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Beyond the A1C:
Targets for Blood Glucose and Methods of Measurement

CARDI·OH
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Glycosylated Hemoglobin or Hemoglobin A1C (HbA1C):
Setting Targets and Interpreting Results

HbA1C is a measure of the proportion of hemoglobin molecules that have been glycated and reflects the plasma glucose concentration in the past 120 days (life span of erythrocytes). The HbA1C goal should be individualized based upon patient characteristics, including age, treatment burden, hypoglycemia risk, longevity, complications, comorbidities, preferences, and capability/motivation of the patient (Table 1).[1]

Randomized controlled trials in type 1 and early type 2 diabetes have demonstrated that an HbA1C target of 7% or less reduces microvascular complications. However, the effect of glucose control on macrovascular disease is modest, and observed only with early implementation and prolonged follow-up (10 years or more).[2]

An HbA1C target of **7%** or less reduces microvascular complications*

*A1C should be individualized based upon overall risk/benefit profile

Table 1. Glucose Targets

Health Status	A1C (%)	Fasting/premeal (mg/dl)	Peak Postprandial (mg/dl)	Bedtime (mg/dl)
General Population				
Healthy*	7.0	80-130	180	*
Older Adults				
Healthy	7.5	90-130	*	90-150
Intermediate	8.0	90-150	*	100-180
Poor	8.5	100-180	*	110-200

* Targets should be individualized. Healthy refers to few comorbidities, intact cognition, and activities of daily living. Poor health indicates end-stage comorbidities, moderate-severe cognitive impairment, or requiring long-term care or dependency in two or more activities of daily living.

Practice Points to Consider when Evaluating HbA1C:

1. **Point-of-care:** Point-of-care assays promote timely treatment decisions but require ongoing proficiency testing.
2. **Conditions affecting HbA1C value[3]:**
   - Race/ethnicity: HbA1C is lower in Caucasians compared to other racial and ethnic groups when accounting for average glucose derived by other methods. However, the prognostic value in predicting complications is similar across race/ethnicity and targets do not differ by race/ethnicity.
   - Recent changes in glycemic control.
   - Medical conditions that interfere with erythrocyte survival time (affects all assays): all forms of anemia and its treatment, kidney disease, pregnancy such that reduced red blood cell survival results in falsely lower HbA1C and vice versa.
   - Other conditions that can interfere with HbA1C measurement (assay dependent): hypertriglyceridemia, uremia (which causes carbamylation of hemoglobin), and hyperbilirubinemia falsely raise HbA1C, while hemoglobin variant effect on HbA1C depends on the variant as well as the assay.
   - Medications and substances (rare, assay dependent): high dose aspirin, chronic opioid, or alcohol use may falsely raise the HbA1C, while vitamin C and E and hydroxyurea falsely lower it.
3. **Alternatives:** If the HbA1C is considered to be unreliable or discordant with glucose monitoring, alternative markers of glycemic control, such as fructosamine, glycated albumin, or continuous glucose monitoring (CGM) can be considered. Additional evaluation, including assessment of red blood cell indices and turnover, as well as hemoglobin variants should be performed.[3]
4. **Role:** The HbA1C is the most validated marker of average glycemia and long-term complications. However, glucose monitoring is necessary for evaluating daily patterns, particularly when adjusting insulin.

Self-Monitored Blood Glucose

Glucose monitoring is important for assessing response to lifestyle or pharmacologic therapy, for identifying hypoglycemia, and for making day-to-day treatment decisions.

