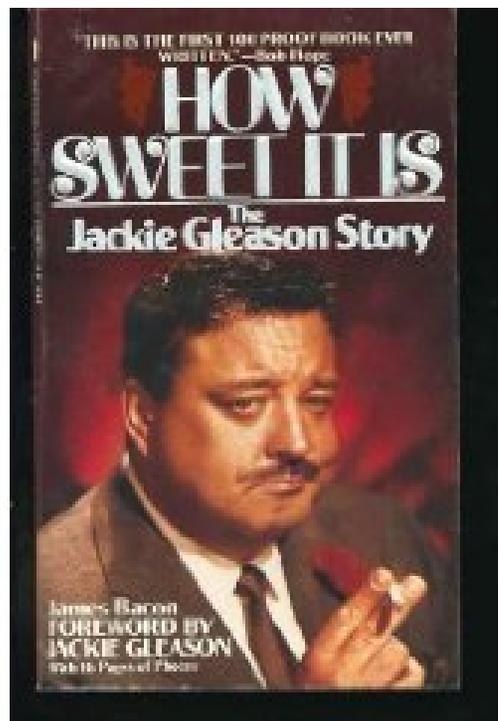


Intraoperative Management of Blood Glucose Levels “How Sweet It Is”



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Objective: Provide insight to the answers of these questions

- Intraoperative BG goals?
- Preop testing for diabetic patients?
- Adjust glycemic control medications preop?
- BG threshold to cancel case?
- BG threshold to treat?
- How treat ↑BG?
- Role for HbA1c?

Management of Hyperglycemia in the Hospital Setting 2005-6 – Tight Control

Inzucchi SE: *N Engl J Med* 2006; 355:1903

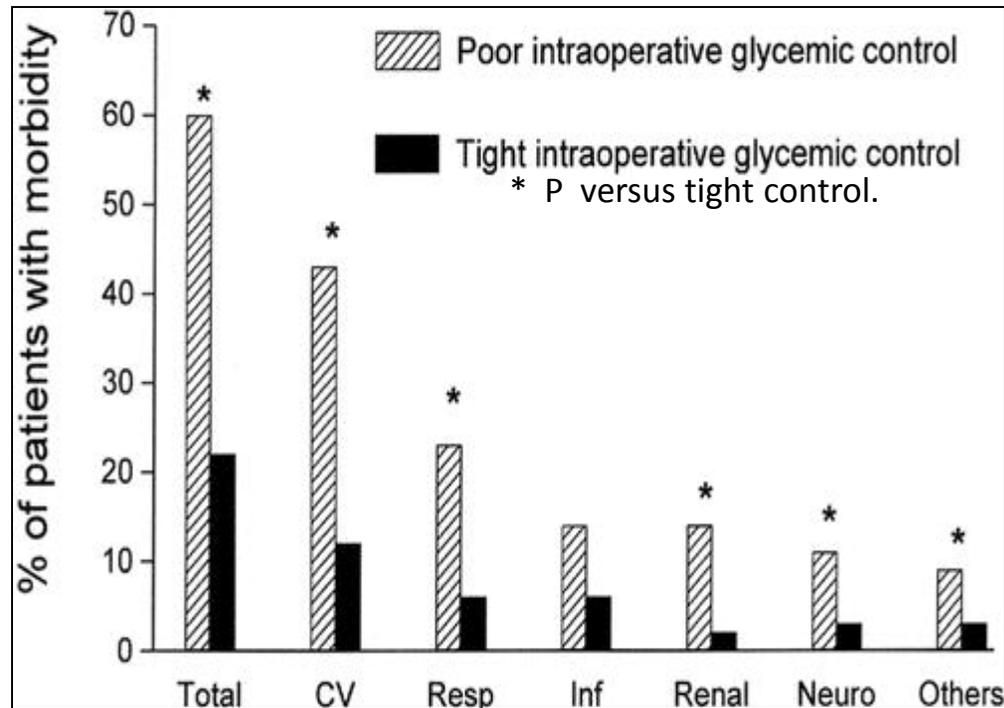
Recommendations: ADA – 2005; ACE - 2004

Table 1. Recommended Target Blood Glucose Levels for Hospitalized Patients.*		
Location	American Diabetes Association³⁶	American College of Endocrinology²
ICU	As close to 110 mg/dl as possible; generally <180 mg/dl	<110 mg/dl
General ward	As close to 90–130 mg/dl as possible; <180 mg/dl postprandial	<110 mg/dl before a meal; maximal <180 mg/dl

* The author believes these targets may be too stringent, on the basis of the available evidence. To convert values for glucose to millimoles per liter, multiply by 0.05551.

