGM devices are more mixed but observational data are supportive of their use, rt-CGM has also been found beneficial in reducing the burden of hypoglycaemia in older adults with type 1 diabetes (68) and those with impaired awareness of hypoglycaemia (40). Most people with type 1 diabetes can benefit from this technology with appropriate initial and ongoing education, including frequent observation of the glucose trends. Some people, however, may not find CGM valuable as they may feel that they do not require it or find it stressful because they dislike being ‘attached to a device’ or constantly reminded of their diabetes or feeling exhausted by alarms (alarm fatigue). Cost considerations can also play a role. Nevertheless, CGM is the standard for glucose monitoring in adults with type 1 diabetes and the choice of the device should be based on individual preferences and needs as well as which devices are available or reimbursed.

Retrospective analysis of CGM data can guide and enhance therapeutic decision-making, patient understanding, and engagement in adjusting behaviours. Standardized glucose reports with visual cues, such as the Ambulatory Glucose Profile (AGP) and daily tracings, should be available for all CGM devices (table 6; Figure 2).

Although healthcare professionals should regularly review CGM data and be responsive and react in a timely manner, people with type 1 diabetes should be encouraged to review their own reports regularly and follow their progress over time, contacting their healthcare professional as needed for worsening or changing trends.

People with type 1 diabetes should be warned that contact dermatitis (both irritant and allergic) may occur with all CGM devices that attach to the skin (69–71). In some instances, the use of an implanted sensor can help avoid skin reactions in those who are sensitive to tape (72,73).

**Section 7: Insulin therapy**

The ideal regimen of insulin replacement maintains blood glucose in a near-normal state, while allowing flexibility in terms of mealtimes and activity levels. Typical insulin replacement regimens incorporate several components: basal insulin to restrain gluconeogenesis and ketogenesis in the pre-prandial state, mealtime insulin to cover the intake of carbohydrate and other macronutrients, and correction insulin to treat hyperglycaemia.
Choice of regimen

Most people with type 1 diabetes should use regimens that mimic physiology as closely as possible, irrespective of the presentation. This is best achieved with either multiple daily injections (MDI) of subcutaneous basal insulin analogues and mealtime rapid-acting insulin analogues or with continuous subcutaneous insulin infusion of a rapid-acting insulin analogue via a pump, delivered as continuous basal insulin combined with manual mealtime boluses. Trials have demonstrated that the latest basal analogues may reduce hypoglycaemia compared to first-generation basal analogues and NPH insulin while rapid-acting analogues achieve better mealtime coverage and less post-meal hypoglycaemia than regular human insulin (74,75). Insulin analogues are therefore considered the insulins of choice.

Ultra-rapid analogues have a slightly earlier time of onset and peak action than rapid-acting analogues. These insulins reduce post-prandial hyperglycaemia but have otherwise not been shown to reduce HbA\textsubscript{1c} or hypoglycaemia to a greater extent than rapid-acting analogues (2). Currently, recombinant human insulin or analogues of human insulin account for the vast majority of insulin used worldwide.

HbA\textsubscript{1c}, time in range, and time below range are improved further when physiological MDI or pump regimens are augmented with CGM usage (76), with the greatest benefits seen with algorithm-driven automated basal (and in some systems correction) insulin delivery, which is commonly called hybrid-closed loop therapy (77,78).

Despite these advantages, the costs of insulin analogues and CGM or pump therapy are barriers for some people, while others do not wish to wear a device or inject multiple times per day. In these cases, subcutaneous regimens of human regular and NPH insulin or pre-mixed insulin, with BGM as frequently as feasible, may be used at a cost of higher glucose variability with higher risk of hypoglycaemia and less flexibility of lifestyle. Figure 6 shows advantages and disadvantages of more- or less-physiological insulin replacement regimens, while Table 7 provides details on various regimens that might be employed.

Mode of delivery

MDI therapy can be administered using vials and insulin syringes or insulin pens, with the latter providing more convenience of dosing but may be at higher cost. Smaller gauge and shorter needles provide almost painless injections. Contrary to common wisdom, skin thickness is not significantly increased with overweight or obesity. Needles as short as 4 mm, injected at a 90-degree angle, enter the subcutaneous space with minimal risk of intramuscular injection in most adults (79). The use of longer needles increases the risk of intra-muscular injection. MDI regimens may be enhanced with emerging technology such as bolus calculators and memory-enabled pens that keep track of insulin doses.

Several insulin pumps for subcutaneous insulin delivery are available in many countries. The primary mechanical differences between pumps are whether they utilize external tubing to connect to an infusion set or a pod directly applied to the skin and controlled via a wireless connection to a controller. Current pumps include bolus calculators programmed with personalized insulin-to-carbohydrate ratio and correction factors. Notably, several insulin pumps now form a component of hybrid closed-loop therapy where an algorithm controls basal insulin delivery, and in some cases correction boluses, based on CGM trends, while the user still boluses manually (77,78). Several such systems are approved in various countries; however, there are growing numbers of people with type 1 diabetes using non-regulated “do-
“it-yourself” systems, which use commercially available CGM systems and pumps, with open-source software algorithms that communicate with both and can reverse-engineer the pump control of basal and corrective doses (80). Healthcare professionals should not recommend these systems, but they should respect an individual’s right to make informed choices about their care and continue to offer support to the people using these systems.

Fully closed loop automated insulin delivery systems are currently being evaluated in clinical trials being conducted by several collaborative groups in both North America and Europe (81). The expectation is that some of these will receive regulatory approval in the next few years. This should allow people with type 1 diabetes to achieve better glycaemic levels with minimal risk of hypoglycaemia. This is a rapidly evolving area, and readers may wish to keep abreast by referring to the Technology section of the ADA Standards of Care which is a living document updated frequently (82).

Adverse Effects

The main adverse effect associated with insulin therapy is hypoglycaemia which is discussed in the next section. The safety and efficacy of insulin therapy is closely related to glucose monitoring and insulin dose adjustments made by the individual with diabetes, or more recently, automatically through control algorithms. Therefore, education in the management of insulin doses is a crucial component of this therapy, both at initiation and during follow-up. This education includes rescue strategies in case of hyperglycaemic or hypoglycaemic deviations, including the measurement of urine or blood ketone bodies or the prescription of carbohydrate intake and glucagon, respectively.

Skin reactions to subcutaneous insulin therapy include local inflammation (often due to the pH of or additives to the insulin), insulin-induced lipoatrophy, and insulin-induced lipohypertrophy. Lipoatrophy has become rare as the purity of manufacture of human and analogue insulin has improved. Lipohypertrophy typically occurs when the same sites are repeatedly used for injections or pump sites and is a cause of glycemic variability (83). People with type 1 diabetes should receive instructions about proper injection technique, including regular site rotation, at the time of insulin initiation with periodic reminders thereafter.

As described above for CGM devices, individuals should be warned about possible skin reactions to pump adhesives.

Alternative routes of administration

Although subcutaneous insulin therapy has been the mainstay of treatment for almost a century, this mode does not mimic physiological insulin secretion well. Healthy β cells secrete a burst of insulin into the portal circulation at the onset of glucose intake, with approximately half the insulin cleared by the liver and not entering the systemic circulation, whereas subcutaneous insulin enters the systemic circulation with some delay and is removed relatively slowly. Inhaled human insulin, available only in the U.S., has a very rapid onset of action and short duration compared to subcutaneous rapid-acting analogues (2). Inhaled insulin ameliorates early post-prandial hyperglycaemia well, but its short duration of action results in less control of later post-prandial hyperglycaemia. Additionally, inhaled insulin can cause cough or sore throat, and therapy must be monitored with periodic spirometry because of possible effects on lung function.
Section 8: Hypoglycaemia

Hypoglycaemia is the main limiting factor in the glycaemic management of type 1 diabetes. Hypoglycaemia is classified into three levels. Although these were originally developed for clinical trials reporting, they are useful clinical constructs. Level 1 corresponds to a glucose value below 70 mg/dL (3.9 mmol/l) and greater than or equal to 54 mg/dl (3.0 mmol/l) and is named as an alert value. Level 2 is for glucose values below 54 mg/dL (3.0 mmol/l) and considered as serious, clinically-important hypoglycaemia. Level 3 designates any hypoglycaemia characterized by altered mental state and/or physical status needing the intervention of a third party for recovery (86). Particular attention should be made to prevent level 2 and 3 hypoglycaemia. Hypoglycaemia can be further sub-divided as symptomatic, asymptomatic, or probable symptomatic (typical symptoms not confirmed by a measured glucose).

Level 1 hypoglycaemia is common, with most people with type 1 diabetes experiencing several episodes per week. Hypoglycaemia with glucose levels below 54 mg/dL (3.0 mmol/l) occurs much more often than previously appreciated (42,87). Severe hypoglycaemia is less common but occurred in 12% of adults with type 1 diabetes over a 6-month period in a recent global observational analysis (88). Several studies have shown that rates of hypoglycaemia have not declined even with more widespread use of insulin analogues and CGM, while other studies have shown benefit with these therapeutic advances (37).