- **Targets:** As with HbA1C, self-monitored blood glucose (SMBG) targets should be individualized (Table 1).
- **Frequency and Use (Table 2):** Glucose monitoring frequency and scope are largely determined by insulin use and hypoglycemia risk. While SMBG in type 2 diabetes on oral diabetes medications alone has not been proven to be beneficial for all people with type 2 diabetes, a comprehensive approach that utilizes periodic structured SMBG with decision support has been shown to improve A1C levels in people who are not at target.[4]
  - » **Multiple daily insulin (MDI) injections:** perform SMBG or CGM prior to meals, at bedtime, during symptoms of hypo/hyperglycemia, and prior to driving and exercise.
  - » **Noninsulin therapies (especially medications that can cause hypoglycemia):** perform SMBG as needed to assess for hypoglycemia, responses to change in therapy, lifestyle, and during illness.
- **Performing SMGB:** Patients should receive training in performing SMBG, as user error is the most frequent source of inaccurate readings. Many meters have incorporated features that minimize user error, but issues with calibration/coding, adequate sample, contamination, application technique, expired test strips, or extremes in temperature, humidity, altitude, or light can still occur.

Table 2. Approach to Glucose Monitoring for Type 2 Diabetes

Health Status	SMBG	CGM
Non-insulin therapy	Structured (varied times of day) as needed to • Inform or monitor treatment adjustment • Inform lifestyle choices • During illness • Monitoring hypoglycemia (SU or glinide)	Consider short-term/ professional CGM if not meeting targets
Basal insulin	1-3+ times/day (especially FBG)	Consider if cost is not a barrier
MDI	3+ times per day • Meals • Exercise • Driving • Hypoglycemia • Occ. Postprandial (dose titration)	• If not meeting A1C target • Real-time alert preferred for people with frequent hypoglycemia, severe events or hypoglycemia unawareness

Continuous Glucose Monitoring

Continuous glucose monitoring measures glucose from interstitial fluid. Thus, there is a physiologic lag time between blood glucose and sensor readings when the glucose is rising or falling quickly. Continuous glucose monitoring may be indicated for persons requiring insulin, particularly those with a history of hypoglycemia or hypoglycemia unawareness (Table 2).[1]

While there is less evidence for patients with type 2 diabetes compared to type 1 diabetes, CGM results in reductions in HbA1C and hypoglycemia.[5] Some methods are factory calibrated and minimize the need for SMBG. Continuous glucose monitoring facilitates recognizing the effects of exercise, diet, sleep, and stress.

CGM types:

- **Real-time CGM:** provides a nearly continuous display of glucose values and audible or tactile alerts when the glucose value exceeds the threshold for hypoglycemia or hyperglycemia (alerts may be customized).
- **Flash glucose monitoring:** records glucose data nearly continually but the user accesses the glucose reading by scanning the sensor on an intermittent basis. The device may or may not provide audible alerts.

Points to keep in mind:

