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CLINICAL GUIDELINE

Treatment of Type 1 Diabetes: Synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes

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Description: The American Diabetes Association (ADA) annually updates Standards of Medical Care in Diabetes to provide clinicians, patients, researchers, payers, and other interested parties with evidence-based recommendations for the diagnosis and management of patients with diabetes.

Methods: For the 2017 Standards of Care, the ADA Professional Practice Committee did MEDLINE searches from 1 January 2016 to November 2016 to add, clarify, or revise recommendations on the basis of new evidence. The committee rated the recommendations as A, B, or C, depending on the quality of evidence, or E for expert consensus or clinical experience. The Standards of Care were reviewed and approved by the Executive Committee of the ADA Board of Directors, which includes health care professionals, scientists, and laypersons. Feedback from the larger clinical community informed revisions.

Recommendation: This synopsis focuses on recommendations from the 2017 Standards of Care about monitoring and pharmacologic approaches to glycemic management for type 1 diabetes.

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The American Diabetes Association (ADA) first released its practice guidelines for health professionals in 1989. The Standards of Medical Care in Diabetes have since provided an extensive set of evidence-based recommendations that are updated annually for the diagnosis and management of patients with diabetes. The 2017 Standards of Care cover all aspects of patient care (1); this guideline synopsis focuses on monitoring and pharmacologic approaches for patients with type 1 diabetes.

Guideline Development and Evidence Grading

To develop the 2017 Standards of Care, the ADA Professional Practice Committee systematically searched MEDLINE from 1 January 2016 (date of previous search) to November 2016. Recommendations were revised on the basis of new evidence or, in some cases, to clarify prior recommendations or match the strength of the wording to the strength of the evidence. The Professional Practice Committee comprises physicians, including both adult and pediatric endocrinologists; diabetes educators; registered dietitians; epidemiologists; public health experts; and others who have expertise in areas relevant to the Standards of Care. This group also solicited feedback from the larger clinical community.

The recommendations are rated as A, B, C, or E depending on the quality of evidence. Those with an A rating are based on large, well-designed, multicenter clinical trials or well-done meta-analyses. Recommendations with lower-quality evidence may be equally important and are based on well-conducted cohort studies (B rating) or uncontrolled studies (C rating). Those assigned an E rating are consensus recommendations for which no evidence has been derived from clinical trials, in which clinical trials may be impractical, or that have conflicting evidence.

The ADA funds development of the Standards of Care from its general revenues and has no industry support or involvement. Details about the methodology, information on committee members and their conflict-of-interest disclosures, and the complete Standards of Care can be downloaded at http://professional.diabetes.org/annals.

Monitoring Glycemia in Type 1 Diabetes

Self-Monitoring Blood Glucose: Recommendations

Most patients receiving intensive insulin regimens (multiple daily injections [MDI] or continuous subcutaneous insulin infusion [CSII] therapy using an insulin pump) should self-monitor blood glucose before meals and snacks, at bedtime, occasionally after meals, when they suspect low blood glucose, after treating low blood glucose until they are normoglycemic, and before exercise and critical tasks like driving (B rating). When prescribed self-monitoring of blood glucose (SMBG), patients must receive ongoing instruction and regular evaluation of technique, results, and ability to use SMBG data to adjust therapy (E rating).

Major clinical trials of glycemic control in type 1 diabetes have included SMBG as an integral part of the multifactorial interventions (2), and in both clinical trials and observational studies, frequent SMBG is associated with lower hemoglobin A_{1c} (HbA_{1c}) levels (3). Accuracy depends on the instrument and user, so providers must evaluate each patient's technique, both initially and at regular intervals thereafter. Many patients with type 1

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diabetes require testing 6 to 10 (or more) times daily, although individual needs may vary. The frequency of SMBG should be reevaluated at each routine visit to avoid overuse (4–6).

Continuous Glucose Monitoring: Recommendations

When used properly, continuous glucose monitoring (CGM), in conjunction with intensive insulin regimens, is a useful tool to lower HbA_{1c} levels in selected adults (aged ≥25 years) with type 1 diabetes (A rating). It may benefit those with hypoglycemia unawareness or frequent hypoglycemic episodes (C rating). When prescribing CGM, a clinician must provide robust diabetes education, training, and support for optimal CGM implementation and ongoing use (E rating). Patients who have been using CGM successfully should have continued access after they turn 65 years of age (E rating).