Risks for hypoglycaemia, particularly severe hypoglycaemia, include longer duration of diabetes, older age, history of recent severe hypoglycaemia, alcohol ingestion, exercise, lower education levels, lower household incomes (37), chronic kidney disease, and impaired awareness of hypoglycaemia and hypoglycaemia-associated autonomic failure (89–91). Older diabetes databases consistently documented that people with lower HbA1c levels had two- to threefold higher rates of severe hypoglycaemia. However, in the Type 1 Diabetes Exchange Clinic Registry, the risk of severe hypoglycaemia was increased not only in those whose HbA1c was below 7.0% (53 mmol/mol) but also in people with an HbA1c above 7.5% (58 mmol/mol) (37).

It is possible that the absence of a relationship between HbA1c and severe hypoglycaemia in real-world settings is explained by relaxation of glycaemic targets by those with a history of hypoglycaemia or confounders, such as inadequate self-management behaviours that contribute to both hyper- and hypoglycaemia. A secondary analysis of the IN CONTROL trial, where the primary analysis showed a reduction in severe hypoglycaemia in people using CGM, demonstrated an increase in the rate of severe hypoglycaemia with lower HbA1c, similar to what was reported in the DCCT (92). This implies that lowering HbA1c may still come with a higher risk of severe hypoglycaemia. This risk is not inevitable and may be avoided through the use of hybrid closed loop systems that result in both improvement in TIR and reduction...
in TBR (78). Furthermore, brief structured education with informed support in active insulin
dose self-adjustment underpinned by targeted blood glucose monitoring leads to sustained
falls in severe hypoglycaemia rates in those at high risk (93).

Mortality from hypoglycaemia in type 1 diabetes is not trivial. One recent trial noted more
than 8% of deaths for those younger than 56 years were from hypoglycaemia (94). The
mechanism for this is complex, including cardiac arrhythmias, activation of both the
coaulation system and inflammation, and endothelial dysfunction (95). What may not be as
well recognized is that severe hypoglycaemia is also associated with major microvascular
events, non-cardiovascular disease, and death from any cause (95). With regards to cognitive
function, in the Diabetes Control and Complications Trial, after 18 years of follow-up severe
hypoglycaemia in middle-aged adults did not appear to affect neurocognitive function (96).
However, CGM data were not available in the DCCT era and so the true extent of serious
hypoglycaemia over time is not known. It appears that older adults with type 1 diabetes are
more prone to mild cognitive impairment associated with hypoglycaemia (97), while
hypoglycaemia occurs more frequently in those with cognitive impairment.

**Impaired awareness of hypoglycaemia**

Impaired awareness of hypoglycaemia (IAH) is the reduced ability to recognize low blood
levels that would otherwise prompt an appropriate corrective therapy (98). Its
prevalence is estimated close to 25% in people with type 1 diabetes but is likely
underestimated according to CGM data (99). IAH increases the risk of severe hypoglycaemia
by 6-fold (100) and may lead the person with diabetes to omit insulin injections intentionally
or loosen tight glucose management to prevent their occurrence.

The pathophysiology of IAH is still not fully understood but includes a partial or total loss of
sympatho-adrenal reactions to hypoglycaemia that prevent catecholaminergic stimulation of
hepatic glucose output and restraint of muscle glucose uptake (90). The connections between
autonomic neuropathy and IAH are complex since both the defect of sympatho-adrenal
reaction to hypoglycaemia can be a component of autonomic neuropathy and hypoglycaemia
itself can promote neuropathy. Indeed, recurrent hypoglycaemia is a major cause of IAH.
Sleep disturbance, psychological stress, and alcohol can also induce IAH (98).

In clinical practice, physicians should be proactive in asking people with type 1 diabetes
whether and at which glucose level they feel hypoglycaemia in order to identify IAH and adjust
individual glucose targets to prevent the occurrence of severe hypoglycaemia. The reference
method to assess IAH is the hyperinsulinaemic-hypoglycaemic clamp (101), although not used
out of a research frame due to its invasiveness, cost and time commitment from people with
diabetes. Self-reported awareness, however, agrees well with the autonomic glucose
threshold (102). The Gold and Clarke questionnaires showing a score equal or above 4 are
indicative of IAH (100,103) and the Pedersen-Bjergaard and HypoA-Q questionnaires can also
identify IAH (104,105). The UK National Institute of Health and Care Excellence recommended
for the first time that an assessment of hypoglycaemia, including awareness, should form part
of clinical consultations (106).

Strict avoidance of hypoglycaemia can help to restore hypoglycaemia awareness (107). CGM
use promotes the identification of current or impending low glucose levels that people may
not feel. Blood glucose awareness training, education to optimize insulin dosing and type, and
hypoglycaemia avoidance motivational programs all improve hypoglycaemia awareness. In
some situations, it may be necessary to increase the glucose target range (107,108). Several
clinical trials failed to show a reduction of IAH by using CGM despite a reduced incidence of severe hypoglycaemia (87,98,107–110).

**Treatment of hypoglycaemia**

The recommended correction of hypoglycaemia is the oral intake of approximately 15 g of glucose or equivalent simple carbohydrate when a capillary blood glucose level is <70 mg/dl (3.9 mmol/l). This should be repeated every 15 minutes until any symptoms have resolved and the blood glucose level is above 70 mg/dl (3.9 mmol/l). A larger amount of glucose may be needed if glucose levels are below 54 mg/dl (3.0 mmol/l). Lower carbohydrate intakes can be used when symptoms are associated with a capillary blood glucose level above 70 mg/dl (3.9 mmol/l).

The specific recommendations for correction of hypoglycaemia or trends for hypoglycaemia according to CGM in people using automated insulin delivery systems will have to be defined as this mode of therapy expands in forthcoming years. Less carbohydrate may need to be ingested to correct hypoglycaemia because the automated insulin delivery system should have already reduced or stopped basal insulin delivery.

In the case of neuroglycopaenic symptoms, including severe confusion or loss of consciousness, oral glucose intake is contraindicated because of risk for aspiration. Instead, glucagon via subcutaneous or intramuscular injection or nasal delivery should be given by attending people. Intravenous glucose injection is a possible alternative for healthcare professionals in the cases of severe hypoglycaemia.

After the acute symptoms have resolved, a further 20g of long-acting carbohydrate should be given and the cause of the hypoglycaemic episode sought to prevent further episodes.

**Section 9: Additional behavioural considerations**

**Nutrition therapy**

Nutrition, in particular carbohydrate intake, has a major effect on glycaemia and people with type 1 diabetes need to understand the effect of food on their diabetes and plan meals accordingly (Table 8). People with type 1 diabetes should be referred for individualized medical nutrition therapy provided by a registered dietitian who is knowledgeable and skilled in providing diabetes-specific nutritional advice. Medical nutrition therapy delivered by a registered dietitian is associated with a reduction HbA1C of 1.0-1.9% (11-21 mmol/mol) for people with sub-optimally managed type 1 diabetes when integrated into an overall management program (111).

There is no one eating pattern recommended for people with type 1 diabetes. The nutrition approach should be individualized based on personal preferences, socioeconomic status, cultural backgrounds and comorbidities. Carbohydrate counting is the most common meal planning approach in type 1 diabetes. In conjunction with promoting healthy eating patterns, carbohydrate counting and insulin-to-carbohydrate ratios can be a useful method for adjusting meal-time insulin dosing for optimal glycaemic outcomes (112,113). While low-carbohydrate and very-low carbohydrate eating patterns have become increasingly popular and reduce HbA1C levels in the short-term, it is important to incorporate these in conjunction with healthy eating guidelines. Additional components of the meal, including high fat and/or high protein, may contribute to delayed hyperglycaemia and the need for insulin dose
adjustments. Since this is highly variable between individuals, postprandial glucose measurements for up to three or more hours may be needed to determine initial dose adjustments (114).

The average BMI of individuals with type 1 diabetes is rising at a faster rate than the general population, partly as a result of insulin intensification and societal factors that also affect the general population such as physical inactivity. Weight loss and maintenance interventions involving nutritional advice and physical activity should be offered to individuals with type 1 diabetes and overweight or obesity. New interactive technologies using mobile phones to provide information, insulin bolus calculations based on insulin-to-carbohydrate ratios, and telemedicine communications with care providers decrease both weight gain and the time required for education (115). In the case of extreme low weight, unhealthy eating habits should be reviewed, including the possibility of insulin omission.

**Alcohol and recreational drug use**

Similar to the general population, many individuals with type 1 diabetes consume alcohol, although its effects on glycaemic management are not always adequately considered by those with diabetes and their healthcare professionals. Increased alcohol consumption is associated with a higher risk of DKA and severe hypoglycaemia (116). Some of this increase may occur through the association with other risk-taking behaviour. However, excessive alcohol consumption impairs cognitive function and symptom awareness, leading to a diminished ability to self-manage the diabetes. Alcohol promotes ketosis, which in the context of consumption of sugary alcoholic beverages may increase the risk of DKA (117). Alcohol also inhibits hepatic gluconeogenesis leading to an increased risk of hypoglycaemia for up to 24 hours after the last drink (118). Hypoglycaemia is particularly hazardous because of the potential to confuse the symptoms of hypoglycaemia with alcohol intoxication.