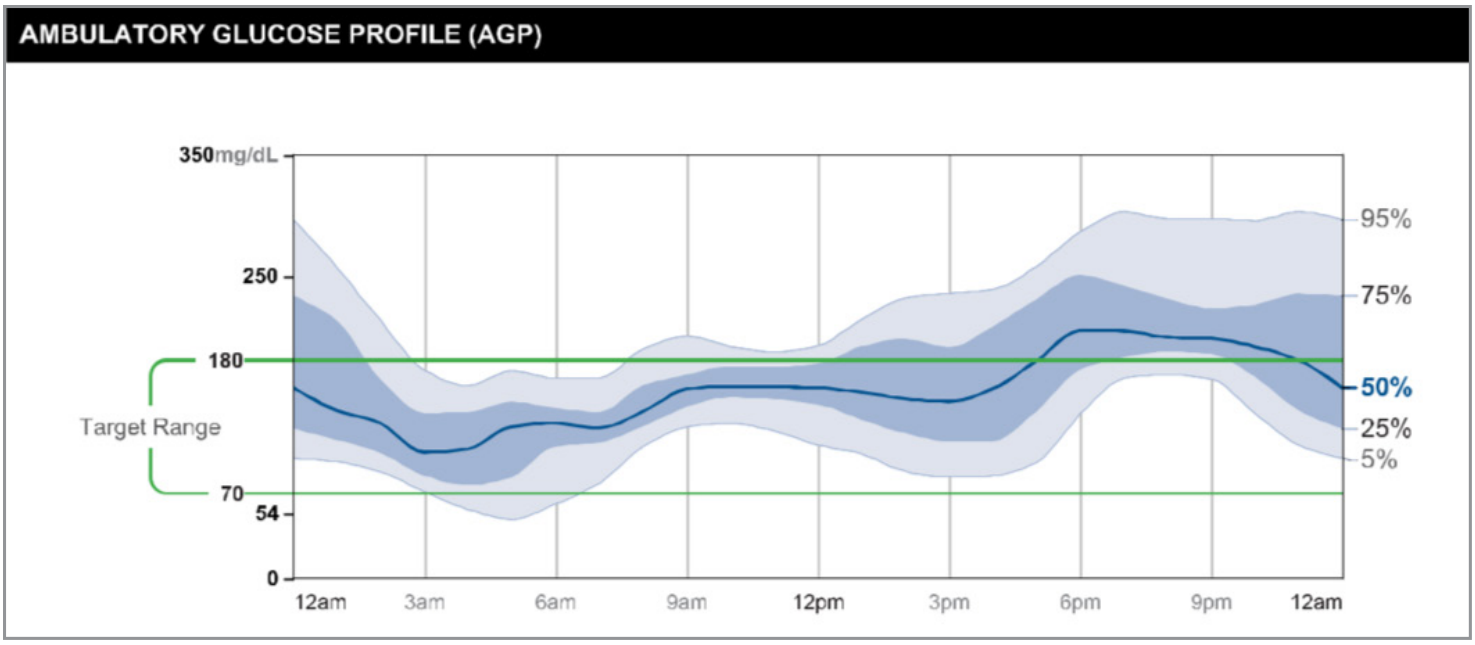
1. Limitations to Use:

- It is not recommended for persons on dialysis or acutely ill hospitalized patients, particularly patients with dehydration, hypotension, diabetic ketoacidosis, or hyperosmolar state.
- Adhesive allergy or failure are limiting factors to use, though they may be mitigated by topical treatments or barriers. Consider Eversense implantable CGM, though availability and coverage is limited.[4]
- Remember to remove before an MRI, CT scan, or X-ray.
- Interferences are device specific and may include high dose vitamin C, aspirin, acetaminophen, or hydroxyurea. [6, 7, 8, 9]
- Education in the limitations and appropriate use of CGM is critical.

2. Interpretation:

- Check blood glucose when advised by the manufacturer, during acute illness or when glucose levels are changing quickly, or when symptoms do not match sensor readings.
- The ambulatory glucose profile (AGP, Figure 1) is a standardized format for assisting healthcare providers in interpreting glucose data.[10]
- CGM targets are shown in Table 2. [1, 11]
- Trend arrows can be utilized to help predict hypoglycemia or hyperglycemia.[12, 13, 14]

Figure 1: The Ambulatory Glucose Profile



AGP is standardized reporting format (14 days): Shows a summary of glucose values percentiles as if occurring in a single day

Table 3. CGM Targets for Non-Pregnant Adults with Diabetes

Glucose Range	% Time in Range	
	Type 1 and Type 2 Diabetes	Older/High Risk Diabetes
>250 mg/dl (13.9 mmol/L)*	<5%	<10%
<180 mg/dl (10 mmol/L)	<25%	<50%
70-180 mg/dl (3.9-10 mmol/L)	>70%	>50%
<70 mg/dl (3.9 mmol/L)**	<4%	<1%
<54 mg/dl (3.0 mmol/L)	<1%	

