GREAT PLAINS DIABETES CENTER

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OBJECTIVES

- REVIEW DIABETES DIAGNOSTIC CRITERIA
- REVIEW GOALS FOR GLUCOSE CONTROL
- HIGHLIGHT WHEN NEW DIABETES MEDS ARE APPROPRIATE AND WHEN OLDER ONES MAY BE NEEDED
- REVIEW DIABETES TECHNOLOGIES INCLUDING INSULIN PUMPS AND CONTINOUS GLUCOSE MONITORS-WHO IS A CANDIDATE

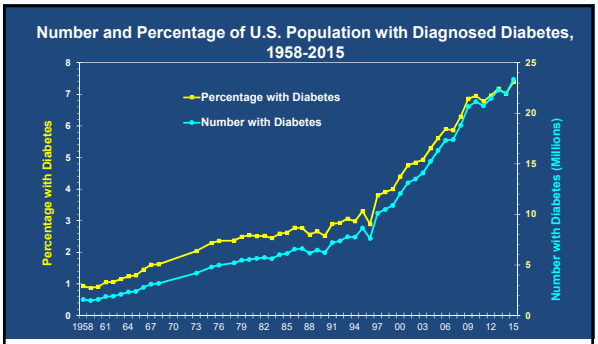
ADA 2015 Guidelines

Collaborative, Integrated Diabetes Management Team

Written diabetes management plan	Include patient, family, physician, healthcare team
Enable individuals to self-manage diabetes	Educate on problem-solving for all aspects of diabetes management *DSME at diagnosis and after*
Individualize treatment goals/plans	Consider: • Age • Physical activity • Eating patterns • Social situation • Cultural factors • Diabetes complications • Health priorities • Comorbidities

DSME=diabetes self-management education

American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S1-S93.



CDC's Division of Diabetes Translation. United States Diabetes Surveillance System available at http://www.cdc.gov/diabetes/data

DIABETES NUMBERS

- **Prevalence**: In 2015, 30.3 million Americans, or 9.4% of the population, had diabetes.
  - Approximately 1.25 million American children and adults have type 1 diabetes.
- **Undiagnosed**: Of the 30.3 million adults with diabetes, 23.1 million were diagnosed, and 7.2 million were undiagnosed.
- **Prevalence in Seniors**: The percentage of Americans age 65 and older remains high, at 25.2%, or 12.0 million seniors (diagnosed and undiagnosed).
- **New Cases**: 1.5 million Americans are diagnosed with diabetes every year.
- **Deaths**: Diabetes remains the 7th leading cause of death in the United States in 2015, with 79,535 death certificates listing it as the underlying cause of death, and a total of 252,806 death certificates listing diabetes as an underlying or contributing cause of death.

PREDIABETES NUMBERS

- Eighty-six million people aged 20 years and older
- 1 in 3 American adults
- The percentage of U.S. adults with prediabetes is similar for non-Hispanic whites (35%), non-Hispanic blacks (39%), and Hispanics (38%)
- Without weight loss and moderate physical activity, 15-30% of people with prediabetes will develop type 2 diabetes within 5 years

COST OF DIABETES

- *Updated March 22, 2018*
- $327 billion: Total costs of diagnosed diabetes in the United States in 2017
- $237 billion for direct medical costs
- $90 billion in reduced productivity
- After adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes were 2.3 times higher than what expenditures would be in the absence of diabetes.
- Difficult to measure cost in relation to quality of life

DIAGNOSTIC CRITERIA FOR DM AND PREDIABETES

	Fasting Glucose	Random BG	A1c	GTT
Normal	< 99 mg/dl		3.5-5.6%	
Prediabetes	100-125 mg/dl		5.7-6.4%	
Diabetes	> 126 mg/dl	≥ 200 mg/dl	>6.5%	
Gestational		50 gm non-fasting 1 hour ≥ 140 mg/dl		100 gm OGTT Fasting ≥ 95 mg/dl 1 hr ≥ 180 mg/dl 2 hr ≥ 155 mg/dl 3 hr ≥ 140 mg/dl