Poor Intraoperative Blood Glucose Control Is Associated with a Worsened Hospital Outcome after Cardiac Surgery in Diabetic Patients. Ouattara A, et al: *Anesthesiology* 2005; 103:687

103:687



200 DM patients undergoing on-pump heart surgery. *S.q.* intermediary insulin given am of surgery. IV insulin initiated intraop for BG \geq 180 mg/dL & titrated according to predefined protocol. Poor intraop control defined as 4 consecutive BG $>$ 200 mg/dL despite insulin. Postop BG $<$ 140 mg/dL attempted with aggressive insulin therapy. **Inability to tightly control BG emerged as major risk factor.**

2009 Consensus Statement

American Association of Clinical Endocrinologists

American Diabetes Association

Moghissi, et al: *Diabetes Care* 2009; 32:119-1

- **Definitions**

- Hyperglycemia: > 140 mg/dL (>7.8 mmol/L)
- Hypoglycemia: < 70 mg/dL (<3.9 mmol/L)
- Conversion: mg/dL to mmol/L, divide by 18

- **Critically ill**

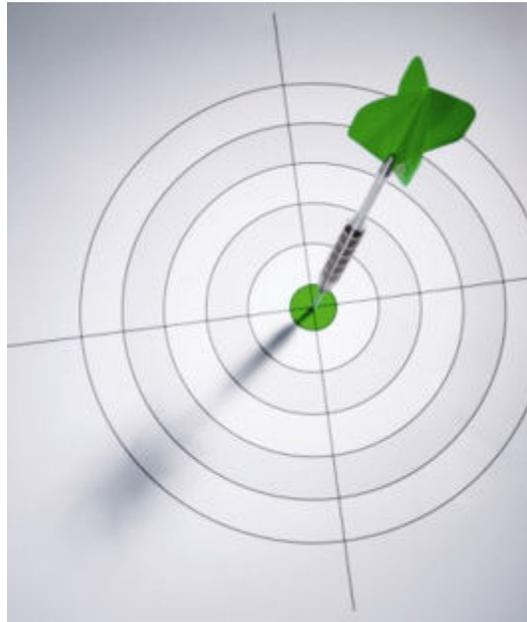
- “no higher than 180 mg/dL (10.0 mmol/L)”
- Iv insulin therapy: 140 – 180 mg/dL
- “Targets <110 mg/dL (6.1 mmol/L) are not recommended”

- **Noncritically ill**

- “Random BG values < 180 mg/dL”
- Reassess therapy if < 100 mg/dL

What Happened to Tight Control?