Additional Resources

Resource 1: CGM Systems

	FreeStyle Libre 14 days[9]	FreeStyle Libre 2[9]	Dexcom G5[10]	Dexcom G6[10]	Medtronic Guardian connect[8,12]	Eversense CGM[13]
Cost	Affordable	Affordable	Expensive without insurance cover-age	Expensive without insurance cover-age	Expensive without insurance cover-age	Expensive without insurance cover-age
Age	18 and above	4 years and above	2 years and above	2 years and above	14-75 years old	14 years and above
Wear Time	14 days	14 days	7 days	10 days	7 days	90 days
Calibration	**No Need**	**No Need**	**Twice a day**	**No Need**	**Twice a day**	**Twice a day**
Insertion site	Back of the arm	Back of the arm	Abdomen or upper buttocks	Abdomen or upper buttocks	Abdomen or back of the arm	Arm implant
Hyper/hypo-glycemic alerts	No alerts	Includes alarm system	Includes alert system	Includes alert system	Includes alert system	Includes alert system
Rapid change in BG	Less reliable	Reliable	More reliable	More reliable, 30 minutes predic-tion	More reliable, 60 minutes predic-tion	Reliable
Data transmission	Every 1 minute; must scan within 8 hours	Every 1 minute; must scan within 8 hours	Every 5 minutes via Bluetooth	Every 5 minutes via Bluetooth	Every 5 minutes via Bluetooth	Every 5 minutes via Bluetooth
Links to app	+	Expected soon	+	+	+	+

Resource 2: How to use trend arrows to predict change in glucose:

Most CGMs are equipped with technology that demonstrates change in blood glucose by displaying arrows on the reader or linked mobile devices. These are useful tool for patients in predicting future hyperglycemia or hypoglycemia as shown below [11,12,13]:

Arrow Trend			
Medtronic Guardian connect	**Dexcom G6**	**FreeStyle Libre**	**Change in Glucose**
Two or three arrows up ↑ ↑ **or** ↑ ↑ ↑	Two Arrows 		Blood glucose increasing quickly >60 mg/dl in the next 30 minutes
One arrow up ↑			Increasing 30-60 mg/dl in the next 30 minutes
No arrow			Steady
One arrow down ↓			Decreasing 30-60 mg/dl in the next 30 minutes
Two or three arrows down ↓ ↓ **or** ↓ ↓ ↓	Two Arrows 		Decreasing quickly >60 mg/dl in the next 30 minutes

Post meal scanning and treatment for patients using CGM
Based upon pre-meal glucose value (3-4 hours after the last meal or bolus)

Glucose value above 180 mg/dl

Arrow Trend	Action
↑ ↑ ↑	Take insulin based on correction scale/factor then rescan after two hours. If hyperglycemia persists with arrow pointing up confirm with fingerstick check. If hyperglycemia confirmed retake correction scale/factor. Avoid taking correction bolus insulin within the first three hours to avoid hypoglycemia due to insulin stacking.
↑ ↗	Take insulin based on correction scale/factor then rescan after two hours.
→	No action required and rescan after one hour.
↓ ↘	No action required and rescan after one hour.
↓ ↓ ↓	No action required and rescan after one hour.

If glucose value is above 180 and patient is planning to exercise or perform any vigorous activity, do not take additional insulin. Recheck 30 minutes after the activity and apply the recommendations above based on glucose values.

Glucose value of 70-180 mg/dl

Arrow Trend	Action
↑ ↑ ↑	No action required and rescan after one hour.
↑ ↗	No action required and rescan after one hour.
→	No action required and rescan after one hour. If it is below 100 consider rescan after 15-30 minutes.
↓ ↘	Rescan after 30 minutes, consider 15 grams of carbs if it persists.
↓ ↓ ↓	Consider 15 grams of carbs (30 grams if symptomatic) and rescan after 30 minutes. If it persists with an arrow downward, confirm with a fingerstick check.

Resource 3: Sample CGM monitoring report

Summary Data and Daily Profiles

GLUCOSE STATISTICS AND TARGETS

July 14, 2020 - July 27, 2020	14 Days
% Time CGM is Active	68%

Ranges And Targets For	Type 1 or Type 2 Diabetes
Glucose Ranges	**Targets** % of Readings (Time/Day)
Target Range 70-180 mg/dL	Greater than 70% (16h 48min)
Below 70 mg/dL	Less than 4% (58min)
Below 54 mg/dL	Less than 1% (14min)
Above 180 mg/dL	Less than 25% (6h)
Above 250 mg/dL	Less than 5% (1h 12min)

Each 5% increase in time in range (70-180 mg/dL) is clinically beneficial.

