Hypoglycemia Unawareness: Pathophysiology and Clinical Care

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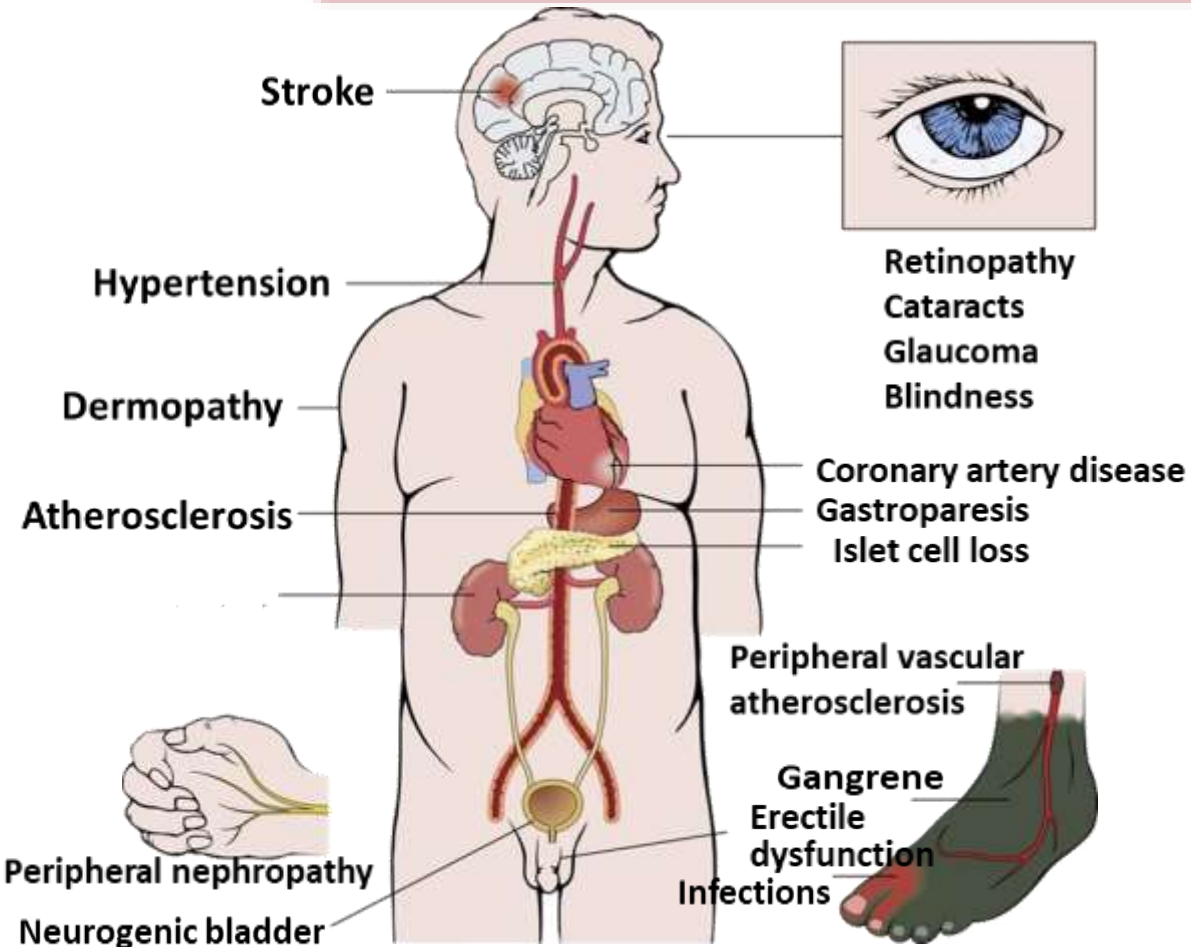St. Louis, MO

Disclosures

- Consulting/advising:
  - Bayer, Boehringer Ingelheim, Jaeb Center, Mannkind, NIH, Novo Nordisk, Provention Bio, Thermo Fisher

- Grants to Washington University:
  - NIH, Beta Bionics, Medtronic, Dexcom, Novo Nordisk

Objectives

- Recognize the frequency of hypoglycemia

- Understand the pathophysiology of hypoglycemia and HAAF

- Routinely assess patients with T1D and T2D for risk and occurrence of hypoglycemia.