Cannabis has been legalised in multiple jurisdictions. An association between recent recreational cannabis consumption and a more than double the risk of ketoacidosis has been reported from countries where cannabis has been legalised, possibly related to the emergence of higher potency formulations of cannabis and other synthetic cannabinoids (119). Use of cocaine and other stimulant-like drugs, such as amphetamine, methamphetamine, and ecstasy (or MDMA) increase glucose production and inhibit glucose clearance, which increases the risk of ketoacidosis. Having a diagnosis of a substance use disorder confers an increased all-cause mortality in populations with diabetes across a range of substances including cocaine, opioids, and cannabis, regardless of consumption.

As people are unlikely to spontaneously report their alcohol or drug use to clinicians, systematic screening for excess alcohol and/or drug use is recommended. Healthcare professionals have a responsibility to inform people with type 1 diabetes about the effects of drugs and alcohol on diabetes and related risks. Otherwise, people with diabetes will seek information elsewhere, which is frequently incorrect and misleading (120). Brief interventions to reduce risky drinking and drug use have been well validated in a variety of populations and offer the potential to improve diabetes medication taking and outcome (121). In the case of alcohol or drug addiction, referral to a specialized clinic is warranted.

**Smoking**

Since smoking increases the risk of macrovascular and microvascular complications in people with diabetes, smoking cessation should be promoted in all individuals with type 1 diabetes.
The direct effect of smoking on glycaemic levels in people with diabetes needs more research to assess impact (122,123).

Physical Activity

People with type 1 diabetes should be encouraged to engage in a combination of aerobic and resistance exercise on most days because exercise is associated with improved fitness, increased insulin sensitivity leading to reduced insulin requirement, improved cardiovascular health with better lipid profile and endothelial function, and decreased mortality (124–127). Independent effects on β-cell function and HbA1c have not been established beyond doubt but appear beneficial. In addition, regular physical activity is associated with reduced risk of microvascular complications, osteoporosis, and cancer in people with type 1 diabetes (128).

Exercise also helps maintain a healthy BMI and promotes sleep quality and mental wellbeing. It is important that physical activity is performed safely. The major risks are from the acute effects of exercise on glucose concentrations, which depend on several factors, including the baseline fitness of the individual, type, intensity and the duration of activity; the amount of insulin in the circulation; the blood glucose concentration before exercise; and the composition of the last meal or snack. People with type 1 diabetes should be taught about the effects of exercise on glucose and how to balance exogenous insulin delivery and carbohydrate intake for the different forms and intensities of exercise.

Glycaemic management during exercise should be made safer with CGM systems. The updated consensus statement for management of exercise in type 1 diabetes highlights very detailed suggestions regarding the use of trend arrows and adjustment of insulin doses and carbohydrate intake (129).

Before recommending exercise, it is important to enquire about symptoms of cardiovascular disease and undertake relevant investigation and treatment as necessary. Advice should be given about appropriate footwear for those with peripheral neuropathy to avoid the risk of ulceration. However, walking does not increase the risk of ulceration in people with peripheral neuropathy (130). Weight-bearing exercise should be avoided in active foot disease. If an individual has proliferative diabetic retinopathy or severe non-proliferative diabetic retinopathy, then vigorous activity requiring straining may be contraindicated because of the risk of vitreous hemorrhage or retinal detachment (131). The individual should be advised to consult an ophthalmologist prior to engaging in an intense exercise regimen.

Additional details regarding the diabetes management during physical activity or exercise have been described elsewhere (132). When there is excessive physical exercise combined with extreme low weight, an eating disorder should be considered.

Sleep

Proper sleep hygiene is essential for all individuals. Sleep may be disrupted in people with type 1 diabetes as a result of both behavioural and physiological aspects of diabetes and its management (133). They may include hyper- and hypoglycaemic episodes, blood glucose variability, and loss of blood pressure decline. However, studies performed so far have not determined causality. On the other hand, sleep disturbances including poor sleep quality and shorter sleep duration are associated with worsening glycemic levels in type 1 diabetes (134,135).
Sick Day/Illness Management

Stressful events, including illness, may impact glucose levels and increase risk of DKA. More frequent glucose and ketone measurements are necessary to identify insulin adjustments. It is recommended that individuals develop a sick day management plan with individualized guidelines with their healthcare professional (136).

Driving

Unrecognized hypoglycaemia and rapidly dropping glucose levels are the most relevant hazards for drivers with type 1 diabetes. These risks may be reduced by the use of CGM or BGM prior to driving and at 2-hourly intervals. Local regulations and recommendations should be followed for driving with type 1 diabetes (137-139).

Employment

People with type 1 diabetes can successfully undertake a wide range of employment but there remains prejudice against those with diabetes that can limit employment opportunities. The main concerns are associated with the risks of acute hypoglycaemia as well as certain situations in which continued supply of effective insulin is not possible, for example working in very hot climates. Additionally, chronic diabetes complications may affect the ability to work in certain situations. For some occupations, any risk of hypoglycaemia is considered unacceptable but efforts have been made to address these risks. For example, in some countries people with type 1 diabetes are now working as commercial airline pilots. For this reason, any person with type 1 diabetes should be supported to undertake professional activity, job, or employment for which they are otherwise qualified and can do safely (140). Employment circumstances should allow the safe use and storage of insulin and unrestrained access to glucose monitoring and self-treatment of hyper- or hypoglycaemia.

Travel

Planning ahead is the key to safe and trouble-free travel for individuals with type 1 diabetes. This includes preparing diabetes-related and emergency supplies which should be available at hand during the travel. A plan of adjusting insulin doses, especially when traveling across time zones, is essential to reduce glucose fluctuations (141). Depending on the locale of travel destinations, it may be advisable to research the estimated carbohydrate content of local foods to aid better insulin adjustment. Frequent glucose measurement with CGM or BGM is advisable for any travel (142). Additionally, it may be helpful to have note cards written in the local language to communicate that the person has type 1 diabetes and may need urgent glucose administration if hypoglycaemic.

Section 10: Psychosocial Care
Type 1 diabetes is a psychologically challenging chronic condition, with treatment outcomes highly dependent on the person’s on-going self-care behaviours. Cognitive, emotional, and social factors are critical determinants of self-care behaviours and consequently treatment success (143,144). Emotional health is an important outcome of diabetes care, warranting a person-centered approach (145).

**Psychosocial problems**

Diabetes-specific emotional distress affects 20-40% of people with type 1 diabetes and can be experienced at any point in time. Two ‘critical’ times, however, are following the diagnosis and when complications develop (146). Feeling powerless and overwhelmed by the daily self-care demands, fear of hypoglycaemia, and worries about complications are among the most cited sources of distress by persons with type 1 diabetes. Prolonged, significant diabetes distress is associated with depressed mood and elevated HbA₁c levels (147).

Lack of social support or feeling ‘policed’ by family, friends or coworkers also evokes emotional distress in individuals with type 1 diabetes (148). Conversely, social support is a protective factor serving as a buffer against stress. Depression and anxiety symptoms are twice as prevalent among people with type 1 diabetes relative to people without diabetes, negatively impacting quality of life (149–151). Anxiety and depression often co-exist and may partly overlap with symptoms of diabetes distress (152). Depression is a risk factor for poor self-care, hyperglycaemia, complications and excess mortality (152–154). The association between generalized anxiety and sub-optimal glycaemia is less clear (155,156).

Given the high prevalence and impact of psychosocial problems in diabetes, screening and monitoring should be integral parts of diabetes care. Validated screening tools have been developed for most problem areas and are available in multiple languages. Clinicians engaging in screening need to understand the psychological and social issues that may complicate diabetes management, have good communication skills, and be able to refer to specialized mental health services where appropriate. Recently, a working group from the International Consortium for Health Outcomes Measurement (ICHOM) made recommendations for a standard set of practical and validated psychosocial measures (157), including the WHO-5 Wellbeing index (WHO-5) (158), Problem Areas in Diabetes scale (PAID) (159), and Patient Health Questionnaire (PHQ-9) (160). For Generalized Anxiety, the Generalized Anxiety Disorder-7 items (GAD-7) is recommended (161). Screening tools can help to ‘flag’ psychological problems that may require follow-up or referral to a mental health specialist. Assessment and periodic monitoring of emotional health combined with the necessary organizational improvements are recommended and promote case-finding, emotional wellbeing and patient satisfaction with care (162,163).

Fear of hypoglycaemia affects up to 10% of adults with type 1 diabetes, particularly among those experiencing repeated episodes of severe hypoglycaemia (164). Fear of hypoglycaemia may translate into avoidance behaviours aimed at keeping blood glucose at a ‘safe’ level, resulting in persistent hyperglycaemia (165). In cases of problematic fear of hypoglycaemia, administering the Fear of Hypoglycaemia Survey (HFS) can help to identify specific worries and level of severity (166). Both disproportional high and low fear of hypoglycaemia warrant attention.

Eating disorders, including anorexia nervosa, bulimia nervosa, and binge eating, are over-represented in type 1 diabetes populations, particularly in young women (167,168) but may also occur in men. Insulin omission as a weight loss strategy (‘diabulimia’) often starting in
teenage years warrants special attention (169,170). If indicated, screening for eating disorders is advised, using a validated instrument suited for use in people with type 1 diabetes, e.g. the Diabetes Eating Problems Survey-Revised (DEPS-R) or Eating Disorders Inventory – 3 Risk Composite (EDI-3RC) (171).