SCREENING RECOMMENDED

- All adults at 45, earlier if
  - BMI ≥ 25
  - First degree relative
  - Physical inactivity
  - High risk race/ethnicity
  - Women delivered > 9# baby or PCOS
  - HDL < 35
  - A1c > 5.7%
  - Hypertension
  - CVD
- Gestational Diabetes
  - Screen for undiagnosed DM at first prenatal visit based on DM risk criteria
  - Screen all women at 24-28 weeks for those not previously known to have diabetes
  - 6 to 12 weeks postpartum, rescreen for diabetes

CHILDREN AT RISK

- Screening to begin age 10 or puberty onset if
  - Weight is >120% ideal body weight
  - Plus any two risk factors
    - Family history of type 2 dm
    - Race/ethnicity (Native American, African American, Latino, Asian American, Pacific Islander
    - Signs of insulin resistance: acanthosis nigricans, hypertension, dyslipidemia, PCOS, small for gestational age
    - Maternal history of DM or GDM during gestation

Staging of Type 1 Diabetes

Table 2.1—Staging of type 1 diabetes (4,5)

	Stage 1	Stage 2	Stage 3
Stage	• Autoimmunity • Normoglycemia • Presymptomatic	• Autoimmunity • Dysglycemia • Presymptomatic	• New-onset hyperglycemia • Symptomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100–125 mg/dL (5.6–6.9 mmol/L) • 2-h PG 140–199 mg/dL (7.8–11.0 mmol/L) • A1C 5.7–6.4% (39–47 mmol/mol) or ≥10% increase in A1C	• Clinical symptoms • Diabetes by standard criteria

American Diabetes Association Standards of Medical Care in Diabetes.
Classification and diagnosis of diabetes. Diabetes Care 2017; 40 (Suppl. 1): S11-S24

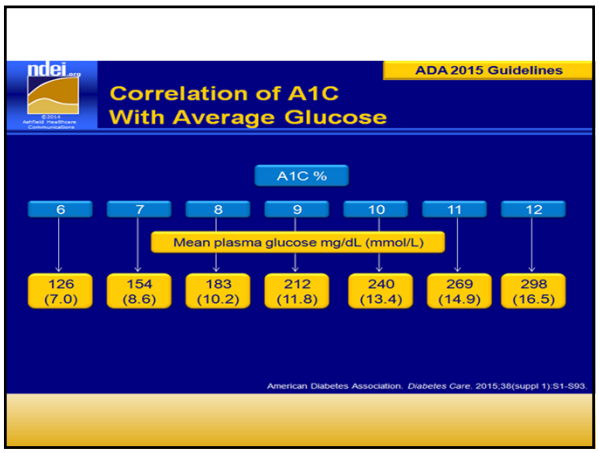
American Diabetes Association

ADA/AACE GLUCOSE GOALS

Glycemic control & A1c Target

	ADA	AACE
A1c (%)	<7	<6.5
Preprandial (mg/dl)	80-120	<110
Postprandial (mg/dl)	140-180	<140
Bedtime (mg/dl)	100-140	100-140

ADA: American Diabetes Association
AACE: American Association of Clinical Endocrinologists

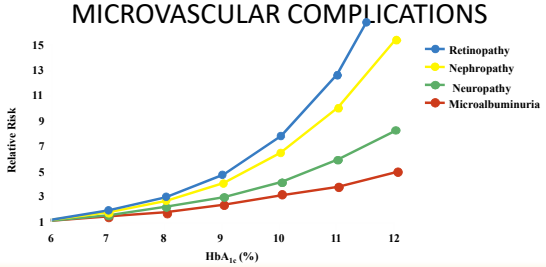


INDIVIDUALIZATION OF GOALS

- More stringent targets if able to achieve without significant hypoglycemia
- Less stringent targets for those with history of severe hypoglycemia, limited life expectancy, advanced micro or macrovascular disease, limited life expectancy
- Standard goal for children -7.5% or less.