- Develop management plans for the prevention and treatment of hypoglycemia.

- Educate patients and their support team on strategies to identify, minimize, and manage hypoglycemia.

Complications of Diabetes and Benefits of Tight Glycemic Control

Stroke
Hypertension
Dermopathy
Atherosclerosis
Peripheral nephropathy
Neurogenic bladder

Retinopathy
Cataracts
Glaucoma
Blindness

Coronary artery disease
Gastroparesis
Islet cell loss

Peripheral vascular atherosclerosis

Gangrene
Erectile dysfunction
Infections

30 years of excellent vs. poor glycemic control substantially reduced the incidence of the following:
- Retinopathy requiring laser therapy (5% vs. 45%)
- End-stage renal disease (0% vs. 5%)
- Clinical neuropathy (15% vs. 50%)
- Myocardial infarction (3% vs. 5%)
- Stroke (0.4% vs. 2%)
- Death (6% vs. 20%)

Excellent glycemic control also resulted in a gain of ~1.62 QALYs and averted ~$90,900 in costs of complications per participant

Herman WH, Braffett BH, Kuo S, et al. *J Diabetes Complicat.* 2018;32(10):911-915.

Hypoglycemia: "The limiting factor in diabetes management."

- 6-8 million persons with diabetes use insulin

- 300,000 emergency room visits yearly for hypoglycemia

- Average cost for ER visit for hypoglycemia is ~$800

- Average cost for hospital admission for hypoglycemia is ~$13,000

- 4%-10% of deaths in patients with type 1 diabetes can potentially be attributed to hypoglycemia

ADA. Fast Facts. Available at: https://professional.diabetes.org/sites/professional.diabetes.org/files/media/fast_facts_12-2015a.pdf. Curkendall, SM. *J Clin Outcomes Manag.* 2011;18:455-62. Wang J, et al. *PLoS One.* 2015;10(8):e0134917. Cryer PE. *Endocrinol Metab Clin North Am.* 2010;39(3):641–654.

Hypoglycemia Unawareness is Relatively Prevalent, Particularly in the Elderly and Children and Adolescents

Across 21 studies spanning 2000-2016...

Adults with T1DM
- Median Prevalence: 19%
- High/Low Prevalence: 58%/10%

Children and Adolescents with T1DM
- Median Prevalence: 25%

Adults with Insulin-treated T2DM
- Median Prevalence: 10%

Choudhary, 2010; Conget, 2016; Geddes, 2008; Hendrieckx, 2016; Henriksen, 2016; Hoi-Hansen, 2010; Holstein, 2003; Kulzer, 2014; Olsen, 2014; Ostenson, 2014; Pedersen-Bjergaard, 2003; Pedersen-Bjergaard, 2004; Peene, 2014; ter Braak, 2000; Abraham, 2016; Ly, 2009; Henderson, 2003; Kulzer 2014; Ostenson, 2014; Peene, 2014; Schopman, 2010.

Non-Severe and Severe Hypoglycemia Can Significantly Impact Hospitalizations, Readmissions, CV Events, and All-Cause Mortality

- Non-Severe Hypoglycemic Events (NSHEs)[1]
  - Of 1400 responders with NSHE, 22.7% were late for work or missed a full day
  - Productivity loss highest for NSHEs occurring during sleep, an average of 14.7 working hours lost
  - In the week following an NSHE, respondents required ~ 5.6 extra BG test strips and insulin-users decreased their insulin dose by 25% → *Fear of hypoglycemia affects treatment decisions*
- Severe Hypoglycemia (SH, blood glucose $\leq$ 54mg/dL)
  - Severe cognitive impairment requiring external assistance for recovery.
  - 21% of severe hypoglycemic episodes require hospitalization
  - Disability includes stroke, cognitive impairment, injury
  - **Death due to hypoglycemia may be the result of accidents, seizure or ventricular arrhythmia**

1. Brod M, et al. *Value Health*. 2011;14(5):665-71. 2. Bronstone A, et al. *J Diabetes Sci Technol*. 2016;10(4):905–913. 3. HCUP Nationwide Inpatient Sample (NIS). http://hcupnet.ahrg.gov/HCUPnet.jsp. 4. Hsieh CJ. *Sci Rep*. 2019;9(1):14240. 5. Rozalina G, et al. *J Gen Intern Med*. 2017. 6. McCoy RG, et al. *J Gen Intern Med*. 2017;32(10):1097–1105. 7. Davis SN, et al. *Diabetes Care*. 2019;42(1): 157-163. 8. Cha SA, et al. *Diabetes Metab J*. 2016;40(3):202–210. 9. Pieber TR, et al. *Diabetologia*. 2018;61(1):58–65.

