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2018 Clinical Practice Guidelines

Glycemic Management in Adults With Type 1 Diabetes

Diabetes Canada Clinical Practice Guidelines Expert Committee

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This chapter is dedicated to Dr. Angela McGibbon who passed away from a sudden illness on February 11, 2018. She had an extraordinary dedication to diabetes care and a passion for teaching the importance of patient care and compassion. Her leadership and outstanding contributions to the diabetes community will always be remembered.

KEY MESSAGES

- Basal-bolus insulin therapies (i.e. multiple daily injections or continuous subcutaneous insulin infusion) are the preferred insulin management regimens for adults with type 1 diabetes.
- Insulin regimens should be tailored to the individual's treatment goals, lifestyle, diet, age, general health, motivation, hypoglycemia awareness status and ability for self-management.
- All individuals with type 1 diabetes should be counselled about the risk, prevention and treatment of hypoglycemia. Avoidance of nocturnal hypoglycemia may include changes in insulin therapy and increased monitoring.
- If glycemic targets are not met with optimized multiple daily injections, continuous subcutaneous insulin infusion may be considered. Successful continuous subcutaneous insulin infusion therapy requires appropriate candidate selection, ongoing support and frequent involvement with the health-care team.
- Continuous glucose monitoring may be offered to people not meeting their glycemic targets, who will wear the devices the majority of the time, in order to improve glycemic control.

KEY MESSAGES FOR PEOPLE WITH DIABETES

- Insulin therapy is required for the treatment of type 1 diabetes.
- There are a variety of insulins and methods of giving insulin to help manage type 1 diabetes.
- Insulin is injected by pen, syringe or insulin pump.
- Your health-care provider will work with you to determine such things as:
  - The number of insulin injections you need per day
  - The timing of your insulin injections
  - The dose of insulin you need with each injection
  - If and when an insulin pump is appropriate for you
  - Your pump settings if you are giving insulin that way.
- The insulin treatment your health-care provider prescribes will depend on your goals, lifestyle, meal plan, age and general health. Social and financial factors may also be taken into account.
- Learning to avoid and treat hypoglycemia (low blood glucose) is an important part of your education. The ideal balance is to achieve blood glucose levels that are as close to target as possible while avoiding hypoglycemia.

Introduction

Insulin is lifesaving pharmacological therapy for people with type 1 diabetes. Insulin preparations are primarily produced by recombinant DNA technology and are formulated either as structurally identical to human insulin or as a modification of human insulin (insulin analogues) to alter pharmacokinetics. Human insulin and insulin analogues are preferred and used by most adults with type 1 diabetes; however, preparations of animal-sourced insulin are still accessible in Canada (1) although rarely required. Inhaled insulin is currently not approved for use in Canada.

Insulin preparations are classified according to their duration of action and are further differentiated by their time of onset and peak actions (see Appendix 6. Types of Insulin). For most adults with type 1 diabetes, premixed insulin preparations are not suitable as frequent adjustments of insulin are required. Insulin delivered by basal-bolus injection therapy or continuous subcutaneous insulin infusion (CSII, also called insulin pump therapy) as basal and bolus regimens are preferred. Avoidance of hypoglycemia with all regimens is a priority.

Achieving optimal glycemic targets, while avoiding hypoglycemia, can be challenging and requires individualized insulin regimens, which may include specialized insulin delivery devices and glucose monitoring often introduced in an escalating manner, starting with basal-bolus injection therapy then, in some cases, moving to CSII either with or without sensor augmentation. Continuous glucose monitoring (CGM) may be used with basal-bolus injection therapy or CSII. The role of adjuvant (noninsulin) injectable or oral antihyperglycemic medications in glycemic control is limited for most people with type 1 diabetes. Noninsulin pharmacotherapy for prevention of complications and treatment of risk factors is addressed in other chapters (see Cardiovascular Protection in People with Diabetes chapter, p. S162; Chronic Kidney Disease in Diabetes chapter, p. S201). Hypoglycemia as it relates to insulin therapy in type 1 diabetes is discussed here, and hypoglycemia in general is addressed in the Hypoglycemia chapter, p. S104.

Conflict of interest statements can be found on page S84.