DCCT

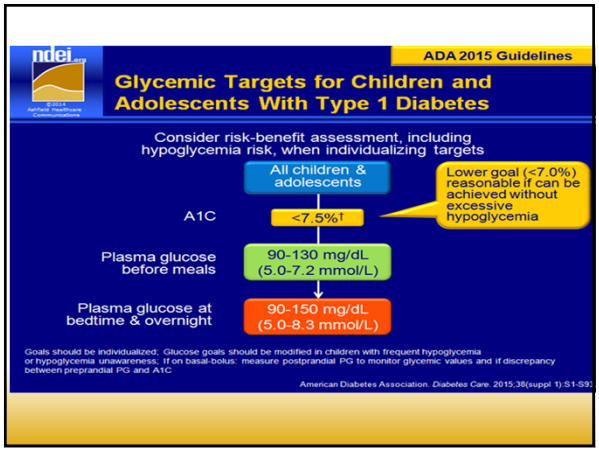
RELATIONSHIP OF HBA_{1C} TO RISK OF MICROVASCULAR COMPLICATIONS



Skyler. *Endocrinol Metab Clin.* 1996;25:243-254, with permission.

WHAT IS HIS A1C GOAL?

a. 8.0%
b. 8.5%
c. 7.5%
d. None of the above



Class	Mechanism	Advantages	Disadvantages	Cost
Biguanides	• Activates AMP-kinase • ↓ Hepatic glucose production	• Extensive experience • No hypoglycemia • Weight neutral • ? ↓ CVD	• Gastrointestinal • Lactic acidosis • B-12 deficiency • Contraindications-**kidney guidelines changing**	Low
SUs / Meglitinides	• Closes KATP channels • ↑ insulin secretion	• Extensive experience • ↓ Microvasc. risk	• Hypoglycemia • Weight gain • Low durability • ? Ischemic preconditioning	Low/ high
TZDs	• PPAR-γ activator • ↑ insulin sensitivity	• No hypoglycemia • Durability • ↓ TGs, ↑ HDL-C • ? ↓ CVD (pio)	• Weight gain • Edema / heart failure • Bone fractures • ? ↑ MI (rosi) • ? Bladder ca (pio)	High
SGLT2 inhibitor	• block the SGLT2 protein • Reabsorption of glucose in the proximal renal tubule • increased renal glucose excretion. • increase insulin sensitivity • decrease gluconeogenesis • improve insulin release	• No hypoglycemia • Weigh neutral or loss	• Bladder infections • Polyuria • Mycotic infections • Hypotension • Ketoacidosis	High

Table 1. Properties of anti-hyperglycemic agents (adapted)

Diabetes Care, Diabetologia. 19 April 2012

Class	Mechanism	Advantages	Disadvantages	Cost
DPP-4 inhibitors	• Inhibits DPP-4 • Increases GLP-1, GIP	• No hypoglycemia • Well tolerated	• Modest ↓ A1c • ? Pancreatitis • Urticaria	High
GLP-1 receptor agonists	• Activates GLP-1 R • ↑ Insulin, ↓ glucagon • ↓ gastric emptying • ↑ satiety	• Weight loss • No hypoglycemia • ? Beta cell mass • ? CV protection	• GI • ? Pancreatitis • Medullary ca • Injectable	High
α-GIs	• Inhibits α--glucosidase • Slows carbohydrate absorption	• No hypoglycemia • Nonsystemic • ↓ Post-prandial glucose • ? ↓ CVD events	• Gastrointestinal • Dosing frequency • Modest ↓ A1c	Mod
Bile acid sequestrants	• Bind bile acids • ↓ Hepatic glucose production	• No hypoglycemia • Nonsystemic • ↓ Post-prandial glucose • ↓ CVD events	• GI • Modest ↓ A1c • Dosing frequency	High
Dopamine-2 agonists	• Activates DA receptor • Modulates hypothalamic control of metabolism • ↑ insulin sensitivity	• No hypoglyemia • ? ↓ CVD events	• Modest ↓ A1c • Dizziness/syncope • Nausea • Fatigue	High

Table 1. Properties of anti-hyperglycemic agents (adapted) *Diabetes Care, Diabetologia.* 19 April 2012]