Average Glucose	162 mg/dL
Glucose Management Indicator (GMI)	7.2%
Glucose Variability	33.6%

Defined as percent coefficient of variation (%CV); target ≤36%

TIME IN RANGES

Very High	>250 mg/dL	6% (1h 26min)
High	181 - 250 mg/dL	26% (6h 14min)
Target Range	70 - 180 mg/dL	65% (15h 37min)
Low	54 - 69 mg/dL	2% (29min)
Very Low	<54 mg/dL	1% (14min)

250
180
70
54

DAILY GLUCOSE PROFILES

Each daily profile represents a midnight to midnight period with the date displayed in the upper left corner.

Tuesday Wednesday Thursday Friday Saturday Sunday Monday

14 15 16 17 18 19 20

180
70

12am 12pm 12am 12pm 12am 12pm 12am 12pm 12am 12pm 12am 12pm 12am 12pm 12am

21 22 23 24 25 26 27

180
70

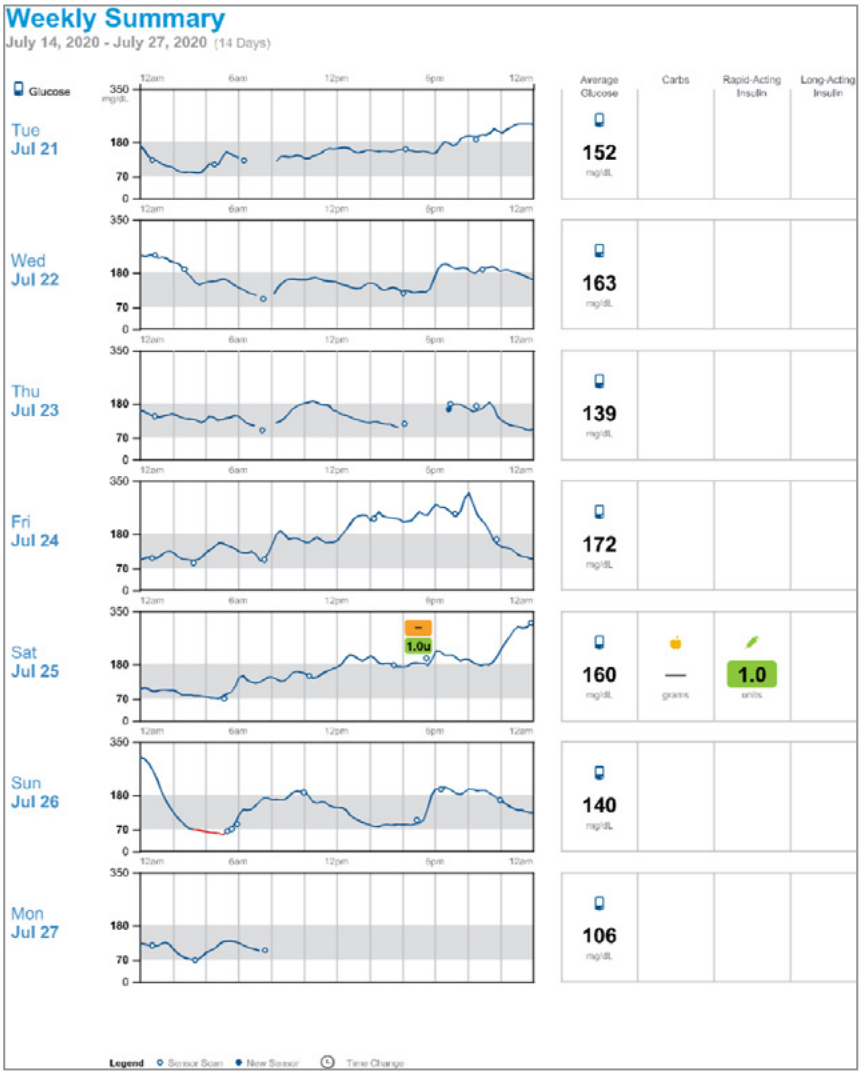
Source: Battelino, Tadej, et al. "Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range." Diabetes Care, American Diabetes Association, 7 June 2019, https://doi.org/10.2337/dci19-0028.