Hypoglycemia: Pathophysiology

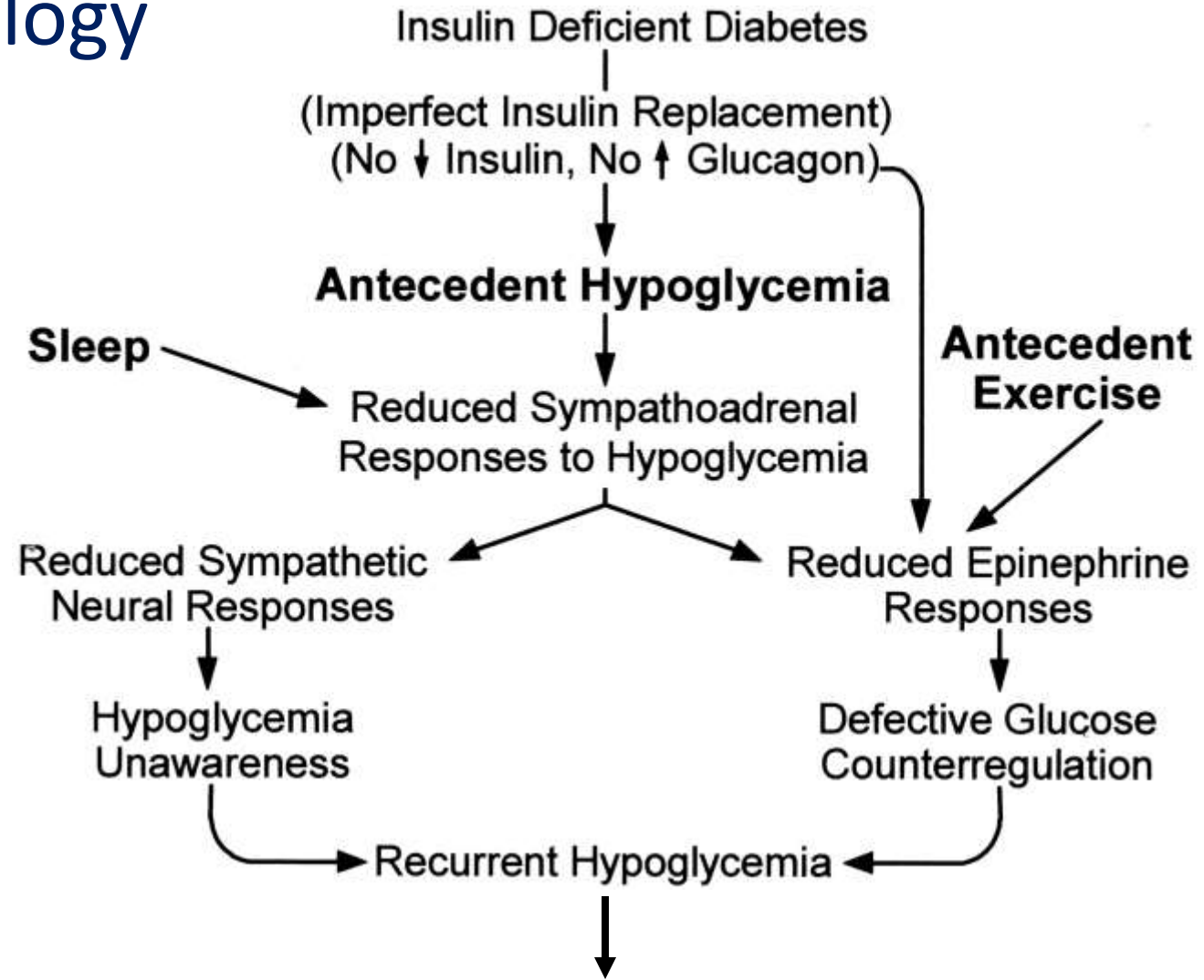| |
|---|
| Loss of the glucagon response: the intraislet insulin hypothesis |
| Reduced awareness: the sympathetic neural hypothesis |
| Reduced sympathoadrenal responses |
| The central nervous system premise |
| The systemic mediator hypothesis |
| The brain fuel transport hypothesis |
| The brain metabolism hypothesis |
| The brain glycogen supercompensation hypothesis |