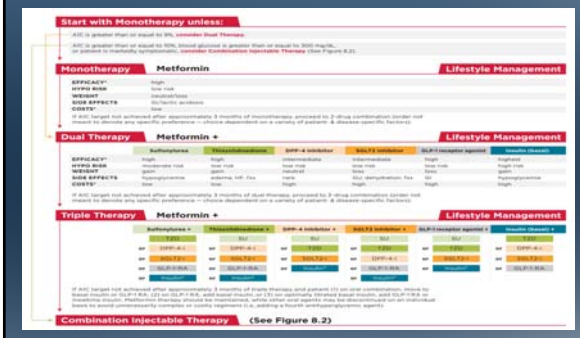
Class	Mechanism	Advantages	Disadvantages	Cost
Insulin	• Activates insulin receptor • ↑ peripheral glucose uptake	• Universally effective • Unlimited efficacy • ↓ Microvascular risk	• Hypoglycemia • Weight gain • ? Mitogenicity • Injectable • Training requirements • "Stigma"	Variable
Amylin mimetics	• Activates amylin receptor • ↓ glucagon • ↓ gastric emptying • ↑ satiety	• Weight loss • ↓ PPG	• GI • Modest ↓ A1c • Injectable • Hypo w/ insulin • Dosing frequency	High

Table 1. Properties of anti-hyperglycemic agents (adapted)

Antihyperglycemic Therapy in T2DM

American Diabetes Association Standards of Medical Care in Diabetes.
Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

American Diabetes Association



Combination Injectable Therapy in T2DM

American Diabetes Association Standards of Medical Care in Diabetes.
Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

American Diabetes Association

Insulin Therapy in T2DM

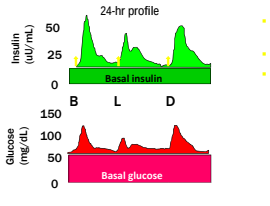
- The progressive nature of T2DM should be regularly & objectively explained to T2DM patients.
- Avoid using insulin as a threat, describing it as a failure or punishment.
- Give patients a self-titration algorithm.

American Diabetes Association Standards of Medical Care in Diabetes.
Approaches to glycemic treatment. Diabetes Care 2017; 40 (Suppl. 1): S64-S74

American Diabetes Association

MIMICKING NATURE WITH INSULIN THERAPY
BASAL/BOLUS CONCEPT

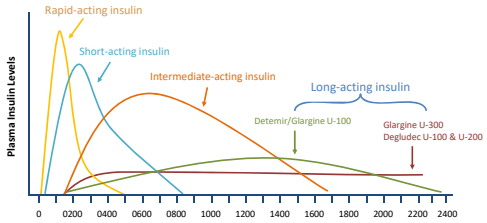
Physiologic Insulin Secretion



Adapted **with** permission from Bergenstal RM et al. In: DeGroot LJ, Jameson JL, eds. *Endocrinology*. 4th ed. Philadelphia, Pa: WB Saunders Co.; 2001:821

DS58

HELPING PATIENTS UNDERSTAND INSULIN REPLACEMENT



Lepore M et al. *Diabetes*. 2000;49:21 42-21 48. Howey DC et al. *Diabetes*. 1994;43:396-402. Plank J et al. *Diabetes Care*. 2005;28:1107-1112. Wittlin SD et al. *Insulin Therapy*. Marcel Dekker, Inc.;2002:73-85.

CURRENTLY AVAILABLE SHORT-ACTING PRANDIAL INSULINS

	Regular Insulin	Insulin Lispro U100 U200 (pen only)	Insulin Aspart	Insulin Glulisine
Insulin type	Human; short-acting	Analogue; rapid acting	Analogue; rapid acting	Analogue; rapid acting
Onset, hr	0.5-1	< 0.3-0.5	< 0.25	< 0.25
Peak, hr	2-3	0.5-2.5	0.5-1.0	1-1.5
Effective duration, hr	3-6	3-6.5	3-5	3-5
Injection: meal timing, min	-30 to -45	-15 to immediately after	-5 to -10	-15 to +20

American Diabetes Association. *Practical Insulin: A Handbook for Prescribing Providers*. 3rd ed. 2011:1-68.