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Insulin Therapy with Basal-Bolus Injection Therapy

People with type 1 diabetes are initiated on insulin therapy immediately at diagnosis. This requires both the selection of an insulin regimen and comprehensive diabetes education. Insulin regimens, usually with basal and bolus insulins, should be tailored to the individual's age, general health, treatment goals, lifestyle, diet, hypoglycemia awareness status, ability for self-management and adherence to treatment. Social and financial aspects also should be considered. After insulin initiation, some individuals experience a "honeymoon period," during which insulin requirements may be lower than expected; however, this period is transient (usually weeks to months), and insulin requirements typically increase and stabilize with time.

The Diabetes Control and Complications Trial (DCCT) conclusively demonstrated that intensive treatment of type 1 diabetes significantly delays the onset and slows the progression of microvascular and cardiovascular (CV) complications (2,3). The most successful management in the majority of adults with type 1 diabetes is based on basal-bolus injection therapy or CSII. Such regimens attempt to replicate normal pancreatic secretion of insulin.

Currently, new concentrated insulin preparations are available in basal and bolus formats. Sometimes they have identical pharmacokinetic and pharmacodynamic properties to the original preparation and other concentrated insulins have different pharmacological properties (see Appendix 6. Types of Insulin). These are further described below in the basal and bolus sections. In addition, biosimilar basal insulin is also available.

Basal insulin and basal-bolus injection therapy

Basal insulin refers to long- or intermediate-acting insulin, which provides control of glucose in the fasting state and between meals. Basal insulin is given once or twice a day and includes long-acting insulin analogues and intermediate-acting insulin neutral protamine Hagedorn (NPH). Insulin onset, peak and duration are shown in Appendix 6. Types of Insulin. Detemir insulin is available as a 100 units/mL formulation (U-100) (Levemir®). Glargine insulin is available as a 100 units/mL formulation (U-100) (Lantus™), a 300 units/mL formulation (U-300) (Toujeo®) and as a 100 units/mL biosimilar product (U-100) (Basaglar®). Degludec insulin is available as a 100 units/mL (U-100) and 200 units/mL (U-200) formulation (Tresiba®).

When used as a basal insulin in type 1 diabetes, the U-100 long-acting analogues, insulin detemir and insulin glargine (with rapid-acting insulin analogues for meals) resulted in lower fasting plasma glucose (FPG) levels and less hypoglycemia (4–7) or nocturnal hypoglycemia compared with once- or twice-daily NPH insulin (4,6–11). Given the potential severe consequences of nocturnal hypoglycemia, the avoidance of this complication is of great clinical importance.

Biosimilar insulin glargine has the identical amino acid sequence as glargine and is produced through a different manufacturing process. Biosimilar insulin glargine has been shown to have similar efficacy and safety outcomes in adults with type 1 diabetes maintained or switched from U-100 glargine (12).

Insulin glargine U-300 is a concentrated basal insulin, which appears to have a consistent, gradual and extended flat release from subcutaneous tissue with a longer duration of action (>30 hours) than U-100 glargine (13,14). Insulin glargine U-300 has been compared to insulin glargine U-100 in adults with type 1 diabetes and found to produce similar changes in A1C and similar or lower risk of hypoglycemia (13,15). Confirmed or severe nocturnal hypoglycemia was significantly lower in 1 study (16) but not in other shorter trials (15). Insulin glargine U-300 may require a higher dose than insulin glargine U-100 and may result in less weight gain (15,17).

Insulin degludec is a basal insulin with a long duration of action (42 hours) (14,18,19) in a once-daily injection that provides a consistent, flat glucose-lowering profile with low day-to-day variability (18,19). It provides similar glycemic control, but with less nocturnal hypoglycemia (20) and reduced basal and total insulin dose when compared to insulin glargine (21–23) and insulin detemir (24,25). The prolonged duration of action of insulin degludec allows for flexible timing of dosing without compromising metabolic control or safety (26). The 2 formulations of insulin degludec (U-100 and U-200) have similar glucose-lowering effects and half-lives (14).