Continuous glucose monitoring measures interstitial glucose (which is correlated with plasma glucose) and includes sophisticated alarms that the user can individualize to identify hypoglycemic and hyperglycemic excursions. Continuous glucose monitors require regular calibration with SMBG, and with most CGM devices, treatment decisions are still based on SMBG. The greatest predictor of HbA_{1c} lowering with CGM for all age groups is frequency of sensor use (7, 8). A registry study of 17 317 patients confirmed that more frequent CGM use is associated with lower HbA_{1c} levels (9). Small, short-term, randomized controlled trials in adults and children with baseline HbA_{1c} levels less than 7.0% to 7.5% have also shown less frequent hypoglycemia and an increased likelihood of maintaining HbA_{1c} levels less than 7% (10–12). Because of variable adherence, optimal CGM requires an assessment of individual readiness to use the technology as well as initial and ongoing education and support (9, 13).

HbA_{1c}: Recommendations

Hemoglobin A_{1c} should be tested at least twice per year in patients who are meeting treatment goals (and who have stable glycemic control) (E rating) and quarterly in those whose therapy has changed or who are not meeting glycemic goals (E rating). Point-of-care testing for HbA_{1c} allows more timely treatment changes (E rating).

Hemoglobin A_{1c} reflects average glycemia over approximately 3 months and has strong predictive value for diabetes complications (14, 15). Measurement every 3 months in patients with type 1 diabetes determines whether glycemic targets have been reached and maintained. It may also confirm the accuracy of the patient's meter (or their reported CGM or SMBG results) and adequacy of the testing schedule. Hemoglobin A_{1c} does not measure glycemic variability or hypoglycemia. In type 1 diabetes, glycemic control is best evaluated using the results of CGM, SMBG, and HbA_{1c} testing. Avoiding hypoglycemia should always take precedence over achieving HbA_{1c} targets. The HbA_{1c} level is an indirect measure of glycemia and may not accurately measure average glycemia in persons with increased turnover of red blood cells. This possibility must be considered when the HbA_{1c} level does not correlate to the patient's CGM- or SMBG-measured glucose levels. Other measures of average glycemia, such as fructosamine and 1,5-anhydroglucitol levels, might be helpful, but their prognostic significance is not as clear.

Glycemic Goals: Recommendations

A reasonable HbA_{1c} goal for many nonpregnant adults is less than 7% (A rating). Providers might suggest more stringent HbA_{1c} goals (such as <6.5%) for selected individuals if this can be achieved without clinically significant hypoglycemia or other adverse effects. Appropriate patients might include those with short duration of diabetes, long life expectancy, or no clinically significant cardiovascular disease (C rating). Less stringent HbA_{1c} goals (such as <8%) may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or macrovascular complications, extensive comorbid conditions, or long-standing diabetes, in whom the goal is difficult to achieve despite diabetes self-management education, appropriate glucose monitoring, and intensive insulin therapy (B rating).

The DCCT (Diabetes Control and Complications Trial) (2), a prospective randomized controlled clinical trial of intensive versus standard glycemic control in patients with type 1 diabetes, showed that near-normal glycemic control is associated with decreased rates of development and progression of microvascular (retinopathy [16] and diabetic kidney disease) and neuropathic complications. Follow-up of the DCCT cohorts in the EDIC (Epidemiology of Diabetes Interventions and Complications) study (17) found persistence of these microvascular benefits, despite the glycemic separation between treatment groups diminishing and disappearing during follow-up. Results from the DCCT showed a lower risk for cardiovascular events with intensive therapy, although that finding was not statistically significant. In the 9-year post-DCCT follow-up of the EDIC cohort, participants previously assigned to intensive therapy had a 57% reduction in risk for nonfatal myocardial infarction, stroke, or cardiovascular death compared with those previously assigned to standard therapy (18). The benefit of intensive glycemic control in this cohort has been shown to persist for several decades (19) and to be associated with a modest reduction in all-cause mortality (20).

Pharmacologic Therapy for Type 1 Diabetes: Recommendations

Most patients with type 1 diabetes should be treated with MDI of both prandial and basal insulin or with CSII (A rating). Most should use rapid-acting insulin analogues to reduce hypoglycemia risk (A rating). Consider educating persons with type 1 diabetes on matching prandial insulin doses to carbohydrate intake, premeal blood glucose levels, and anticipated physical activity (E rating). Patients who have been using CSII

successfully should have continued access after they turn 65 years of age (E rating).