**Social Determinants of Health**

Social and financial hardships can negatively impact an individual’s mental health, motivation, and capacity to engage in self-management practices, increasing the risk for elevated HbA$_1c$ and complications. In a review of social determinants of health and diabetes (172), the importance of the following domains is discussed: (a) Neighbourhood and physical environment e.g. housing stability; (b) Built environment e.g. walkability, access to green spaces; (c) Environmental exposures e.g. pollution; d) Food access, availability and affordability, and; (e) Healthcare access, affordability and quality.

Socioeconomic challenges, particularly the inability to pay for food, insulin, other medications and supplies, need to be recognized and addressed. Several screening tools are available (173–178). Sample questions that have been used include: How hard is it for you to pay for the very basics like food, housing, medical care, and heating? At any time since the last interview or in the last 2 years have you ended up taking less insulin than was prescribed for you because of cost? In the past 12 months has lack of transportation kept you from attending medical appointments or from getting insulin?

**Psychosocial interventions**

All members of the diabetes care team have a responsibility for providing psychosocial care. Preferably, the diabetes care team should include a psychologist or social worker to advise the team and consult with people with diabetes in need of psychosocial support (179). Three levels of psychosocial support can be distinguished, and diabetes teams have an important role in offering diabetes self-management education and support at all three levels.

At the first level, people living with type 1 diabetes do not require professional mental health care. They may engage in self-help programs and/or receive informal coaching as well as family, peer, and community support to assist them in coping with the psychological demands of self-managing type 1 diabetes as well as socioeconomic challenges. At the second level, which concerns approximately one quarter of individuals with type 1 diabetes, some degree of professional psychosocial support is warranted. Support for social needs can be provided by a social worker and/or community organization. It is important that therapists have a good understanding of diabetes treatments and integrate diabetes management in the psychological treatment. Psychological therapies, including time-limited (online) Cognitive Behavioural Therapy (CBT), mindfulness and interpersonal therapies are effective with regard to a range of psychological outcomes, including diabetes distress and depression. The effects of psychotherapy on glycaemic levels are generally small but tend to increase when diabetes self-management education is incorporated in the treatment (180). Approximately 5% of the adults with type 1 diabetes are in need of psychiatric treatment (level 3), which may involve psychotropic medication that can impact glycaemic management. Psychiatric comorbidities, such as anorexia nervosa and schizophrenia, require close collaboration between the mental health specialist and diabetes care team (181,182).
Section 11: Diabetic Ketoacidosis

Diabetic ketoacidosis (DKA) is a life-threatening but preventable acute complication of type 1 diabetes, characterized by hyperglycaemia, metabolic acidosis, and ketosis. There are times when the glucose levels are normal or only minimally elevated. The underlying cause is insulin deficiency, either absolute (new diagnosis of type 1 diabetes or omission of insulin in those with diagnosed disease) or relative (increased counter-regulatory hormones due to infection or other stressors without an adequate increase in insulin doses).

The prevalence of DKA and risk factors for the complication have been less well studied in adults with type 1 diabetes than in children. In the USA, national surveillance of emergency department visits and hospital admissions suggests a rate of 28 cases per 1000 adults with diabetes per year, with a worrisome increase in emergency department visits and admissions for DKA seen since 2009 (183). The U.S. Type 1 Diabetes Exchange Clinic Network reported that 4.8% of participants (age 26 to 93 years) had been hospitalized for DKA in the prior year (37,184). In a European (predominantly Germany and Austria) registry, adults with type 1 diabetes had DKA at a rate of 2.5 per 100 patient years (184).

As DKA occurs repeatedly in some persons with diabetes, risk factors should be identified and approached in a prevention strategy. Some known risk factors are non-modifiable, such as low socioeconomic status, younger age, female sex, and ethnicity (37,184), whereas others associated with increased risk of DKA are potentially modifiable. These include having had one previous episode of DKA, high HbA1c, low self-management skills including omission of insulin therapy, psychiatric disorders, infections, somatic comorbidity, alcohol and drug abuse, and less interaction with the healthcare team (185–187). Older studies demonstrated a higher risk of DKA in those using insulin pumps likely due to the lack of depot insulin when continuous delivery of insulin is disrupted (188). However, more recent studies have not found this to be the case (37,184,189). Adjunctive use of sodium glucose cotransporter (SGLT) inhibitors (see below) in adults with type 1 diabetes increases the risk of DKA by an absolute rate of about 4% per year, suggesting the need for intensive diabetes self-management education and monitoring (190,191). DKA in the setting of SGLT inhibitor use is often so-called euglycaemic DKA, with initial case reports describing admission glucose levels of 96-224 mg/dL (5.3-12.4 mmol/L) (192).

Diabetes self-management education is an effective tool in reducing DKA risk. Additional medical, behavioural health interventions and psychosocial support are often needed. Telemedicine offers the potential to reach populations with decreased access to care, and 24-hour access to advice about managing hyperglycaemia and ketosis/ketonemia at home can reduce the risk of hospital admission (185).

A detailed description of the management of DKA is beyond the scope of this report but the general principles of treatment are replacement of fluid, insulin, and potassium. Due to a lack of rigorous evidence, there are different protocols for DKA treatment in different parts of the world (193,194). For further information regarding treatment, refer to previous reviews (195,196).

Section 12: Pancreas and Islet transplantation
Whole organ pancreas and pancreatic islet transplantation are currently the only means of clinical β-cell replacement (figure 7). Both therapeutic options can effectively prevent hypoglycaemia, restore normoglycaemia, and possibly stabilize the progression of complications of type 1 diabetes (197–201). However, chronic systemic immunosuppression is needed in both forms to prevent allogeneic rejection. Therefore, the indication must thoroughly balance risk and benefit, taking into consideration psychological factors as well (202). In the U.S., islet transplantation is not yet approved for clinical use and reimbursement.

Most whole pancreas transplants are performed simultaneously with a kidney transplant (SPK). This is the “gold standard” therapy for people with type 1 diabetes and pre-final or end-stage renal disease if no contraindications (malignancies, chronic infections, insufficient self-management, and severe cardiovascular conditions) are present. Simultaneous pancreas-kidney transplants show a 5-year pancreas graft survival of 83% and are superior to pancreas transplant alone or pancreas after a kidney transplant (55 and 70% respectively) (203). With an SPK transplant, most recipients can expect amelioration of problematic hypoglycaemia for more than a decade (203–205).

Pancrase transplants alone (PTA) are usually performed in people who are relatively young (<50 years) and do not have obesity (<30 kg/m²) or coronary artery disease. These selection criteria minimize operative mortality (<1%) and reduce early technical pancreas graft loss (<10%) (203,206). The main indications are a history of frequent, acute, and severe metabolic complications (hypoglycaemia, hyperglycaemia, ketoacidosis), clinical and emotional problems with exogenous insulin therapy as to be incapacitating, or consistent failure of insulin-based management including technological aids (207).

Islet transplantation, a less invasive procedure, is indicated in people with excessive glycaemic lability and frequent severe hypoglycaemia despite optimal medical therapy and allows for inclusion of older people and those with coronary artery disease who would not be eligible for a whole-pancreas transplant (198,208,209). Careful patient selection and protocol optimization have led to substantial clinical improvements (198). Insulin independence can be maintained for 5 years in 50% of recipients (210,211). Although achievement of insulin independence remains an important objective, several multi-centre clinical trials of islet transplants in people with type 1 diabetes and problematic hypoglycaemia have adopted a combination of near-normal glycaemic levels (HbA₁c <7.0%, 53 mmol/mol) together with the elimination of severe hypoglycaemia as the primary end point and the clinically relevant dual goal of intervention (212–214). These outcomes can translate into improved patient-reported outcomes, but research in this area is limited (215).

Regardless of the β-cell replacement approach (pancreas or islets), the majority of recipients experience reliable prevention of problematic hypoglycaemia with near-normal glycaemic levels. Islet and pancreas transplants are the only approaches to date that confer both sustained recovery from hypoglycaemia-associated autonomic failure and restoration of glucose counter-regulation and, thereby, reliable protection from severe hypoglycaemia in people with longstanding type 1 diabetes (216). However, these approaches have not been compared with the newer systems of hybrid closed loop technology which might render immunosuppression requiring therapies less necessary.

Section 13: Adjunctive therapies
While insulin therapy is essential for people with type 1 diabetes, obtaining glycaemic goals with insulin alone is difficult because of the risks of hypoglycaemia. Furthermore, insulin therapy is often associated with undesirable weight gain which may worsen insulin resistance, does not address other pathophysiological abnormalities (apart from endogenous insulin deficiency including α-cell dysfunction), and leaves the individuals at an increased risk of cardiovascular disease. Adjunctive therapies aim to augment insulin therapy by addressing some of these critical unmet needs.

To date, although several drugs have been licensed as adjunctive therapies, the evidence of their effectiveness is limited. It is not possible to make a general recommendation about their use, but they can be considered in individual cases (table 9). However, before these drugs are prescribed, insulin therapy should be optimized.