Bolus insulin and basal-bolus injection therapy

Bolus insulin refers to rapid- or short-acting insulin given to control the glycemic rise at meals and to correct hyperglycemia. The prandial injection dose is decided based on carbohydrate content, carbohydrate-to-insulin ratio for each meal, planned exercise, time since last insulin dose and blood glucose level. Bolus insulins include rapid-acting insulin analogues (insulin aspart, insulin faster-acting aspart, insulin glargine, insulin lispro) and short-acting insulin (regular insulin).

Preprandial injections of rapid-acting insulin analogues result in a lower postprandial glucose and improved overall glycemic control (27–30). Insulin aspart, glulisine and lispro should be administered 0 to 15 minutes before the start of the meal while short-acting regular insulin should be administered 30 to 45 minutes before the start of the meal. Faster-acting insulin aspart may be administered at the start of the meal or, when necessary, up to 20 minutes after the start of the meal (31). When required, insulin aspart, glulisine and lispro can be administered from 0 to 15 minutes after the start of a meal although better control of postprandial hyperglycemia is seen with preprandial injections.

Insulin aspart and lispro have been associated with reduced nocturnal hypoglycemia, slightly lower A1C, improved postprandial glucose (30,32) and improved quality of life (33) when compared to short-acting insulin. Insulin glulisine has been shown to be equivalent to insulin lispro for glycemic control, with most effective A1C reduction when given before meals (27,34). Faster-acting insulin aspart has an earlier onset than insulin aspart (see Appendix 6. Types of Insulin). In type 1 diabetes, faster-acting insulin aspart demonstrated noninferiority with respect to A1C reduction and superior postprandial glucose control vs. insulin aspart (31).

Hypoglycemia and Insulin Therapy

Hypoglycemia is the most common adverse effect of insulin therapy in people with type 1 diabetes (for definitions see Hypoglycemia chapter, p. S104). In the DCCT, 35% of participants in the conventional treatment group and 65% in the intensive group experienced at least 1 episode of severe hypoglycemia (2,35,36). In a meta-analysis of 14 trials, the median incidence of severe hypoglycemia was 4.6 and 7.9 episodes per 100 patient-years in the conventionally treated and intensively treated people with type 1 diabetes, respectively (37). With adequate self-management education, appropriate glycemic targets, self-monitoring of blood glucose and support, intensive therapy may result in less hypoglycemia than reported in the DCCT (38–41), particularly with modern insulin formulations.

The frequency of hypoglycemic events is reduced with rapid-acting insulin analogues compared with regular insulin (8,42–44) although there are no differences in the magnitude and temporal pattern of the physiological, symptomatic and counterregulatory hormonal responses to hypoglycemia induced by regular human insulin or rapid-acting analogues (45,46).

Long-acting insulin analogues reduce the incidence of hypoglycemia and nocturnal hypoglycemia when compared to

intermediate-acting insulin as the basal insulin (10,47–51). Lifestyle factors and changes from usual self-management behaviours (e.g. eating less food, taking more insulin, increased physical activity) account for 85% of hypoglycemic episodes (52,53). Adding bedtime snacks may be helpful to prevent nocturnal hypoglycemia among those taking NPH as the basal insulin or in those individuals at high risk of severe hypoglycemia (regardless of insulin type), particularly when bedtime plasma glucose (PG) levels are <7.0 mmol/L (54,55).

Knowledge of the acute effects of exercise is essential. Low- to moderate-intensity exercise lowers BG levels both during and after the activity, increasing the risk of a hypoglycemic episode. These effects on BG levels can be modified by altering diet, insulin, and the type and timing of physical activity. In contrast, high-intensity exercise raises BG levels during and immediately after the event but may result in hypoglycemia hours later. SMBG before, during and after exercise is important for establishing response to exercise and guiding the appropriate management of exercise. If ketosis is present, exercise should not be performed as metabolic deterioration can occur (56) (see Physical Activity and Diabetes chapter, p. S54).

Hypoglycemia prevention and treatment is discussed in more detail in the Hypoglycemia chapter, p. S104; however, it is the limiting factor in most treatment strategies for type 1 diabetes. Increased education, monitoring of blood glucose, changing insulins and insulin routines, and the use of new diabetes technologies may be required (57,58). An educational program for people with impaired hypoglycemia awareness in which participants were randomized to either CSII or basal-bolus injection therapy and to either SMBG or real-time CGM showed that severe hypoglycemia and hypoglycemia awareness were improved to a similar degree regardless of the insulin delivery method or monitoring method used, although treatment satisfaction was higher with CSII compared with basal-bolus injection therapy (59).