Insulin Therapy

Insulin is the basis of therapy for type 1 diabetes (Table 1) (21–23). The starting total daily insulin dose is typically weight-based, ranging from 0.4 to 1.0 units/kg of body weight. A typical total daily starting dose in patients who are metabolically stable is 0.5 units/kg. Higher weight-based starting doses may be needed for patients who present with diabetic ketoacidosis. Higher insulin doses are often required during puberty. The ADA Position Statement on type 1 diabetes management through the life span provides a thorough overview of type 1 diabetes treatment and associated recommendations (24).

Education about matching prandial insulin dosing to carbohydrate intake, premeal glucose levels, and anticipated physical activity should be considered, and persons who have mastered carbohydrate counting should be educated on fat and protein gram estimation (25–27). Although most studies of MDI versus CSII have been small and of short duration, a systematic review and meta-analysis concluded that the 2 forms of intensive insulin therapy differed slightly in HbA_{1c} levels (combined mean between-group difference favoring CSII, −0.30 percentage point [95% CI, −0.58 to −0.02 percentage point]) and severe hypoglycemia rates in children and adults (28). Intensive management using CSII and CGM should be encouraged in those with active patient and family participation (29–31). A hybrid closed-loop insulin pump and CGM system (MiniMed 670G Insulin Pump System [Medtronic]) than can automatically adjust basal insulin rates on the basis of blood glucose values is now available in the United States, and more are expected to be approved in the next few years.

The DCCT demonstrated that intensive therapy with MDI or CSII delivered by a multidisciplinary team improved glucose control and resulted in better long-term outcomes (2, 18, 32). However, despite better microvascular, macrovascular, and all-cause mortality outcomes, intensive therapy with short- and intermediate-acting human insulin was associated with a high rate of severe hypoglycemia (61 episodes per 100 patient-years of therapy). Rapid-acting and long-acting insulin analogues developed since the DCCT are associated with less hypoglycemia in type 1 diabetes and match the HbA_{1c} improvements obtained with human insulins (33, 34).

The ideal time to administer premeal insulin varies with the type of insulin used (such as regular, rapid-acting analogue, and inhaled), measured blood glucose level, timing of meals, and carbohydrate consumption. Therefore, the timing of premeal insulin administration should be individualized.

Rapid-acting inhaled insulin dosed before meals in patients with type 1 diabetes was shown to be noninferior to aspart insulin with respect to HbA_{1c} lowering. Less hypoglycemia was seen with inhaled insulin therapy (35). Inhaled insulin cartridges are available only in 4-, 8-, and 12-unit doses, so persons with type 1 diabetes may have limited ability to fine-tune premeal insulin doses when using this approach.

Other Treatments

Although insulin is clearly the mainstay of treatment for patients with type 1 diabetes, many other treatments are being used or investigated. Pramlintide is an injectable amylin analogue that is indicated as an adjunct to mealtime insulin for patients with type 1 diabetes who have not achieved blood glucose goals after optimizing insulin therapy. Pramlintide delays gastric emptying, blunts pancreatic secretion of glucagon, and enhances satiety. If pramlintide is used, prandial insulin dosing should be reduced to minimize the risk for severe hypoglycemia.

Pancreas transplantation has been shown to normalize blood glucose control in type 1 diabetes but requires lifelong immunosuppression and thus is generally reserved for patients who are also having renal transplantation or those with recurrent ketoacidosis or severe hypoglycemia despite intensive glycemic management. Islet transplantation remains investigational.

Investigational Agents

Many agents generally used for type 2 diabetes (not currently approved by the U.S. Food and Drug Administration for type 1 diabetes) are being studied. Metformin, when added to insulin therapy, was not found to lower HbA_{1c} levels in patients with poorly controlled type 1 diabetes (absolute HbA_{1c} reduction, 0.11 percentage point; $P = 0.42$) but did reduce insulin requirements (reduction, 6.6 units/d; $P < 0.001$) and led to small reductions in weight and total and low-density lipoprotein cholesterol (36). Glucagon-like peptide-1–receptor agonists and dipeptidyl peptidase-4 inhibitors are also being studied in patients with type 1 diabetes. The glucagon-like peptide-1–receptor agonist liraglutide showed benefit in patients with type 1 diabetes over a 52-week period but was associated with increased adverse events. The trial included 1398 adults with type 1 diabetes who were randomly assigned to

Table 1. Pharmacokinetic Properties of Insulin Products*

Insulin Type	Onset	Peak	Duration
Rapid-acting insulins Insulin lispro Insulin aspart Insulin glulisine Inhaled human insulin	5–15 min	30–90 min	4–6 h
Short-acting insulin Regular human insulin	30–60 min	2–3 h	8–10 h
Intermediate-acting insulin Neutral protamine Hagedorn	2–4 h	4–10 h	12–18 h
Long-acting insulin analogues			
Insulin detemir	1–2 h	None†	12–24 h
Insulin glargine (U-100)	2–4 h	None†	20–24 h
Insulin glargine (U-300)	6 h	None	>24 h
Insulin degludec	30–90 min	None	>24 h

* The time course of each insulin varies significantly between persons and in the same person on different days; therefore, the periods listed should be used as guidelines only.
† Both insulin detemir and insulin glargine (U-100) can produce a peak effect in some persons, especially at higher doses.