Metformin
Metformin has been evaluated in numerous trials in people with type 1 diabetes with hopes that its insulin-sensitizing properties would improve glycaemic management and/or reduce cardiovascular risk (217). The largest study to date assessed the use of metformin 1g twice daily in 493 people with type 1 diabetes who were treated for 3 years with a primary endpoint of changes in carotid intimal thickness, a marker of cardiovascular disease risk. The study ultimately found no difference in the primary endpoint, minimal and non-sustained effects on HbA1c, minimal effects on weight (~1 Kg reduction), and no change in total daily insulin dose (218).

Pramlintide
Pramlintide, an amylin analogue, is approved for therapeutic use in the U.S., but not in Europe, as an adjunctive therapy to insulin. It remains the only FDA-approved adjunctive therapy for type 1 diabetes. Injection prior to meal acts to suppress glucagon secretion, delay gastric emptying, and promote satiety (219–222). Clinical trials have shown a reduction in HbA1c (0.3-0.4%; 3-4 mmol/mol) and modest (~1 kg) weight loss (223–226). As a result of its adverse effects and need for additional injections, clinical uptake of pramlintide has been limited. However, co-formulations of amylin with insulin are currently in development, as is the possibility of use of pramlintide in pumps or artificial pancreas systems.

Glucagon like peptide-1 receptor agonists
Glucagon like peptide-1 receptor agonists have been explored in people with type 1 diabetes for two indications. This first aimed to ameliorate β-cell decline at the time of diagnosis and there are ongoing trials of this approach. In one study of 308 people with recently diagnosed type 1 diabetes, liraglutide when used in combination with anti-IL-21 preserved β-cell decline (227). The second is as an adjunctive therapy in established type 1 diabetes by blunting glucagon secretion, decreasing gastric emptying, and promoting satiety and weight loss (228). The largest clinical trials in people with type 1 diabetes were conducted with liraglutide and showed modest decreases in HbA1c at daily doses of 1.8 mg (~0.4%; 4 mmol/mol), decreases in weight (~5 kg), and reductions in insulin doses (229,230). However, increased rates of hypoglycaemia and ketosis were shown. Subgroup analysis in people with residual C-peptide production suggests greater HbA1c reduction and improved safety with lower risk of ketosis. Trials in people with type 2 diabetes have shown convincing reductions in cardiovascular events with human GLP-1 analogues (231); whether these benefits would also be seen in
people with type 1 diabetes is unknown. GLP-1 receptor agonists may have a role for those who have concomitant obesity.

**Sodium-glucose co-transporter (SGLT) inhibitors**

In several phase III programs in people with type 1 diabetes, the use of SGLT inhibitors reduced HbA1c, improved time in range, reduced body weight and improved blood pressure (217). However, an increased rate of diabetic ketoacidosis led to rejection of market authorization for type 1 diabetes by the FDA, whereas the European Medicines Agency has approved low-dose dapagliflozin (5mg) and sotagliflozin (200mg) for those with a BMI >27 kg/m² (232). While no risk mitigation strategies have been proven to lower the risk of DKA, a consensus statement on SGLT2 inhibitors and DKA suggested careful patient selection, appropriate insulin dose adjustment to avoid insulinopaenia, starting with a low dose of SGLT2 inhibitors and regular ketone measurements with prompt action to elevated values as sensible precautions aimed at preventing DKA (190).

In people with type 2 diabetes, improved cardiovascular outcomes, mainly due to a reduction in congestive heart failure, and improved renal outcomes have been established, but the applicability of these data to people with type 1 diabetes is uncertain (233). However, increasingly, data on SGLT2 inhibitors have shown renal and heart failure benefits in people without diabetes suggesting that people with type 1 diabetes and these comorbidities may also benefit.

**Section 14: Special populations**

**Pregnancy including pre-conception and post-natal care**

Both maternal and fetal pregnancy outcomes are worse in women with type 1 diabetes compared with women without diabetes. Hyperglycaemia before and during pregnancy increases the risk of complications in the pregnant woman and developing fetus and also affects further child development. Thus, women should be supported to achieve blood glucose ranges close to those seen in pregnant women without diabetes with an HbA1c target of ≤6.5% (48 mmol/mol) (234,235). The woman should aim for fasting and pre-meals glucose concentrations below 95 mg/dL (5.3 mmol/L) and post-prandial values of below 140 mg/dL (7.8 mmol/L) 1 hour after a meal and below 120 mg/dL (6.7 mmol/L) 2 hours after a meal. Although the use of CGM is not approved in the U.S. for use of pregnancy and no studies in pregnancy have used CGM alone, the CONCEPTT trial showed that when CGM was used in conjunction with BGM, CGM was associated with better pregnancy outcomes (236). Many women rely on CGM during pregnancy and its use should be encouraged with the caveat that BGM should be performed if there are concerns that the CGM reading is inaccurate.

The major limiting step to achieving normoglycaemia is hypoglycaemia which occurs more frequently in the first half of pregnancy, in part because of diminished awareness of hypoglycaemia and pregnancy associated nausea and vomiting (237). Pregnant women with type 1 diabetes are at risk of DKA at lower blood glucose levels than the non-pregnant state and should receive education on diabetic ketoacidosis prevention and detection (238). Postpartum breastfeeding, erratic sleep and eating schedules may increase the risk of hypoglycaemia and insulin dosing may require adjustment (239,240).
The management of pregnancy begins before conception as a planned pregnancy is associated with improved outcomes for both the women and offspring. Effective contraception should be used until the woman is ready for pregnancy. All women of childbearing age with type 1 diabetes should be informed about the importance of seeking professional help prior to trying to conceive; this provides an opportunity not only to improve glycaemic management but to offer folic acid to prevent neural tube defects, screen for diabetes-related complications, and stop potentially teratogenic medications.

Diabetes in pregnancy is best managed by a multidisciplinary team including a diabetologist/endocrinologist, obstetrician, dietitian, diabetes nurse/educator, and diabetes midwife. A detailed description of the management of pregnancy in women with type 1 diabetes is beyond the scope of this report but is available elsewhere (241,242).

**Older people with type 1 diabetes**

Insulin regimens in older adults should be individualized and patient safety is a key priority. Glycaemic targets should be based on functional status and life expectancy, rather than chronological age. As older adults with type 1 diabetes are especially vulnerable to hypoglycaemia, target glucose values should be adjusted to minimize the occurrence of hypoglycaemic events. Since in some older adults with type 1 diabetes, administration of insulin may become more difficult, simplification of insulin management may be justified in cases of individuals with complications, or functional or cognitive impairment. The use of advanced technologies in older individuals is useful and should not be discontinued or a priori excluded because of the older age (68,243).

**People with late complications of type 1 diabetes.**

As there is no evidence that intensive glycaemic management slows the progression of late, microvascular complications of diabetes, glycaemic targets in individuals with advanced complications should be individualized and based on the balance of risks and benefits (35,244). Diabetes management may be particularly challenging in individuals with chronic kidney disease who may be at an increased risk of hypoglycaemia and in whom HbA1c can be falsely low (245) and in people with gastroparesis and unpredictable rates of food absorption (246). The rate of optimizing glycaemia in this group of people should also be individualized as rapid improvement may be associated with transient early worsening of retinopathy or the development of acute painful neuropathy (247,248). In people with cardiovascular complications, hypoglycaemia avoidance should be one of the management priorities (249).

**Section 15: In-patient Management of Type 1 Diabetes**

There have been no large, randomized controlled trials specifically assessing glycaemic targets for in-patients with type 1 diabetes. Therefore, type 2 diabetes guidelines should be followed, which recommend target glucose ranges of 140-180 mg/dl (7.8-10.0 mmol/l) for the majority of non-critically and critically ill patients (250). However, it is important that the care team recognizes key differences between type 1 diabetes and type 2 diabetes. People with type 1 diabetes are at higher risk of hypoglycaemia, which should be avoided by careful insulin and carbohydrate matching (251). Furthermore, people with type 1 diabetes are at
high risk of developing ketosis if insulin is withheld (252). People with type 1 diabetes often find the in-patient care of their diabetes stressful and disempowering. Therefore, in-patients with type 1 diabetes should be clearly identified to avoid common errors such as omission of mealtime insulin or withholding of basal insulin for procedures or surgery. Whenever a dedicated in-patient diabetes service is available, they should be consulted for glycaemic management, diabetes self-management education and support, and discharge planning (253). Finally, the use of diabetes technology (CGM and insulin pumps) can be continued in selected, non-critically ill patients, with clear mentation, and previous training and education (254,255). Institutions should develop clear guidelines to manage in-patient type 1 diabetes safely.

Section 16: Emergent and Future Perspectives

Both xenotransplantation and stem cells are under investigation to solve the problem of limited availability of donors for pancreas or islet transplantation (256). Stem cell strategies have used either patient specific stem cells or generic allogeneic cells. In the former, the patient’s own stem cells are reprogrammed or transdifferentiated to become β cells. By contrast, generic allogeneic cells may be used for multiple patients and centrally produced from a bank of embryonic stem cells (hESCs) or of induced pluripotent stem cells (iPSCs). One of the key issues is protecting the cells from immune attack, both rejection and recurrent autoimmunity. Three general strategies are being investigated – [1] immunosuppressive or immunomodulatory drugs, [2] use of a physical barrier e.g. encapsulation (257), and [3] gene editing for immune evasion and/or immune protection (258). Both academic and commercial groups are pursuing these approaches and some are already in clinical trials.