Continuous Subcutaneous Insulin Infusion Therapy

CSII or insulin pump therapy is a safe and effective method of intensive insulin delivery in type 1 diabetes. Both CSII and basal-bolus injection therapy are considered the standard of care for adults with type 1 diabetes. While many people with type 1 diabetes are on CSII due to personal preference, there are some medical indications for CSII therapy. In particular, CSII can be considered in people with type 1 diabetes who do not reach glycemic targets despite optimized basal-bolus injection therapy, as well as in the following individuals: those with significant glucose variability; frequent severe hypoglycemia and/or hypoglycemia unawareness; significant "dawn phenomenon" with rise of blood glucose early in the morning; very low insulin requirements; adequate glycemic control but suboptimal treatment satisfaction and quality of life or women contemplating pregnancy (60–63).

It is important to select the appropriate individual for pump therapy. Appropriate candidates should be motivated individuals, currently on optimized basal-bolus injection therapy, who are willing to frequently monitor BG, understand sick-day management and attend follow-up visits as required by the health-care team (62,63). The health-care team should ideally be interprofessional and include a diabetes educator and a physician/nurse practitioner with special interest and expertise in CSII therapy. Comprehensive preparation, initiation and follow up should be provided by the team and are critical for the success of CSII. The health-care team should periodically re-evaluate whether continued pump therapy is appropriate for the individual (62).

Rapid-acting insulin analogues have replaced short-acting insulin in CSII therapy for several reasons, including their demonstrated safety, efficacy and more physiologic and rapid action (64). Although not recommended in Canada, insulin Humulin R® is still indicated for use in CSII while insulin Novolin Toronto® is not. The 3 rapid-acting insulin analogues approved for CSII are insulin lispro, aspart and glulisine. Faster-acting insulin aspart is not yet approved in Canada for use in CSII. Among people using CSII, insulin lispro has been demonstrated to provide similar (65) or superior (66,67) A1C lowering, overall improvement in postprandial hyperglycemia (66,67), and no increase in hypoglycemia (66,67) when compared to short-acting insulin. Insulin aspart provides a similar effect on A1C and hypoglycemia risk as short-acting insulin or lispro (65). Insulin glulisine has a similar effect on A1C when compared to aspart (68,69) and lispro (68); however, the rate of symptomatic hypoglycemia was higher with use of glulisine in 1 crossover study (68).

Clinical trial data on the rate of catheter occlusions among users of the 3 rapid-acting insulins do not show any consistent differences (68,69). In vitro studies have demonstrated some differences in product stability and catheter occlusions (64). Insulin glulisine is indicated to be changed at least every 48 hours in the infusion set and reservoir; aspart and lispro are to be changed according to the pump manufacturer's recommendations.

A1C benefit of CSII therapy

CSII treatment has gone through many advances since it was first introduced. Many studies using CSII have been limited by small numbers of participants, short duration and the inability to adequately blind participants. Interpretation of meta-analyses is difficult as some included trials with short-acting insulin in the CSII arm (70,71), and another included trials with only NPH-based basal-bolus injection therapy as the comparator (72). The most relevant meta-analyses included trials using rapid-acting insulin analogues in the CSII arms and NPH- or glargine-based basal-bolus injection therapy as the comparators (73–75). Trials using other basal analogues as the comparator were not identified. Use of CSII was shown to reduce A1C by 0.19% to 0.3% in adults (73,75) or in participants with a mean age over 10 years (74). An observational study of real-life outcomes using CSII therapy demonstrated that those who had a pre-CSII A1C of >9.0% had the greatest improvement in A1C after CSII initiation; people with a pre-CSII A1C of ≤7.0% were likely to maintain their A1C in the same range on CSII; and for all groups, A1C values slowly increased with time but remained below the pre-CSII levels (76).