Cryer PE. *Diabetes,* 2005; 54(12):3592–3601

Insulin Deficient Diabetes
|
(Imperfect Insulin Replacement)
(No ↓ Insulin, No ↑ Glucagon)
↓
Antecedent Hypoglycemia
↓

Sleep → Reduced Sympathoadrenal Responses to Hypoglycemia

Antecedent Exercise

Reduced Sympathetic Neural Responses → Hypoglycemia Unawareness

Reduced Epinephrine Responses → Defective Glucose Counterregulation

→ Recurrent Hypoglycemia ←
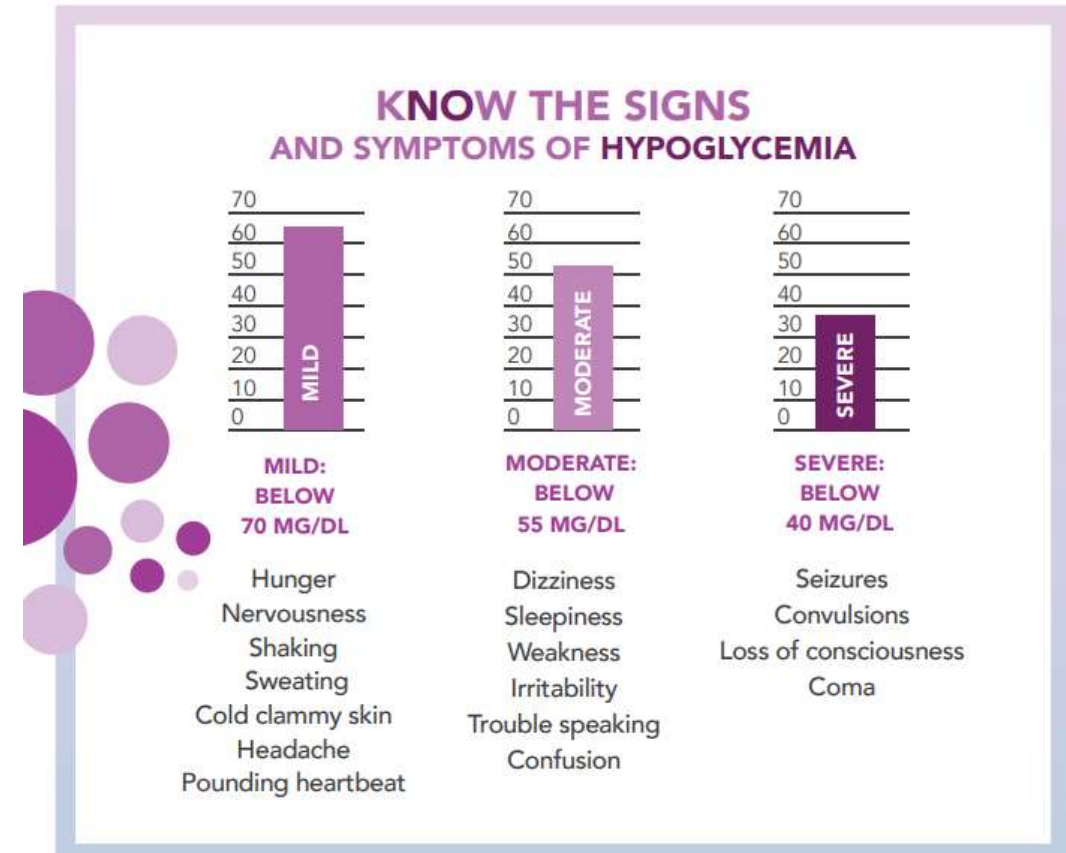↓

Hypoglycemia Associated Autonomic Failure

Hypoglycemia Unawareness ⬌ HAAF

- Failure of counter-regulatory systems to provide symptoms
  - Loss of glucagon and epinephrine response to hypoglycemia
  - Loss of ability to detect symptoms (sleep, alcohol, distraction)
  - Symptoms occur too late or with glucose that is below cognition level (rapid drop)
  - **Hypoglycemia-associated autonomic failure (HAAF)** posits that recent antecedent iatrogenic hypoglycemia causes both defective glucose counterregulation (by reducing epinephrine responses) and hypoglycemia unawareness (by reducing sympathoadrenal and the resulting neurogenic symptom responses to subsequent hypoglycemia) and thus a vicious cycle of recurrent hypoglycemia.
  - The mechanism by which hypoglycemia shifts the glycemic thresholds for sympathoadrenal activation to lower plasma glucose concentrations, the key feature of both components of HAAF, is not known.