Slide 26

JS58 SA word doc: I know this is the conventional slide but neither detemir nor U100 Lantus last 24 hours in most people – the Lantus people now admit this as they market U300 and we add a point below

Julia Sawyers, 6/6/2018

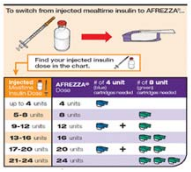
CURRENTLY AVAILABLE BASAL INSULINS

	NPH Insulin	Insulin Glargine U-100 & U-300	Insulin Detemir
Insulin Type	Human; intermediate-acting	Analogue; long-acting	Analogue; long-acting
Onset	2-4 hours	N/A	N/A
Peak	4-10 hours	No pronounced peak	Relatively flat
Effective Duration	10-16 hours	U-100: Up to 24 hrs U-300: Beyond 24 hrs (pen only)	Up to 24 hours

Lilly U500 regular similar in duration of NPH

Lucidi D, et al. *Diabetes Care.* 2011;34:1312-1314.
Niswender K, et al. *Clin Diabetes.* 2009;27:60-68.
Tillner J, *et al.* EASD September 23–27 2013; Barcelona, Spain, (Abstract 1033).
Jax T, *et al.* EASD September 23–27 2013; Barcelona, Spain, (Abstract 1029).

INHALED INSULIN - AFREZZA

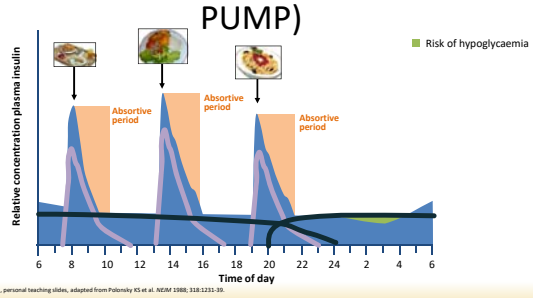


Now have 12 unit dosing available

Spirometry prior to starting, at 6 months, and then annually

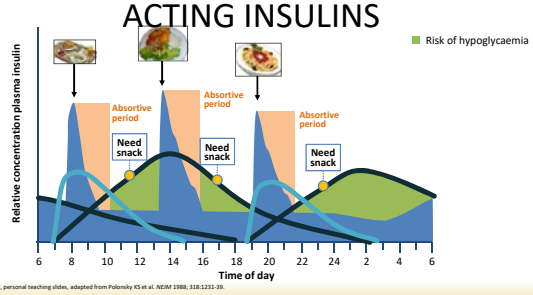
AFREZZA® [prescribing information]. Bridgewater, NJ: Sanofi-Aventis U.S. LLC; 2015.

INSULIN REPLACEMENT WITH BASAL-BOLUS (INJECTIONS OR PUMP)



Aschner P, personal teaching slides, adapted from Polonsky KS et al. *NEJM* 1988; 318:1231-39.

INSULIN REPLACEMENT WITH INTERMEDIATE- AND SHORT-ACTING INSULINS



Aschner P, personal teaching slides, adapted from Polonsky KS et al. *NEJM* 1988; 318:1231-39.

Pharmacologic Therapy for Type 1 Diabetes Management

ADA 2015 Guidelines

Insulin treatment for most patients with type 1 diabetes	• Treat with multiple-dose insulin injections (3-4 injections/day of basal and prandial insulin) or continuous subcutaneous insulin infusion • Match prandial insulin dose to carbohydrate intake, premeal blood glucose, and anticipated activity • Use insulin analogs to reduce risk of hypoglycemia • Consider using sensor-augmented low glucose suspend threshold pump in patients with frequent nocturnal hypoglycemia and/or hypoglycemia unawareness

Other agents	Investigational agents
Pramlinitide (amylin analog) • Delays gastric emptying • Blunts pancreatic secretion of glucagon • Enhances satiety • Induces weight loss • Lowers insulin dose • Use only in adults	Metformin + insulin • Reduces insulin requirements & improves metabolic control in obese/ overweight with poor glycemic control Incretins • GLP-1 receptor agonists • DPP-4 inhibitors SGLT2 inhibitors

Slide covers investigational agents not yet FDA approved for the treatment of type 1 diabetes in the United States

American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S1-S93.