A major advancement in CSII treatment has been the addition of continuous glucose monitoring systems (CGM) and sensor-augmented pumps (SAP) which is the use of CSII plus CGM. In people with type 1 diabetes with suboptimal control on basal-bolus injection therapy and SMBG, the introduction of CSII and CGM at the same time offers a more substantial A1C benefit over continuation of basal-bolus injection therapy with SMBG. In 2 major trials, participants suboptimally controlled on basal-bolus injection therapy were randomized to either continue basal-bolus injection therapy or to start SAP. One small trial in adults showed a mean difference in change in A1C of -1.21% in favour of the SAP arm (77), without an increase in hypoglycemia. In a larger trial of children and adults, end-of-trial mean difference in change in A1C was -0.6% in favour of the SAP arm, in all participants and in adults specifically (78) without an increase in hypoglycemia. Duration of sensor use was associated with the greatest decline in A1C in 1 trial (78) but not the other (77).

Further enhancement of sensor-augmented CSII technology has been the low glucose suspend function in which insulin delivery is stopped for a defined period of time if a critically low glucose threshold is detected on the CGM. To date, only 2 major trials have been published regarding this technology (79,80). Hypoglycemia benefit, rather than the change in A1C, was the primary focus of

these trials and no conclusions can be made about A1C benefit of SAP with low glucose suspend.

CSII and hypoglycemia

The benefit of CSII with regard to hypoglycemia has been difficult to evaluate given that many studies were of short duration, had small numbers and rates of severe hypoglycemia were generally low. Severe hypoglycemia has not been significantly different between users of CSII and basal-bolus injection therapy, based on meta-analyses which included only rapid-acting insulin analogues in the CSII arms (73–75). However, in a meta-analysis of trials of participants with a high baseline rate of severe hypoglycemia (>10 episodes per 100 patient-years while on basal-bolus injection therapy), the use of CSII was associated with a reduction of severe hypoglycemia (81) when compared to basal-bolus injection regimens using older nonanalogue basal insulins.

Nonsevere hypoglycemia has been inconsistently defined and reported but, overall, CSII does not appear to reduce the frequency of nonsevere hypoglycemia. No differences have been found between CSII and basal-bolus injection therapy for nocturnal hypoglycemia (75). No consistent conclusions could be drawn regarding nonsevere hypoglycemia in 2 meta-analyses (73,74). In 1 meta-analysis, minor hypoglycemia, calculated as the mean number of mild episodes per patient per week, was found to be nonsignificantly lower in users of CSII in crossover trials of adolescents and adults (75).

When CSII has been introduced together with CGM (SAP), A1C has been consistently lowered without increasing the rate of hypoglycemia (77,78). Time spent in hypoglycemia and severe hypoglycemia was not consistently different (77,78) but hypoglycemia fear improved more in adults randomized to SAP compared to those randomized to continuation of basal-bolus injection therapy (82).

One large randomized controlled trial in adults compared the use of SAP with and without the low glucose suspend feature (80). Participants were randomized if they had demonstrated nocturnal hypoglycemia and high sensor compliance during the run-in phase. SAP with low glucose suspend led to a reduction in nocturnal hypoglycemia with no increase in A1C or ketoacidosis (80). In another trial of adults and children with hypoglycemia unawareness, the use of SAP with low glucose suspend, compared to the use of CSII and SMBG, was shown to reduce the rate of moderate and severe hypoglycemia (79) although this outcome lost significance when outliers were excluded. Overall, the use of SAP with low glucose suspend is promising for nocturnal hypoglycemia and hypoglycemia unawareness but more studies are needed.

CSII and quality of life

Several studies have demonstrated improved quality of life (QOL) or improved treatment satisfaction (TS) with CSII therapy whether due to improved glycemic control, flexibility in insulin administration, patient selection and/or motivation. The various studies used different measurement tools or older insulin regimens (70). Compared with basal-bolus injection therapy plus SMBG, CSII plus SMBG has been associated with improved diabetes-specific QOL (73) and TS (70). When compared with basal-bolus injection therapy plus SMBG, CSII plus CGM (SAP) has been associated with improved diabetes-specific health-related QOL (82), diabetes-related distress (77), TS (77,82), perceived frequency of hyperglycemia (77), fear of hypoglycemia (82), and general health and social functioning (77). Compared with CSII plus SMBG, SAP has been associated with improved TS (83,84), lower perceived frequency of hypoglycemia (83), less worry about hypoglycemia (83), and better treatment convenience and flexibility (84).