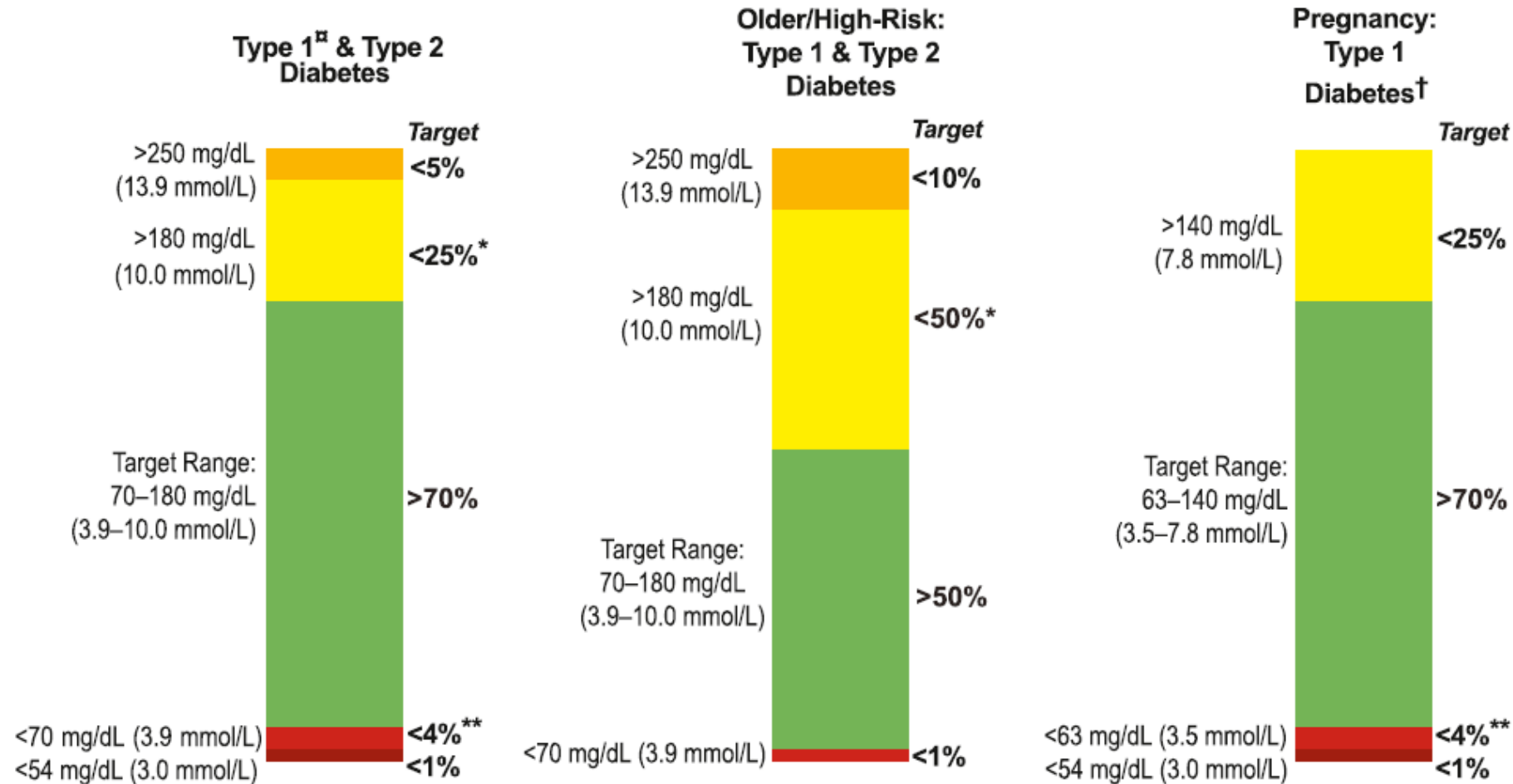- Antecedent hypoglycemia, exercise and sleep induced hypoglycemia are risk factors for HAAF

Every patient taking insulin is at risk for HAAF!