Immunotherapy approaches are being evaluated for their potential to prevent clinical type 1 diabetes, and for the preservation of β-cell function shortly after onset of clinical type 1 diabetes (259). Many interventions have been tested in clinical trials, but to date the most promising results have been from the anti-CD3 monoclonal antibody teplizumab, from low-dose anti-thymocyte globulin (ATG), and from the anti-TNF drug, golimumab. These have shown promise in preserving β-cell function in recent onset type 1 diabetes, and teplizumab also has delayed the clinical onset of type 1 diabetes. Several other trials are underway with the hope of not only preserving but even improving β-cell function and being able to interdict the type 1 diabetes disease process sufficiently to prevent the development of the disease.
Table 1: Glycaemic targets for most adults with type 1 diabetes

<table>
<thead>
<tr>
<th></th>
<th>HbA₁c or GMI</th>
<th>Pre-prandial capillary glucose</th>
<th>1-2 hr post-prandial capillary glucose</th>
<th>Time in range</th>
<th>Time below range</th>
<th>Time above range</th>
<th>Glycaemic variability (%CV)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&lt;7.0% (53 mmol/mol)</td>
<td>80–130 mg/dL (4.4–7.2 mmol/L)</td>
<td>&lt;180 mg/dL (10.0 mmol/L)</td>
<td>&gt;70%</td>
<td>• % of readings and time 54–69 mg/dL (3.0–3.8 mmol/L) Level 1</td>
<td>• % of readings and time &lt;54 mg/dL (&lt;3.0 mmol/L) Level 2</td>
<td>&lt;4%</td>
</tr>
</tbody>
</table>

All glycaemic targets should be individualized and agreed with the person with diabetes. HbA₁c: Haemoglobin A₁c; GMI: Glucose Management Indicator. *Some studies suggest that lower %CV targets (<33%) provide additional protection against hypoglycaemia.
### Table 2: Schedule of Care

<table>
<thead>
<tr>
<th>Medical and Family History</th>
<th>Diabetes History</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Date of diagnosis</td>
</tr>
<tr>
<td></td>
<td>Presentation at onset</td>
</tr>
<tr>
<td></td>
<td>Islet autoantibodies (date)</td>
</tr>
<tr>
<td></td>
<td>C-peptide (date)</td>
</tr>
<tr>
<td></td>
<td>Episodes DKA or severe hypoglycaemia</td>
</tr>
<tr>
<td></td>
<td>Hypoglycaemia awareness</td>
</tr>
</tbody>
</table>

**Family history**
- Type 1 diabetes or type 2 diabetes in first degree relatives
- Other autoimmune disorders

**Personal history of chronic complications**
- Microvascular
  - Retinopathy, macular edema, laser/injection therapy,
    Date of last retinal evaluation (exam or photos)
  - Peripheral neuropathy, autonomic neuropathy
  - Nephropathy
- Macrovascular
  - Heart, cerebrovascular and peripheral arterial disease
- Foot ulcers or amputations

**Personal history of common comorbidities**
- Autoimmune disorders (thyroid, coeliac, others)*
- Hypertension
- Lipid disorder
- Overweight and obesity
- Eating disorders
- Hearing loss
- Sleep disorder
- Dermopathy
- Fractures
- Joint and soft tissue disorders
  - Cheiroarthropathy
  - Capsulitis
  - Carpal tunnel syndrome
- Dental health

**Pregnancy and birth control history**

**Immunization history**

<table>
<thead>
<tr>
<th>Additional Behavioral Factors</th>
<th>Diet and Nutrition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Use of carbohydrate counting</td>
</tr>
<tr>
<td></td>
<td>Weight history</td>
</tr>
</tbody>
</table>

**Physical activity**
- Smoking, alcohol, substance use
| Sleep | **Diabetes Management** | Current insulin regimen  
- Multiple daily injections  
- Insulin pump (type/model):  
  - Settings  
  - Back-up injection plan  
Other diabetes medications  
Blood glucose monitoring  
- Type of meter/strip  
- Frequency of use  
- Mean (SD), range  
- Pattern  
Continuous glucose monitoring  
- Type/model  
- Data sharing: if yes with whom  
- Glucometrics  
- Pattern  
Glucagon prescribed  
Ketone testing supplies prescribed (where available)  
Software/app use |
|---|---|---|
| **Psychosocial Issues** | Monitor psychological well-being  
- diabetes-specific distress  
- depressive symptoms  
- anxiety symptoms  
Consider also the potential presence of fear of hypoglycaemia and disordered eating  
Screen for social determinants of health and social support  
Assess cognitive status | **Diabetes Self-Management Education and Support** | Assess and plan for meeting individual needs  
- Consider contraception and pregnancy planning |
| **Physical Examination** | Height  
Weight, BMI: every visit  
Blood pressure and pulse: At least once a year  
Skin including injection/infusion sites  
  - every visit if skin complaints or erratic glucose readings, otherwise annual  
Cardiovascular:  
  - Annual; more often if previous abnormality or symptoms  
Feet  
  - Every visit if peripheral vascular disease, neuropathy, foot complaints or history of foot ulcer; otherwise annual |
### Laboratory Testing

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency/Specimen Ownership</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c</td>
<td>every 3-12 months</td>
</tr>
<tr>
<td>Creatinine</td>
<td>annual</td>
</tr>
<tr>
<td>Urine Albumin: Creatinine ratio</td>
<td>annual</td>
</tr>
<tr>
<td>Lipid panel</td>
<td>frequency dependent on the presence of previous lipid abnormality or treatment</td>
</tr>
<tr>
<td>ALT and AST</td>
<td>at least once and as indicated clinically</td>
</tr>
<tr>
<td>Serum potassium (if taking ACE-I, ARB or diuretic)</td>
<td></td>
</tr>
<tr>
<td>TSH, vitamin B12, coeliac screen</td>
<td>at least once and as indicated clinically*</td>
</tr>
</tbody>
</table>

### Goals Setting

- Individualized, attainable, realistic
  - Behavioural considerations: Diet and nutrition, activity, smoking cessation

- Glycaemic
  - HbA1c, time in range, hypoglycaemia

### Treatment Plan

Formulate treatment plan with shared decision-making

### Referrals

As needed: podiatry, cardiology, nephrology, vascular surgery, others

---

* Individuals with type 1 diabetes are also at increased risk for the development of other autoimmune diseases including autoimmune thyroid disorders, pernicious anaemia, coeliac disease, collagen vascular diseases, and Addison's disease (260,261). The optimal frequency of screening for these conditions in adults has not been established.
### Table 3: Key content areas of Diabetes Self-Management Education and Support (DSMES).

<table>
<thead>
<tr>
<th>Key Content areas</th>
<th>Examples that focus on type 1 diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes pathophysiology and treatment options</td>
<td>Immunology of β-cell destruction</td>
</tr>
</tbody>
</table>
| Healthy eating | Basic and advanced carbohydrate counting versus intuitive dosing  
Impact of composition of meals (fat, protein, glycaemic index, fiber, sugar alcohols) on glucose levels;  
Use of technology to enhance dosing recommendations |
| Physical activity | Impact on glucose and insulin dose recommendations |
| Medication usage | Types of available insulins |
| Monitoring and using patient-generated health data (PGHD) | Technology and its impact on the ability to have more frequent communication – reviewing CGM, pump downloads, apps |
| Preventing, detecting and treating acute complications including hypoglycaemia, hyperglycaemia, diabetes ketoacidosis, sick day guidelines, and severe weather or situation crisis and diabetes supplies management | Euglycaemic DKA  
DKA prevention with pump use  
Glucagon use  
Ketone testing |
| Preventing, detecting and treating chronic complications including immunizations and preventive eye, foot, dental and renal examinations as indicated per the individual participant’s duration of diabetes and health status | Understanding the individual risk for complications in type 1 diabetes  
How to prevent development and progression of complications in the future |
| Healthy coping with psychosocial issues and concerns | Discussing diabetes distress and burnout |
| Problem solving | Goal setting  
Developing personal strategies to promote health and behaviour change  
Problem identification and solutions  
Identifying and accessing resources  
Sick day rules |
### Table 4: Needs assessment for Diabetes Management, Education and Support

<table>
<thead>
<tr>
<th>Key assessment features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health history</td>
</tr>
<tr>
<td>Functional health literacy and numeracy</td>
</tr>
<tr>
<td>Diabetes distress and support systems</td>
</tr>
<tr>
<td>Cultural influences</td>
</tr>
<tr>
<td>Health beliefs and attitudes</td>
</tr>
<tr>
<td>Physical limitations</td>
</tr>
<tr>
<td>Social determinants of health e.g. financial status</td>
</tr>
<tr>
<td>Barriers</td>
</tr>
</tbody>
</table>
Table 5: Non-Glycaemic Factors That Alter HbA1c Levels (61)