Data regarding long-term diabetes complications, adverse events, cost and mortality among users of CSII have been limited (70). An observational study of a large population-based Swedish national diabetes registry revealed lower cardiovascular (CV) mortality in users of CSII compared with users of basal-bolus injection therapy (85).

Continuous Glucose Monitoring

Adults with type 1 diabetes derive an A1C benefit from CGM, when compared to SMBG, regardless of the baseline level of A1C or the type of intensive insulin therapy and delivery. CGM may be done in a blinded manner ("professional" CGM), so that results are not immediately visible to the person with diabetes, or more commonly, in "real-time" where people with diabetes can immediately see values and take action if necessary. The discussion here refers to the studies using "real-time" CGM. The recommendations and findings presented here are consistent with those of the Endocrine Society Clinical Practice Guideline on this topic, which recommended the use of real-time CGM for adult patients with either A1C above target or who are well-controlled (at A1C target), provided that the devices are worn nearly daily (63).

In people with diabetes with a baseline A1C >7.0%, the use of CGM compared to SMBG results in an A1C reduction of approximately 0.4% to 0.6%. This A1C change has been demonstrated in adults using CSII (86), adults and children using either basal-bolus injection therapy or CSII (87), adults and children using CSII (88,89) and adults using basal-bolus injection therapy (90,91). In contrast, two trials in adults and children using CSII showed no A1C difference between users of CGM and SMBG (92,93) except in those who wore the sensor at least 70% of the time in 1 of the studies (92). Even with a baseline A1C <7.0%, in adults and children using basal-bolus injection therapy or CSII, the A1C benefit of CGM has been -0.27 to -0.34% (94,95). Meta-analyses of trials regardless of the baseline A1C have estimated the overall between-group change from baseline A1C to be approximately -0.2% to -0.3% in favour of CGM (73,96,97), and in adults specifically the A1C benefit has been -0.38% (73). The greatest A1C benefit has been demonstrated with the greatest duration of sensor use (97,73) and with the highest A1C at baseline (97).

The A1C benefits of CGM do not appear to be associated with excess hypoglycemia. Time spent in hypoglycemia was either lower in the CGM group (88,90,93,95) or was not significantly different between groups (86,92,94). Severe hypoglycemia was uncommon in these studies, and 1 study showed an increase in severe hypoglycemia with CGM (93) but this was not consistent in other trials.

People with type 1 diabetes with an A1C <7.0% may find that the use of CGM allows them to maintain their A1C at target without more hypoglycemia. One trial in patients with an A1C <7.5% (mean A1C at randomization, 6.9%) demonstrated shorter time in hypoglycemia with reduction of A1C in the CGM group compared with the SMBG group (95). In another trial of subjects with an A1C <7% (mean baseline A1C 6.4%-6.5%), while time in hypoglycemia was not significantly reduced, combined A1C and hypoglycemia endpoints favoured the CGM group, including the reduction of A1C without a substantial increase of hypoglycemia, and the reduction of hypoglycemia without worsening of A1C by 0.3% or more (94).

When CGM is introduced together with CSII therapy (SAP), the A1C benefit has been larger when compared to maintenance of basal-bolus injection therapy plus SMBG, without an increase of hypoglycemia (73,77,78,96).

Among adults with impaired hypoglycemia awareness, CGM has been shown to reduce severe hypoglycemia and increase time in normoglycemia in 1 trial of participants with high compliance of sensor use (98). In contrast, in another trial using a standardized

education program, hypoglycemia awareness and severe hypoglycemia improved to a similar degree in participants randomized to CGM or SMBG, but sensor compliance was not high in this trial (59). This technology is, therefore, promising in this group but more studies are required.