Table 2. Classification of Hypoglycemia*

Level	Glycemic Criteria	Description
Glucose alert value (level 1)	≤3.9 mmol/L (70 mg/dL)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	<3.0 mmol/L (54 mg/dL)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

* Reproduced with permission from Diabetes Care. 2017;40:155-7.

receive once-daily injections of liraglutide (1.8, 1.2, or 0.6 mg) or placebo added to insulin therapy. Hemoglobin A_{1c} levels improved by 0.34 to 0.54 percentage point from a mean baseline of 8.2% and improved significantly more with 1.8 or 1.2 mg of liraglutide than placebo. Body weight reduction was 2.2 to 4.9 kg greater with liraglutide than placebo. However, hypoglycemia rates increased by 20% to 30%, and hyperglycemia with ketosis was 2.2 times more likely at the higher 1.8-mg/d dosage (37). The sodium–glucose cotransporter-2 inhibitors provide insulin-independent glucose lowering by blocking glucose reabsorption in the proximal renal tubule. They also promote weight loss and lowering of blood pressure. In May 2015, the U.S. Food and Drug Administration issued a warning that sodium–glucose cotransporter-2 inhibitors may lead to ketoacidosis occurring in the absence of significant hyperglycemia, termed "euglycemic diabetic ketoacidosis." If patients develop symptoms of ketoacidosis, which may include dyspnea, nausea, vomiting, and abdominal pain, they should stop taking sodium–glucose cotransporter-2 inhibitors and seek medical attention immediately (38).

Hypoglycemia: Recommendations

Patients with type 1 diabetes should be asked about symptomatic and asymptomatic hypoglycemia at each encounter (C rating). Glucose (15 to 20 g) is the preferred treatment for conscious persons with hypoglycemia (glucose alert value of ≤3.9 mmol/L [70 mg/dL]), although any form of carbohydrate that contains glucose may be used. If SMBG shows continued hypoglycemia 15 minutes after treatment, it should be repeated. Once CGM or SMBG values return to normal, the person should consume a meal or snack to prevent recurrence (E rating). Glucagon should be prescribed for all patients at increased risk for clinically significant hypoglycemia, defined as blood glucose less than 3.0 mmol/L (54 mg/dL), so that it is available if needed. Glucagon administration is not limited to health care professionals (E rating); thus, caregivers, school personnel, and family members should know where the glucagon is stored and when and how to administer it. Insulin-treated patients with hypoglycemia unawareness or an episode of clinically significant hypoglycemia should be advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks. This should partially reverse hypoglycemia unawareness and reduce the risk for future episodes (A rating).

Hypoglycemia is the major limiting factor in the glycemic management of patients with type 1 diabetes. A classification scheme proposed by the International Hypoglycaemia Study Group is outlined in Table 2. Symptoms of hypoglycemia can include shakiness, irritability, confusion, tachycardia, and hunger. Patients with repeated episodes of hypoglycemia may develop hypoglycemia unawareness. Severe hypoglycemia can progress to loss of consciousness, seizure, coma, or death. Hypoglycemia is reversed by administration of rapid-acting glucose or glucagon. Clinically significant hypoglycemia can result in acute harm to the patient and others, especially if it causes falls or motor vehicle accidents. Prevention is critical for type 1 diabetes management. Self-monitoring of blood glucose and, for some patients, CGM are important tools to monitor glucose levels and prevent hypoglycemia. Patients should be educated about times when they may be at increased risk for hypoglycemia, such as while fasting for tests, with delayed meals, during or after exercise, and during sleep. Hypoglycemia episodes may be particularly dangerous while driving, and some patients may benefit from having a glucose meter and rapid-acting glucose treatment in the car if needed.

Glucagon is indicated for the treatment of hypoglycemia in patients unable or unwilling to consume carbohydrates by mouth. Those in close contact with a patient who has type 1 diabetes, such as family members, roommates, school personnel, child care providers, correctional institution staff, or coworkers, should be instructed on the safe use of glucagon kits in case of an emergency.

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