Pedersen-Bjergaard U, et al. *Curr Diab Rep.* 2017;17:131.
Riddlesworth T, et al. *Diabetes Ther.* 2017; 8:947.

Hypoglycemia: History

- Do you have low glucoses?
  - How often?

- How low are your glucoses?
  - Level 1 (mild) → <3.9 mmol/L (<70 mg/dL)
  - Level 2 (mod) → <3 mmol/L (<54 mg/dL)
  - Severe hypoglycemia
    - <2.2 mmol/L (<40 mg/dL)
    - Seizure, loss of consciousness
    - Needing help from another person

- Quantify hypoglycemia by CGM, % time <3.9 mmol/L or <54 mmol/L

- Adverse events from hypoglycemia?

KNOW HYPO
STAY SAFE FROM
SEVERE
HYPOGLYCEMIA

KNOW THE SIGNS
AND SYMPTOMS OF HYPOGLYCEMIA

MILD:
BELOW
70 MG/DL

Hunger
Nervousness
Shaking
Sweating
Cold clammy skin
Headache
Pounding heartbeat

MODERATE:
BELOW
55 MG/DL

Dizziness
Sleepiness
Weakness
Irritability
Trouble speaking
Confusion

SEVERE:
BELOW
40 MG/DL

Seizures
Convulsions
Loss of consciousness
Coma

Endocrine Society Guidance for Patients

CGM Based Targets for Different Populations

Type 1¤ & Type 2 Diabetes

	Target
>250 mg/dL (13.9 mmol/L)	<5%
>180 mg/dL (10.0 mmol/L)	<25%*
Target Range: 70–180 mg/dL (3.9–10.0 mmol/L)	>70%
<70 mg/dL (3.9 mmol/L)	<4%**
<54 mg/dL (3.0 mmol/L)	<1%

Older/High-Risk: Type 1 & Type 2 Diabetes

	Target
>250 mg/dL (13.9 mmol/L)	<10%
>180 mg/dL (10.0 mmol/L)	<50%*
Target Range: 70–180 mg/dL (3.9–10.0 mmol/L)	>50%
<70 mg/dL (3.9 mmol/L)	<1%

Pregnancy: Type 1 Diabetes†

	Target
>140 mg/dL (7.8 mmol/L)	<25%
Target Range: 63–140 mg/dL (3.5–7.8 mmol/L)	>70%
<63 mg/dL (3.5 mmol/L)	<4%**
<54 mg/dL (3.0 mmol/L)	<1%

1% of the day is ~15 minutes

Battelino T et al, Diabetes Care 2019 June;dci190028.

Case 1: Elderly patient with T1D

- Patient is an 83 yo woman, retired from owning a business and managing property. T1D was diagnosed at age 53 after presenting as LADA, but with complete loss of C-peptide in 5 – 7 years. She lives alone with family nearby. She has had many episodes of severe hypoglycemia, mostly at night, and with the following consequences:

  - Left hand paralysis ("Saturday night palsy")

  - Seizures on multiple occasions

  - TIA vs stroke - facial weakness and slurred speech with recovery in about 48 hours

  - Falls at home, one with a closed head injury

  - Impaired cognition after the CLI, such that forgetting to take medications resulted in TSH >300

- The patient has had an aid watching her overnight, who is capable of administering glucagon. This has been required periodically, however the administration typically takes so long that EMS has visited her house about every other month until recently.