Adjunctive Therapy for Glycemic Control

As the incidence of obesity and overweight increases in the population, including in those with type 1 diabetes, there is growing interest in the potential use of noninsulin antihyperglycemic agents that improve insulin sensitivity or work independently of insulin and may provide additional glucose-lowering benefits without increasing hypoglycemia risk (99,100). In several studies, the use of metformin in type 1 diabetes reduces insulin requirements and may lead to modest weight loss (101) without increased hypoglycemia. In the clinical trial setting, metformin does not result in improved A1C, fasting glucose or triglyceride (TG) levels (101) and changes do not persist long term (102).

Several small trials using SGLT2 inhibitors in type 1 diabetes demonstrated a reduction in mean glucose levels (103) and A1C (104,105). An increase in diabetic ketoacidosis (DKA) was also seen, which may be as high as 6% of participants in an 18-week study (105). DKA may have been precipitated by other factors, and several presented with glucose <13.9 mmol/L (106). A1C reduction and increased risk of ketosis was found when this class was added to insulin and liraglutide (107). Although early data are cautiously positive for the use of this class in type 1 diabetes, better understanding of the risk for euglycemic DKA is needed (99,100,108) and SGLT2 inhibitors do not have an indication for use in type 1 diabetes (see Hyperglycemic Emergencies in Adults chapter, p. S109).

GLP-1 receptor agonists have been studied as add-on therapy to insulin in type 1 diabetes (109–111). Addition of liraglutide allowed a reduction in insulin dose and weight (110,111) without consistent results on hypoglycemia risk or A1C reduction in normal weight (112) or overweight (113) people with type 1 diabetes. Liraglutide may be associated with hyperglycemia and ketosis with the 1.8 mg dose in some studies (110,111) but not others (109). There is no current indication for use of liraglutide in type 1 diabetes. Studies of other GLP-1 receptor agonists in type 1 diabetes have been limited (109).

RECOMMENDATIONS

1. In adults with type 1 diabetes, basal-bolus injection therapy or CSII as part of an intensive diabetes management regimen should be used to achieve glycemic targets [Grade A, Level 1A (2)].

2. In adults with type 1 diabetes using basal-bolus injection therapy or CSII, rapid-acting insulin analogues should be used in place of regular insulin to improve A1C and to minimize the risk of hypoglycemia [Grade B, Level 2 (30,32) for basal-bolus injection therapy; Grade B, Level 2 (66,67) for lispro in CSII; Grade B, Level 2 (65) for aspart in CSII; Grade D, Consensus, for glulisine in CSII] and to achieve postprandial BG targets [Grade B, Level 2 (32) for basal-bolus injection therapy; Grade B, Level 2 (66) for CSII].

3. In adults with type 1 diabetes on basal-bolus injection therapy:
   a. A long-acting insulin analogue may be used in place of NPH to reduce the risk of hypoglycemia [Grade B, Level 2 for detemir (7,50); Grade B, Level 2 for glargine U-100 (4,5,51); Grade D, Consensus for degludec and glargine U-300], including nocturnal hypoglycemia [Grade B, Level 2 (7) for detemir; Grade B, Level 2 (4) for glargine U-100; Grade D, Consensus for degludec, and glargine U-300].
   b. Degludec may be used instead of detemir or glargine U-100 to reduce nocturnal hypoglycemia [Grade B, Level 2 (24) compared to detemir; Grade C, Level 3 (20) compared to glargine U-100].

4. All individuals with type 1 diabetes and their support persons should be counselled about the risk and prevention of hypoglycemia, and risk factors for severe hypoglycemia should be identified and addressed [Grade D, Consensus].

5. In adults with type 1 diabetes and hypoglycemia unawareness, the following nonpharmacological strategies may be used to reduce the risk of hypoglycemia:
   a. A standardized education program targeting rigorous avoidance of hypoglycemia while maintaining overall glycemic control [Grade A, Level 1A (59)]
   b. Increased frequency of SMBG, including periodic assessment during sleeping hours [Grade D, Consensus]
   c. CGM with high sensor adherence in those using CSII [Grade C, Level 3 (98)]
   d. Less stringent glycemic targets with avoidance of hypoglycemia for up to 3 months [Grade C, Level 3 (15,16)].

6. In adults with type 1 diabetes on basal-bolus injection therapy who are not achieving glycemic targets, CSII with or without CGM may be used to improve A1C [Grade B, Level 2 (77,78) with CGM; Grade B, Level 2 (73–75) without CGM].