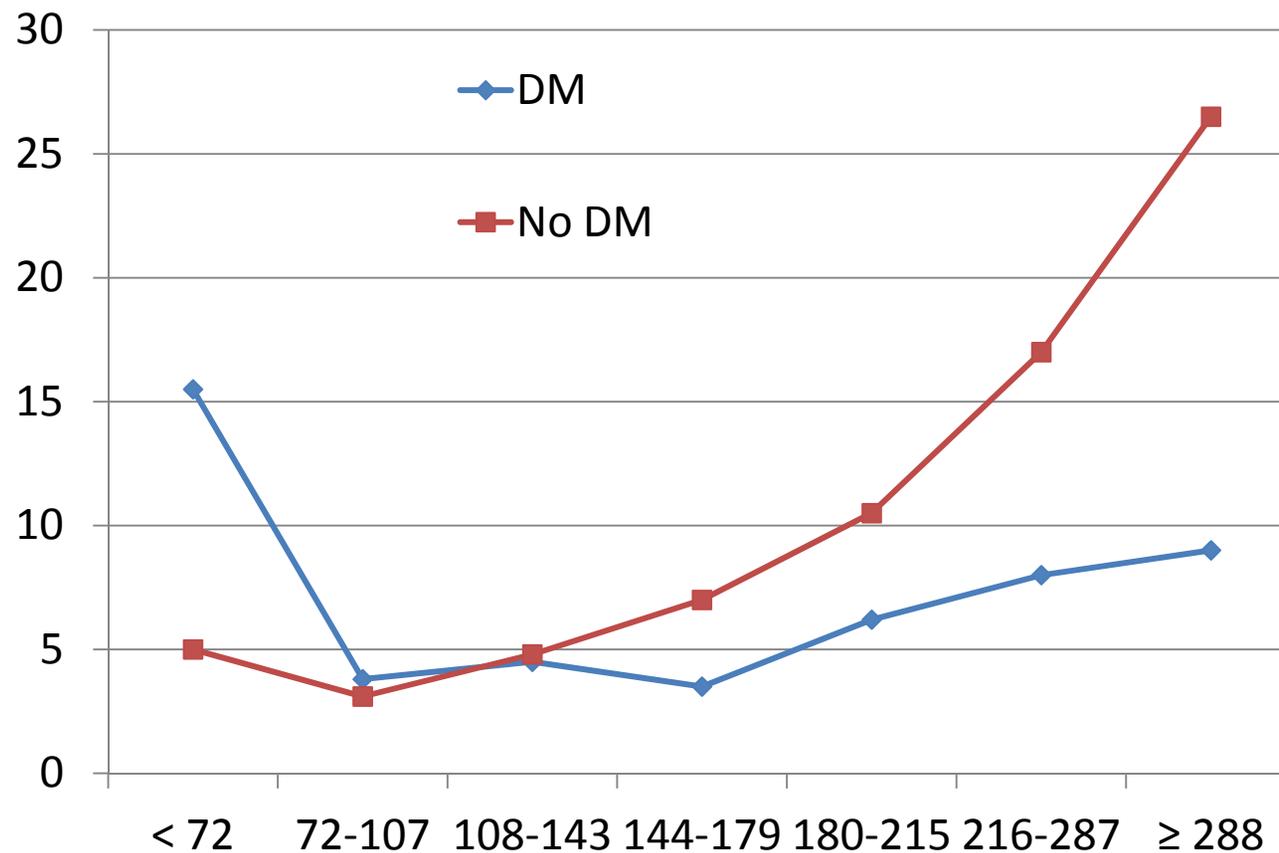
2004-6 Target **was** < 110 mg/dL



2011-2 Target **is** < 180 mg/dL

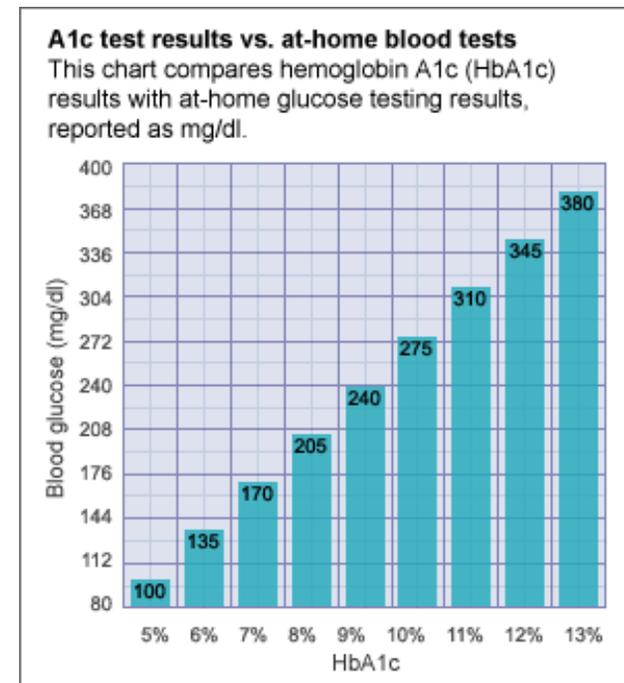
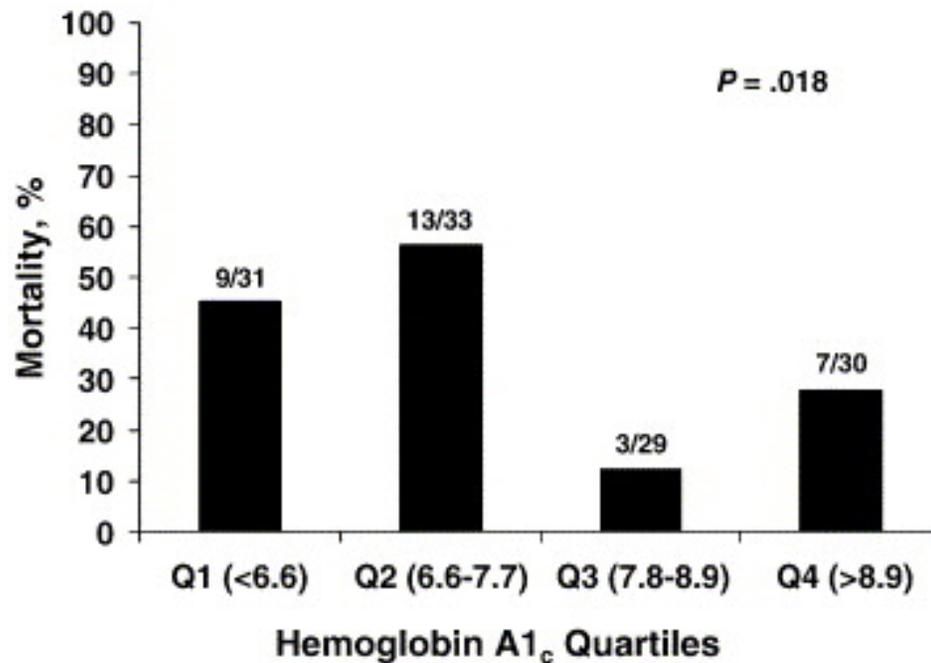
Mortality (%) vs Admission Glucose (mg/dL)