Remedy for hypoglycemia with unawareness: automated insulin delivery

CGM trend with use of automated insulin delivery:
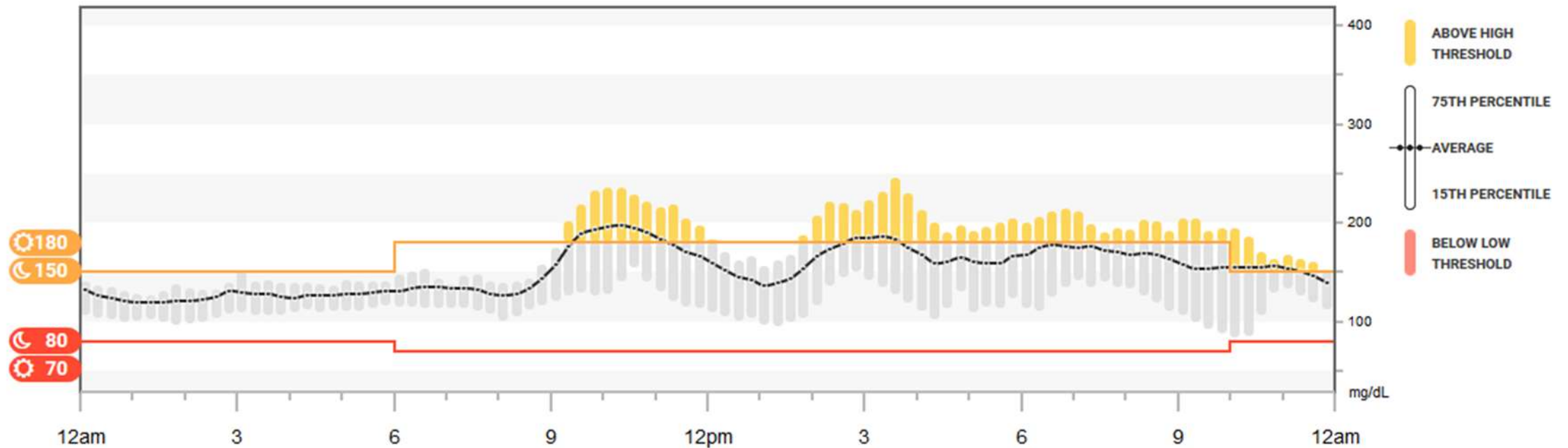
Case 2: Man with new ESRD, started on dialysis

- A 56 yo man is referred for evaluation of diabetes therapies. He recently started hemodialysis, but in the first month he had a serious hypoglycemic event that resulted in a fall and subdural hematoma. He was mostly recovered from the fall at the office visit.

- His anti-diabetes therapy at the initial visit:

    - 70/30 insulin, 30 units in the morning, 20 units in the evening.

    - BMI is 26, and A1c was 9.1%.

    - When asked if he takes his insulin, he responded, "sometimes, but if I take it all the time bad things happen."

- He checks his glucose intermittently also, did not bring in his meter, and reports values of about 200 mg/dl, sometimes higher, sometimes lower.

Case 2: Recommendations and Outcome

- My recommendations:
  - Structured glucose testing, minimum of twice daily
  - Start a DPP4 inhibitor
  - Basal insulin dose was adjusted by SMBG, final dose 22 units on non-dialysis days, 16 units after dialysis
  - Teach a family member how to recognize and treat hypoglycemia with glucagon
- Outcome
  - Home glucose testing showed values of 130 – 190 mg/dL
  - A1c was 7.1%
  - Rare hypoglycemic symptoms, rare glucose <100 mg/dL was reported, no severe events.
  - Wife feels prepared to identify and treat a very low glucose.

Summary: Clinician's Role in Identification and Prevention of Hypoglycemia

- Identification of hypoglycemia
    - History with direct questions about frequency and severity of hypoglycemia
    - Examination of SMBG or CGM downloads
- Prevention
    - Adjustment of therapy
        - Lower hypoglycemia risk agents in T2D, or combination therapy
    - Adjust goals of therapy
        - Less aggressive glucose targets for persons in high risk categories
    - Use of CGM in appropriate patients to provide alarms
    - Use of automated insulin delivery in T1D and other high-risk patients
    - Education
        - Reduces occurrence of severe hypoglycemia, does not abolish it

Standardized CGM Metric for Clinical Care: 2019

1. Number of days CGM worn (14 days)
2. Percentage of time CGM is active (70% of data captured from 14 days)
3. Mean glucose
4. Glucose management indicator (GMI)
5. Glycemic variability (%CV) target ≤36% (*some studies suggest <33%*)

>250mg/dl — Level 2 Hyperglycemia

>180mg/dl — Level 1 Hyperglycemia

70-180mg/dl — In Target

<70mg/dl — Level 1 Hypoglycemia

<54mg/dl — Level 2 Hyperglycemia

Battelino T, Danne, T, Bergenstal R, et al. *Diabetes Care*. 2019;doi.org/10.2337/dci19-0028