7. In adults with type 1 diabetes,
   a. CSII may be used instead of basal-bolus injection therapy to improve treatment satisfaction [Grade C, Level 3 (70)]
   b. CSII plus CGM may be used instead of basal-bolus injection therapy or CSII with SMBG to improve quality of life, treatment satisfaction and other health-quality-related outcomes [Grade B, Level 2 (77,84)].

8. Adults with type 1 diabetes on CSII should undergo periodic evaluation to determine whether continued CSII is appropriate [Grade D, Consensus].

9. In adults with type 1 diabetes and an A1C at or above target, regardless of insulin delivery method used, CGM with high sensor adherence may be used to improve or maintain A1C [Grade B, Level 2 (97)] without increasing hypoglycemia [Grade C, Level 3 (97)].

10. In adults with type 1 diabetes experiencing nocturnal hypoglycemia and using CSII and CGM, SAP with low glucose suspend may be chosen over SAP alone to reduce nocturnal hypoglycemia [Grade B, Level 2 (80)].

Abbreviations:
A1C, glycated hemoglobin; *BG*, blood glucose; *CGM*, continuous glucose monitoring; *CSII*, continuous subcutaneous insulin infusion; *DHC*, diabetes health care; *QOL*, quality of life; *RAIA*, rapid-acting insulin analogues; *SAP*, sensor augmented pump, *SMBG*, self-monitoring of blood glucose. *TS*, treatment satisfaction.

Other Relevant Guidelines

Targets for Glycemic Control, p. S42
Monitoring Glycemic Control, p. S47
Physical Activity and Diabetes, p. S54
Pharmacologic Glycemic Management of Type 2 Diabetes in Adults, p. S88
Hypoglycemia, p. S104
In-Hospital Management of Diabetes, p. S115
Management of Acute Coronary Syndromes, p. S190
Type 1 Diabetes in Children and Adolescents, p. S234
Type 2 Diabetes in Children and Adolescents, p. S247
Diabetes and Pregnancy, p. S255
Diabetes in Older People, p. S283

Relevant Appendix

Appendix 6. Types of Insulin

Author Disclosures

Dr. Adams reports personal fees from Novo Nordisk, Sanofi, Merck, AstraZeneca, Medtronic, Boehringer Ingelheim, Janssen, and Valeant,

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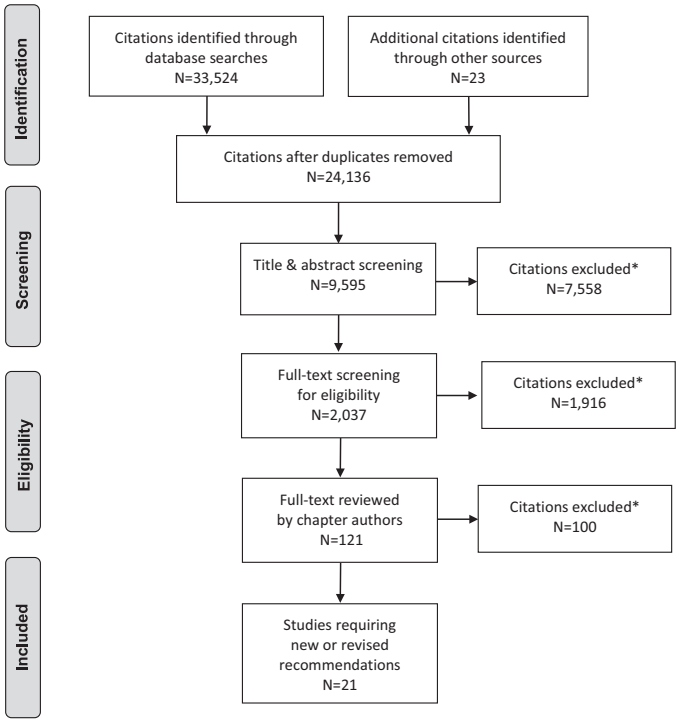
Literature Review Flow Diagram for Chapter 12: Glycemic Management in Adults with Type 1 Diabetes



*Excluded based on: population, intervention/exposure, comparator/control or study design.

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