<table>
<thead>
<tr>
<th>Effect on HbA1c</th>
<th>Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apparent increase</td>
<td>Age</td>
</tr>
<tr>
<td></td>
<td>Ethnicity</td>
</tr>
<tr>
<td></td>
<td>• HbA1c is slightly higher in African Americans than in people of white Northern European ancestry*</td>
</tr>
<tr>
<td></td>
<td>Anaemias with decreased red cell turnover</td>
</tr>
<tr>
<td></td>
<td>• Iron, vitamin B12, folate</td>
</tr>
<tr>
<td></td>
<td>Severe hypertriglyceridemia</td>
</tr>
<tr>
<td></td>
<td>Severe hyperbilirubinemia</td>
</tr>
<tr>
<td></td>
<td>Chronic alcohol consumption</td>
</tr>
<tr>
<td></td>
<td>Chronic salicylate consumption</td>
</tr>
<tr>
<td></td>
<td>Chronic opioid ingestion</td>
</tr>
<tr>
<td>Apparent decrease</td>
<td>Pregnancy (second and third trimester)</td>
</tr>
<tr>
<td></td>
<td>Anaemias of chronic disease</td>
</tr>
<tr>
<td></td>
<td>Haemolytic anaemia</td>
</tr>
<tr>
<td></td>
<td>Splenomegaly and splenectomy</td>
</tr>
<tr>
<td></td>
<td>Acute blood loss</td>
</tr>
<tr>
<td></td>
<td>Renal failure</td>
</tr>
<tr>
<td></td>
<td>Advanced liver disease Drugs</td>
</tr>
<tr>
<td></td>
<td>• Dapsone</td>
</tr>
<tr>
<td></td>
<td>• Trimethoprim/ sulfamethoxazole</td>
</tr>
<tr>
<td></td>
<td>Vitamin E ingestion</td>
</tr>
<tr>
<td></td>
<td>Ribavirin and interferon alpha</td>
</tr>
<tr>
<td></td>
<td>Red blood cell transfusion</td>
</tr>
<tr>
<td>Apparent increase or decrease</td>
<td>Haemoglobin variants</td>
</tr>
<tr>
<td></td>
<td>Vitamin C ingestion</td>
</tr>
</tbody>
</table>

*Variability within races is greater than variability between races (262)
Table 6: Standardized continuous glucose monitoring (CGM) metrics for clinical care

<table>
<thead>
<tr>
<th>Description</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of days CGM device is worn</td>
<td>recommend 14 days</td>
</tr>
<tr>
<td>Percentage of time CGM device is active</td>
<td>recommend 70% of data from 14 days</td>
</tr>
<tr>
<td>Mean glucose</td>
<td></td>
</tr>
<tr>
<td>Glucose management indicator</td>
<td></td>
</tr>
<tr>
<td>Glycaemic variability (%CV)</td>
<td></td>
</tr>
<tr>
<td>Time above range (TAR)</td>
<td></td>
</tr>
<tr>
<td>% of readings and time &gt;250 mg/dL (&gt;13.9 mmol/L) Level 2</td>
<td></td>
</tr>
<tr>
<td>% of readings and time 181–250 mg/dL (10.1–13.9 mmol/L) Level 1</td>
<td></td>
</tr>
<tr>
<td>Time in range (TIR)</td>
<td></td>
</tr>
<tr>
<td>% of readings and time 70–180 mg/dL (3.9–10.0 mmol/L) in range</td>
<td></td>
</tr>
<tr>
<td>Time below range</td>
<td></td>
</tr>
<tr>
<td>% of readings and time 54–69 mg/dL (3.0–3.8 mmol/L) Level 1</td>
<td></td>
</tr>
<tr>
<td>% of readings and time &lt;54 mg/dL (&lt;3.0 mmol/L) Level 2</td>
<td></td>
</tr>
</tbody>
</table>

CV, coefficient of variation. Adapted from (43).
### Table 7: Examples of subcutaneous insulin regimens

<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>TIMING AND DISTRIBUTION</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
<th>ADJUSTING DOSES</th>
</tr>
</thead>
</table>
| Insulin pump therapy:  
Hybrid closed loop  
Low glucose suspend  
CGM-augmented open loop  
BGM-augmented open loop | Basal delivery of URAA or RAA; generally 40-60% of TDD  
Mealtime and correction: URAA or RAA by bolus based on ICR and/or correction (sensitivity factor and target glucose) | Can adjust basal rates for varying insulin sensitivity by time of day, for exercise, for sick days  
Flexibility in meal timing and content  
Pump can deliver insulin in increments of fractions of units  
Potential for integration with CGM for low-glucose suspend or hybrid closed-loop  
% Time in range highest and % time below range lowest: hybrid closed loop > low glucose suspend > CGM-augmented open loop > BGM-augmented open loop | Most expensive regimen  
Must continuously wear one or more devices  
Risk of rapid development of ketosis, DKA with interruption of insulin delivery  
Potential reactions to adhesives, site infections  
Most technically complex approach—harder for people with lower numeracy or literacy skills | Mealtime insulin: if carbohydrate counting accurate, change ICR if glucose after meal consistently out of target  
Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range  
Basal rates: adjust based on overnight, fasting, or daytime glucose outside of activity of URAA/RAA bolus |
| Multiple daily injections:  
LAA + flexible doses of URAA or RAA at meals | LAA once daily (detemir or glargine may require twice daily dosing); generally 50% of TDD  
Mealtime and correction: URAA or RAA based on ICR and/or correction (sensitivity factor and target glucose) | Can use pens for all components  
Flexibility in meal timing and content  
Insulin analogues cause less hypoglycaemia than human insulins | At least four daily injections  
Most costly insulins  
Smallest increments of insulin one unit (one-half unit with some pens)  
LAAAs may not cover strong dawn phenomenon as well as pump therapy  
Limited in terms of giving premeal doses, especially prelunch | Mealtime insulin: if carbohydrate counting accurate, change ICR if glucose after meal consistently out of target  
Correction insulin: adjust ISF and/or target glucose if correction does not consistently bring glucose into range  
LAA: based on overnight or fasting glucose or daytime glucose outside of activity time-course or URAA or RAA injections |
<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>TIMING AND DISTRIBUTION</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
<th>ADJUSTING DOSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple daily injection regimens with less</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>flexibility</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 injections daily with fixed doses of N and</td>
<td>Pre-breakfast: RAA ~20% of TDD</td>
<td>May be feasible if unable to carb count</td>
<td>Shorter duration RAA may lead to basal deficit during day; may need twice-daily</td>
<td>Pre-breakfast RAA: based on BGM after breakfast or before lunch</td>
</tr>
<tr>
<td>RAA</td>
<td>Pre-lunch: RAA ~10% of TDD</td>
<td>All meals have RAA coverage</td>
<td>N</td>
<td>Pre-lunch RAA: based on BGM after lunch or before dinner</td>
</tr>
<tr>
<td></td>
<td>Pre-dinner: RAA ~10% of TDD</td>
<td>N less expensive than LAAs</td>
<td>Greater risk of nocturnal hypoglycaemia with N</td>
<td>Pre-dinner RAA: based on BGM after dinner or at bedtime</td>
</tr>
<tr>
<td></td>
<td>Bedtime: N ~50% of TDD</td>
<td></td>
<td>Requires relatively consistent mealtimes and carb intake</td>
<td>Evening N: based on fasting or overnight BGM</td>
</tr>
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<tr>
<td>4 injections daily with fixed doses of N and R</td>
<td>Pre-breakfast: R ~20% of TDD</td>
<td>May be feasible if unable to carb count</td>
<td>Greater risk of nocturnal hypoglycaemia with N</td>
<td>Pre-breakfast R: based on BGM after breakfast or before lunch</td>
</tr>
<tr>
<td></td>
<td>Pre-lunch: R ~10% of TDD</td>
<td>R can be dosed based on ICR and correction</td>
<td>Greater risk of delayed post-meal hypoglycaemia with R</td>
<td>Pre-lunch R: based on BGM after lunch or before dinner</td>
</tr>
<tr>
<td></td>
<td>Pre-dinner: R ~10% of TDD</td>
<td>All meals have R coverage</td>
<td>Requires relatively consistent mealtimes and carb intake</td>
<td>Pre-dinner R: based on BGM after dinner or at bedtime</td>
</tr>
<tr>
<td></td>
<td>Bedtime: N ~50% of TDD</td>
<td>Least expensive insulins</td>
<td>R must be injected at least 30 minutes before meal for better effect</td>
<td>Evening N: based on fasting or overnight BGM</td>
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<tr>
<td>Regimens with fewer daily injections</td>
<td></td>
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</tr>
<tr>
<td>Three injections daily:</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>N+R or N+RAA</td>
<td>Pre-breakfast: ~40% N + ~15% R/RAA</td>
<td>Morning insulins can be mixed in one syringe</td>
<td>Greater risk of nocturnal hypoglycaemia with N than LAAs</td>
<td>Morning N: based on pre-dinner BGM</td>
</tr>
<tr>
<td></td>
<td>Pre-dinner: ~15% R/RAA</td>
<td>May be appropriate for those who cannot take injection in middle of day</td>
<td>Greater risk of delayed post-meal hypoglycaemia with R than RAAAs</td>
<td>Morning R: based on pre-lunch BGM</td>
</tr>
<tr>
<td></td>
<td>Bedtime: 30% N</td>
<td>Morning N covers lunch to some extent</td>
<td>Requires relatively consistent mealtimes and carb intake</td>
<td>Morning RAA: based on post-breakfast or pre-lunch BGM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Same advantages of RAAs over R</td>
<td></td>
<td>Evening R: based on bedtime BGM</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Least (N + R) or less expensive insulins than MDI with analogs</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BGM: Blood Glucose Monitoring
ICR: Insulin Correction Ratio
MDI: Multiple Daily Insulin
RAA: Rapid Acting Analog
N: Regular Insulin
R: Rapid Insulin
TDD: Total Daily Dose
<table>
<thead>
<tr>
<th>REGIMEN</th>
<th>TIMING AND DISTRIBUTION</th>
<th>ADVANTAGES</th>
<th>DISADVANTAGES</th>
<th>ADJUSTING DOSES</th>
</tr>
</thead>
<tbody>
<tr>
<td>Twice-daily “split-mixed” N + R or N + RAA</td>
<td>Pre-breakfast: ~40% N + ~15% R or RAA Pre-dinner: ~30% N + ~15% R or RAA</td>
<td>Least number of injections for people with strong preference for this Insulins can be mixed in one syringe Least (N+R) or less (N+RAA) expensive insulins compared to analogs Eliminates need for doses during the day</td>
<td>Coverage of post-lunch glucose often sub-optimal R must be injected at least 30 minutes before meal for better effect</td>
<td>Evening RAA: based on Post-dinner or bedtime BGM Evening N: based on fasting BGM</td>
</tr>
</tbody>
</table>