CLASSIFICATION OF HYPOGLYCEMIA

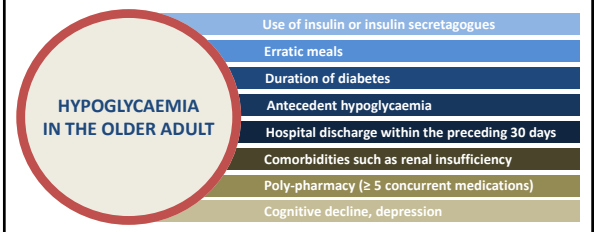
Table 6.3—Classification of hypoglycemia (61)

Level	Glycemic criteria	Description
Glucose alert value (level 1)	≤70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	<54 mg/dL (3.0 mmol/L)	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

Glycemic targets. Diabetes Care 2017; 40 (Suppl. 1): S48-S56

RISK FACTORS FOR HYPOGLYCAEMIA IN THE OLD ADULT

Member Input at meeting



Shorr RI et al. *Arch Intern Med.* 1997;157:1681–86. Zammitt NN, Frier BM. *Diabetes Care.* 2005:28:2948-61.

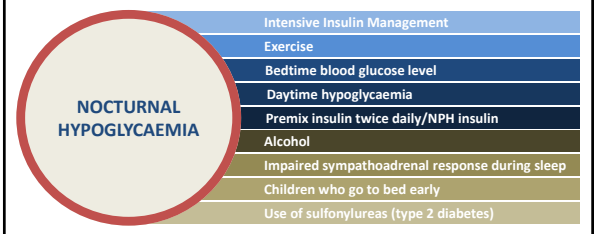
NOCTURNAL HYPOGLYCAEMIA

- During sleep, the neuroendocrine response against hypoglycaemia is markedly blunted (the response threshold is shifted to lower glucose levels)
- While symptoms of hypoglycaemia trigger awakening in healthy subjects, individuals with type 1 diabetes frequently fail to respond to symptoms during sleep

Jauch-Chara K, et al. *Best Pract Res Clin Endocrinol Metab* 2010;24:801-815. Jones TW et al. *N Engl J Med* 1998;338:1657. Banarer S, Cryer PE. *Diabetes* 2003;52:1195.

RISK FACTORS FOR NOCTURNAL HYPOGLYCAEMIA

Member Input at meeting



Wilson DM et al. **Factors Associated with Nocturnal Hypoglycemia in At-Risk Adolescents and Young Adults with Type 1 Diabetes. Diabet Technol Ther 2015; 17:385-91.**
Bae JP et al. **Risk factors for nocturnal hypoglycemia in insulin-treated patients with type 2 diabetes.** Clin Ther. 2017; 39:1790-98.

Slide 34

g310 Suggest adding one more slide dealing with elderly issues
gbauer, 6/11/2018

Slide 36

BC243 where did these come from? reference? children who go to bed early.
Belinda Childs, 6/10/2018

BC244 If we are adding these, we need references and to discuss
Belinda Childs, 6/10/2018

JS75 During the last member review Simon had provided feedback to include this information. References have been added
Julia Sawyers, 6/11/2018

HYPOGLYCEMIA

- Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each visit
  - At what number do you feel your low blood glucose
  - Have you had any hypoglycemia that required the assistance of another person or glucagon
  - Not limited to only those on insulin

ADA 2015 Guidelines

Management of Hypoglycemia

At-risk patients	Ask about symptomatic and asymptomatic hypoglycemia at each encounter
Preferred treatment: glucose (15-20 g)* • After 15 mins of treatment, repeat if SMBG shows continued hypoglycemia • When SMBG normal: patient should consume meal or snack to prevent recurrence	
Prescribe glucagon if significant risk of severe hypoglycemia	
Hypoglycemia unawareness or episode of severe hypoglycemia	• Reevaluate treatment regimen • Insulin-treated patients: raise glycemic targets for several weeks to partially reverse hypoglycemia unawareness and reduce recurrence
Low or declining cognition	Continually assess cognitive function with increased vigilance for hypoglycemia

*Any form of glucose-containing carbohydrate can be used; SMBG=self-monitoring of blood glucose

American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S1-S93.