High/Low target range: Cannot be calibrated in some CGMs and are set to the recommended standard

Target range: Best to be 70% or above to achieve an A1c of 7 or less

Glucose Management Indicator (GMI): Very useful tool if the patient checks blood glucose without gaps and it will give aproximate A1C level based on the readings for 14 days

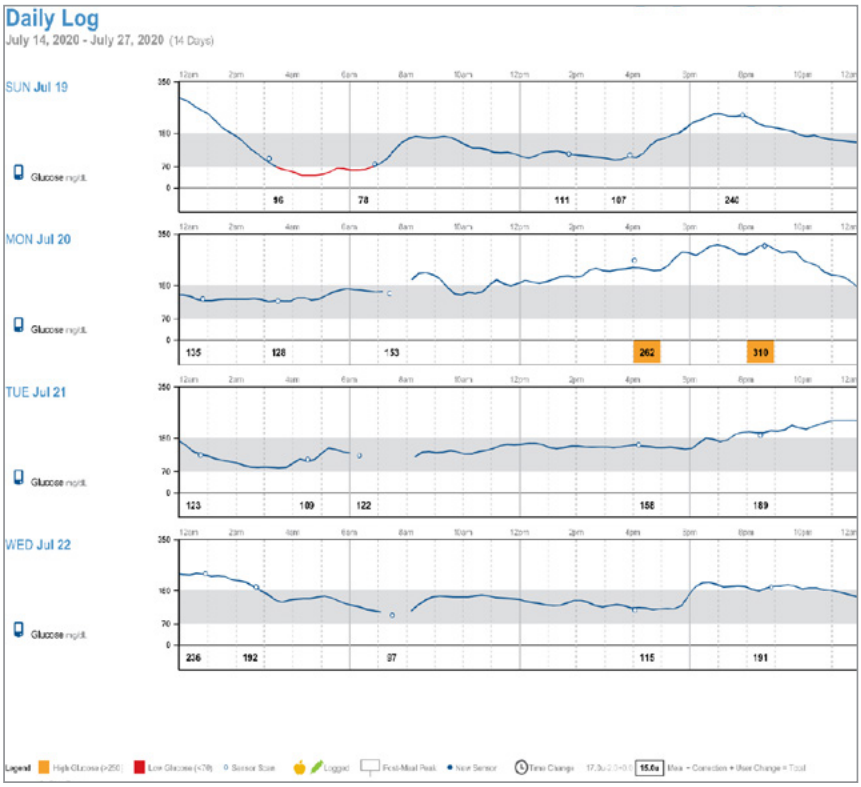
- **Glucose Management Indicator:** a very helpful tool if the patient checks blood glucose as recommended; it may give approximate A1C level based on the available readings for the 14 days.
- **High/Low Target Range:** cannot be calibrated in some CGM and are set to the recommended standards.
  - » High range >180 mg/dl: less than 25% for adults and less than 50% for older adults
  - » Target range 70-180 mg/dl: 70% and above for adults and above 50% for older adults
  - » Low range <70 mg/dl: less than 4% in adults and less than 1% for older adults



Insulin/Carb: Patient can log the number of units and the carb amount to aid in adjusting medications

Average glucose calculated for that day

Low glucose: The line turns red below 70 mg/dl and for how long patient has been hypoglycemic



Rapid-acting insulin: If units are logged it will be shown in white box

Postprandial glucose: Shown in white box

Long-acting insulin: If units are logged, it will be shown in green box

Carbohydrate: If value logged it will be shown as grams

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