Table 8: Goal of Nutrition therapy for type 1 diabetes (114)

- Promote healthful eating patterns, emphasizing a variety of nutrient-dense foods in appropriate sizes to improve overall health and to:
  - Improve HbA1C, blood pressure, cholesterol and aid in maintaining weight
- Individualize nutrition needs based on personal and cultural preferences, health literacy, access to healthful food choices
- Provide practical tools for day-to-day meal planning
- Focus on matching insulin doses with meal composition through advanced carbohydrate counting
| **Table 9: Adjunctive therapies for type 1 diabetes** |
|---------------------------------|----------------|----------------|----------------|----------------|
| **Metformin** | **Pramlintide** | **GLP-1 RA** | **SGLT-2** |
| **HbA1c Reduction** | ~0.1% (1 mmol/mol) | ~0.3% (3 mmol/mol) | 0.2-0.3% (2-3 mmol/mol) | 0.2-0.4% (2-4 mmol/mol) |
| **Fasting Glucose** | Minimal Effect | No Effect | Minimal Effect | Modest Decrease 15 mg/dl; 0.8 mmol/l |
| **Postprandial Glucose** | Minimal Effect | Significant Decrease | Modest Decrease | Modest Decrease |
| **Time in Range** | No Data | No Data | No Data | Increased (~12% at higher doses) |
| **Insulin Dose** | Unchanged | Mealtime reductions | Predominantly mealtime reductions | Mealtime and basal reductions ~10% total reduction) |
| **Body Weight** | Modest (~1 kg) | Modest (~1 kg) | Significant (~5 kg) | Moderate (2-3 kg) |
| **Systolic Blood Pressure** | No Change | No Change | 4 mmHg decrease (with increase in heart rate) | 3-4 mmHg Decrease |
| **Hypoglycaemia** | | | | Increase in hypoglycaemia |
| **Side Effects** | GI side effects | GI side effects | GI side effects Increase in ketosis | Genital mycotic infections Increased risk of DKA |
| **Approval Status for type 1 diabetes in EU/US** | - | US approved | - | EU approved low dose when BMI ≥ 27 kg/m² |
| **Specific groups for whom treatment may be of benefit** | Women with polycystic ovary syndrome | | Overweight and obesity High insulin dose Risk of cardiovascular and renal disease |
Figures and Legends

Figure 1:  Flow chart for investigation of suspected type 1 diabetes in newly diagnosed adults, based on data from White European populations
1: No single clinical feature confirms type 1 diabetes in isolation. The most discriminative feature is younger age at diagnosis (<35 years), with lower BMI (<25 kg/m²), unintentional weight loss, ketoacidosis, and glucose >360 mg/dL (20 mmol/L) at presentation also being informative. Other features classically associated with type 1 diabetes, such as ketosis without acidosis, osmotic symptoms, family history, or a history of autoimmune diseases are weak discriminators.

2: Glutamic Acid Decarboxylase (GAD) should be the primary antibody measured and, if negative, should be followed by islet tyrosine phosphatase 2 (IA2) and/or Zinc transporter 8 (ZNT8) where available. In those diagnosed below the age of 35 years who have no clinical features of type 2 diabetes or monogenic diabetes, a negative result does not change the diagnosis of type 1 diabetes as 5-10% of people with type 1 diabetes do not have antibodies.

3: Monogenic diabetes is suggested by the presence of one or more of the following features: HbA₁c <58mmol/mol (7.5%) at diagnosis, one parent with diabetes, features of specific monogenic cause (e.g., renal cysts, partial lipodystrophy, maternally inherited deafness, severe insulin resistance in the absence of obesity). Monogenic diabetes prediction model probability >5%: www.diabetesgenes.org/exeter-diabetes-app/ModyCalculator

4: Features of type 2 diabetes include overweight or obesity, absence of weight loss, absence of ketoacidosis, and less marked hyperglycaemia. Less discriminatory features include non-white ethnicity, family history, longer duration and milder severity of symptoms prior to presentation, features of the metabolic syndrome and absence of a family history of autoimmunity.

5: Type 2 diabetes should be strongly considered in older individuals. In some cases investigation for pancreatic or other types of diabetes may be appropriate.

6: A person with possible type 1 diabetes who is treated without insulin will require careful monitoring and education, so that insulin can be rapidly initiated in the event of glycaemic deterioration. Where a person is insulin treated, C-peptide must be measured prior to insulin discontinuation, to exclude severe insulin deficiency.

7: A C-peptide test is only indicated in people receiving insulin treatment. A random sample (with concurrent glucose) within 5 hours of eating can replace a formal stimulations test in the context of classification. If the result is ≥600 pmol/L the circumstances of testing do not matter. If result is <600 pmol/L and the concurrent glucose is <4 mmol/L (<72 mg/dl) or the person may have been fasting, consider repeating the test. Very low levels (<80 pmol/L) do not need to be repeated. Do not test C-peptide within 2 weeks of a hyperglycaemic emergency.

8: C-peptide values 200-600 pmol/L are usually consistent with type 1 diabetes or MODY, but may occur in insulin-treated type 2 diabetes, particularly in people with normal or low body mass index or after long duration.

9: If genetic testing does not confirm monogenic diabetes, the classification is unclear and a clinical decision should be made about treatment.
Figure 2: CGM visualization in an AGP-report. (Use AGP report from 2021 SOC)
Figure 3: A framework for initial assessment and treatment of an individual with newly diagnosed type 1 diabetes.

HbA1c: glycated haemoglobin; CGM: continuous glucose monitoring; BGM: blood glucose monitoring; TIR: time in range; TBR: time below range; MDI: multiple daily injection. 1The availability of blood and urine ketone measurement varies across health care systems.
Figure 4: A framework for the follow-up treatment of an individual with type 1 diabetes. CGM: continuous glucose monitoring; DSMES: Diabetes self-management education and support; MDI: multiple daily injection. The availability of blood and urine ketone measurement varies across health care systems.
Figure 5: The four critical times when diabetes self-management education and support are particularly needed (add also when technology changing)

DSMES: diabetes self-management education and support
**Representative relative attributes of insulin delivery approaches in people with type 1 diabetes**

<table>
<thead>
<tr>
<th>Injected Insulin Regimens</th>
<th>Flexibility</th>
<th>Lower Risk of Hypoglycaemia</th>
<th>Higher Costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multiple daily injections with LAA + RAA or URAA</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Less preferred injected insulin regimens</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple daily injections with NPH + RAA or URAA</td>
<td>++</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Multiple daily injections with NPH + regular</td>
<td>++</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Two daily injections with NPH + regular or premixed</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Continuous Insulin Infusion Regimens</td>
<td>Flexibility</td>
<td>Lower Risk of Hypoglycaemia</td>
<td>Higher Costs</td>
</tr>
<tr>
<td>Hybrid closed-loop technology</td>
<td>+++++</td>
<td>++++</td>
<td>+++++++</td>
</tr>
<tr>
<td>Insulin pump with threshold/predictive low glucose suspend</td>
<td>+++++</td>
<td>++++</td>
<td>+++++</td>
</tr>
<tr>
<td>Insulin pump therapy without automation</td>
<td>+++</td>
<td>+++</td>
<td>+++</td>
</tr>
</tbody>
</table>

LAA: long acting insulin analogue; RAA: rapid acting insulin analogue; URAA: ultra-rapid acting insulin analogue; NPH: neutral protamine Hagedorn

**Figure 6: Choices of insulin regimens and glucose monitoring strategies in people with type 1 diabetes**

LAA: Long acting insulin analogue; RAA: rapid acting insulin analogue; URAA: ultra-rapid insulin analogue; NPH: neutral protamine Hagedorn
Figure 7: Simplified overview of indications for beta cell replacement therapy in people with type 1 diabetes

GFR: glomerular filtration rate
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