ADA 2015 Guidelines

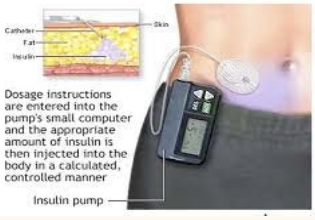
Self-Monitoring of Blood Glucose (SMBG)

Encourage for patients receiving multiple dose insulin or insulin pump therapy to perform SMBG:	• Prior to meals and snacks • Occasionally postprandially • At bedtime • Prior to exercise • When low blood glucose is suspected • After treating low blood glucose until normoglycemic • Prior to critical tasks (eg, driving)
Results may be useful for guiding treatment and/or self-management for patients using less frequent insulin injections or noninsulin therapies • Provide ongoing instruction and regular evaluation of SMBG technique and results and patient's ability to use data to adjust therapy	

American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S1-S93.

INSULIN INFUSION PUMP OPTIONS

INSULIN PUMP-HOW IT WORKS



MEDTRONIC 670 G

TSLIM X2 WITH BASAL IQ

DEXCOM G6

FREESTYLE LIBRE

Recommendations: Glucose Monitoring (2)

- Most patients on multiple-dose insulin (MDI) or insulin pump therapy should do SMBG B
  - Prior to meals and snacks
  - At bedtime
  - Prior to exercise
  - When they suspect low blood glucose
  - After treating low blood glucose until they are normoglycemic
  - Prior to critical tasks such as driving
  - Occasionally postprandially

American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. Diabetes Care 2017; 40 (Suppl. 1): S48-S56

American Diabetes Association

Recommendations: Glucose Monitoring (3)

- When used properly, CGM in conjunction with intensive insulin regimens is a useful tool to lower A1C in selected adults (aged ≥ 25 years) with type 1 diabetes. A
- Although the evidence for A1C lowering is less strong in children, teens, and younger adults, CGM may be helpful in these groups. Success correlates with adherence to ongoing use of the device. B
- CGM may be a supplemental tool to SMBG in those with hypoglycemia unawareness and/or frequent hypoglycemic episodes. C

American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. Diabetes Care 2017; 40 (Suppl. 1): S48-S56

American Diabetes Association

Recommendations: Glucose Monitoring (4)

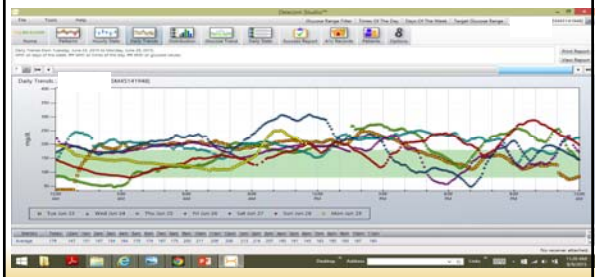
- Given variable adherence to CGM, assess individual readiness for continuing use of CGM prior to prescribing. E
- When prescribing CGM, robust diabetes education, training, and support are required for optimal CGM implementation and ongoing use. E
- People who have been successfully using CGM should have continued access after they turn 65 years of age. E

American Diabetes Association Standards of Medical Care in Diabetes. Glycemic targets. Diabetes Care 2017; 40 (Suppl. 1): S48-S56

American Diabetes Association

DEXCOM PERSONAL KR

DEXCOM DIAGNOSTIC HS



Continuous Glucose Monitoring (CGM)

ADA 2015 Guidelines

Useful for A1C lowering in select adults (aged ≥25 yrs) with type 1 diabetes requiring intensive insulin regimens	• May be useful among children, teens, and younger adults* • Success related to adherence to ongoing use
May be a useful supplement to SMBG among patients with	• Hypoglycemia unawareness and/or • Frequent hypoglycemic episodes
Variable adherence to CGM	• Assess individual readiness for continuing prior to prescribing • Robust diabetes education, training, support critical for optimal CGM implementation

*Evidence for A1C lowering less strong in these populations
SMBG=self-monitoring of blood glucose

American Diabetes Association. *Diabetes Care*. 2015;38(suppl 1):S1-S93.

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Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association Diabetes Care July 2014 37:7 2034-2054; doi:10.2337/dc14-1140

Carlson AL, Mullen, DM, Bergenstal RM. Clinical use of continuous glucose monitoring in adults with type 2 diabetes. Diabetes Technologies 2017; (Suppl 2): S4-S11.

Hirsch IB, Veerdersese CA. Professional flash continuous glucose monitoring (3rd Edwith ambulatory glucose profile reporting to supplement A1C: rationale and practical implementation. Endro Practice 2017; 23:1333-1344.

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