Cheung NW, et al: *Diabetologia* 2008; 51:952



An unexpected inverse relationship between HbA_{1c} levels and mortality in patients with diabetes and advanced heart failure

Eshaghian S, et al: *Am Heart J* 2006; 151:e1-6



Mortality (%) vs Admission Plasma Glucose

Cheung NW, et al. *Diabetologia* 2008; 51:952

“Counterintuitive” conclusions = new thinking:

Hyperglycemia: significant mortality marker in non-DM

HYPERglycemia bad for non-diabetics

Tight control in ICU most beneficial in this group

Hypoglycemia: significant mortality marker in DM

HYPOglycemia bad for diabetics

“Value of short-term tight glycemic control in patients with diabetes has not been proven. Current commercially available technology does not enable us to consistently achieve tight control without overshooting.” S. Akhtar

Peri-operative Glycemic Control Regiments for Preventing Surgical Site Infections in Adults (Review)

Kao LS, et al: *The Cochrane Library* 2009; Issue 4

- “There is insufficient evidence [based on the only 5 RCTs to date] to support strict glycaemic control versus conventional management (maintenance of glucose < 200 mg/dL) for the prevention of SSIs.”

Tale of Two Quotes

“Convincing evidence suggests clinical outcome is improved in cardiac surgery patients treated to maintain blood glucose \leq 110 mg/dL.”

- **Coursin DB**, Prielipp RC: The new anesthesia diet plan: keeping perioperative carbs in check. *Anesth Analg* **2004**; 99:316

“Will any of us claim, or admit, that we were secretly targeting their recommended serum glucose goal of $<$ 180 mg/dL (as opposed to 80-110 mg/dL)...?”

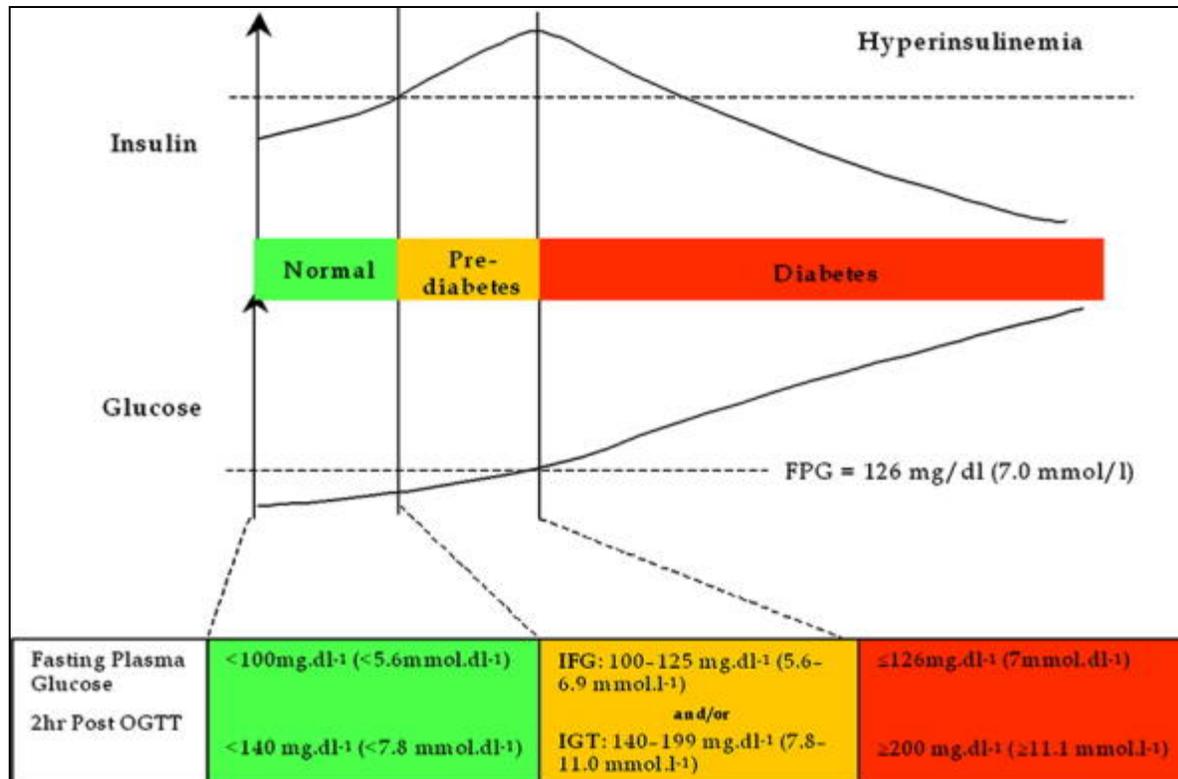
- Keegan MT, **Coursin DB**: *Anesth Analg* **2010**; 110:296 [editorial commenting on Akhtar S, et al: Scientific principles and clinical implications of perioperative glucose regulation. *Anesth Analg* 2010; 110:478]

Background Pathophysiology

- Hyperglycemia is bad
- Diabetes mellitus is bad
- True, true, but not equivalent
 - ↑BG
 - Acute and chronic effects
 - Unclear whether ↑BG above healthy normal range
 - Always appropriate
 - Appropriate in certain acute situations
 - Appropriate in certain chronic disease states
 - Appropriate until exaggerated (level, duration)
 - DM: end-organ diseases

Metabolic Syndrome and Insulin Resistance: Perioperative Considerations

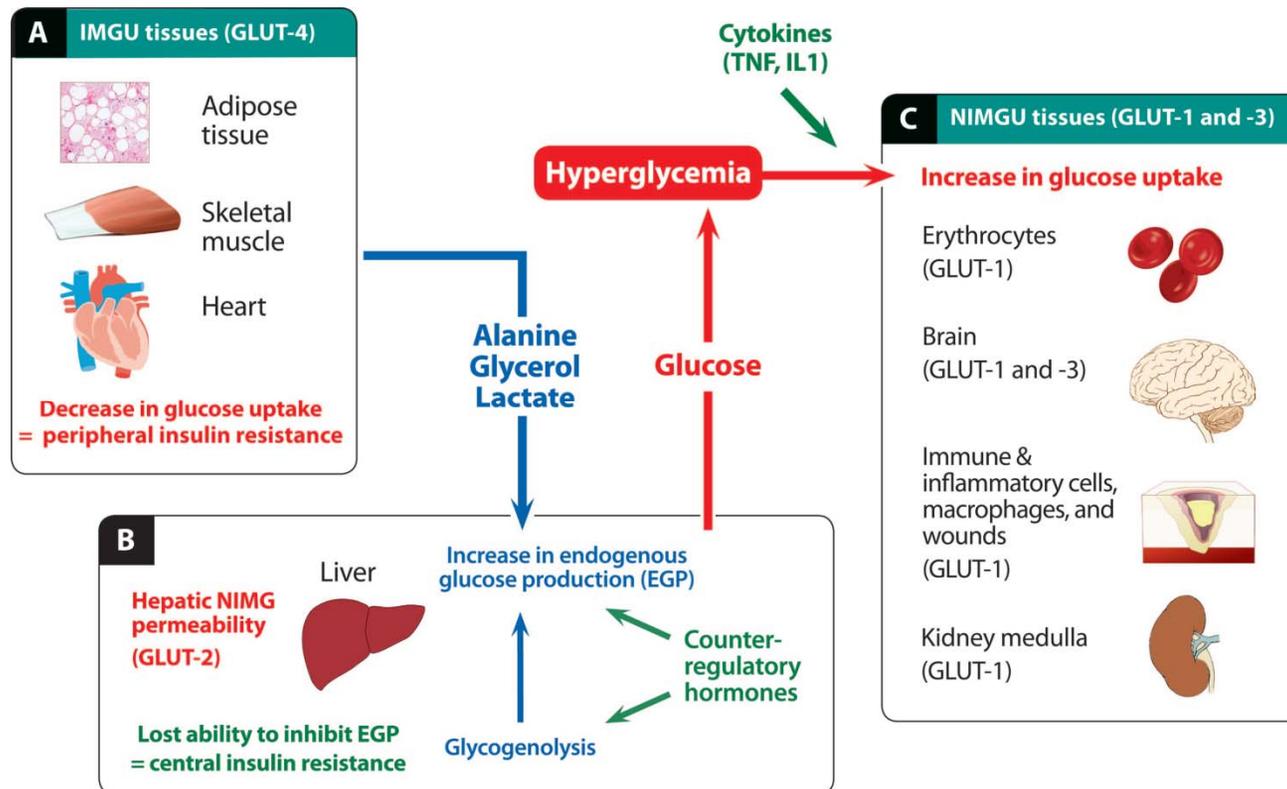
Bagry H, et al. *Anesthesiology* 2008; 108(3):506-23.



Schematic representation of temporal progression of insulin resistance. FPG = fasting plasma glucose; IFG = impaired fasting glucose, elevated fasting glucose levels but with normal response to oral glucose tolerance test (OGTT); IGT = impaired glucose tolerance, abnormal postprandial glucose excursion but with normal fasting glucose levels.

Schematic Representation of Stress Hyperglycemia

Lena, et al. *Anesthesiology* 2011; 114:438-44



(A) Under stress tissues that absorb glucose through insulin-mediated glucose uptake IMGU become resistant to insulin. Glucose is diverted from IMGU tissues. Neoglucogenic substrates (*alanine, glycerol, and lactate*) are released and used by liver to produce glucose. (B) Liver glycogenolysis and neoglucogenesis is stimulated by counterregulatory hormones and is less inhibited by circulating glucose (central insulin resistance). (C) Resulting hyperglycemia leads to increased non-insulin-mediated glucose uptake (NIMGU) in tissues under influence of proinflammatory cytokines. [GLUT glucose transporters; IL interleukin; TNF tumor necrosis factor.]

Perioperative Management of Hyperglycemic Patients

“One size (probably) does not fit all”

- Surgical stress-induced \uparrow BG in non-DM (normal)
- Non-surgical stress-induced \uparrow BG in non-DM (worst prognosis)
- Pre-DM type 2 (obese, metabolic syndrome)
- DM-type 2
- DM-type 1 (require basal insulin to avoid ketosis)

Tight Perioperative Control

Advantages

- Minimize adverse effects of hyperglycemia
 - Less myocardial ischemia & damage if MI?
 - Decreased surgical site infection
 - Less neurologic injury during intracranial surgery?

Disadvantages

- ↑ M&M in several patient populations
- ↑ risk of hypoglycemia
- ↑ labor burden & cost to implement

Problems with tight control

- \uparrow iatrogenic hypoglycemia
- \downarrow accuracy of POC monitor at \downarrow BG
- Symptoms of hypoglycemia masked
 - Analgesics, anesthetics, β -blockers, sedatives
- Consequences of hypoglycemia unclear
 - M&M: DM > non-DM; \downarrow BG > \uparrow BG in DM

Neurologic Consequences of Hypoglycemia

Prielipp RC, Coursin DB

- Duration and reversibility?
- BG < 45 mg/dL = neuroglycopenia
 - Altered mentation, seizures, LOC, coma
- BG < 36 mg/dL = EEG changes
 - EEG changes persist after normalization of BG
- BG < 18 mg/dL = neuronal necrosis

Signs & Symptoms of Hypoglycemia in Awake Males (< 50 mg/dL) & Females (< 40 mg/dL)

- Behavior changes
 - Emotional lability, irritability
- Physical symptoms
 - Diaphoresis, tremor, paresthesias, tachycardia
- Neuroglycopenic signs and symptoms
 - Hypothermia, weakness, fatigue, slurred speech, LOC, hemiparesis, seizures, brain damage

Glucose measurement in the operating room: more complicated than it seems

Rice MJ, Pitkin AD, Coursin DB: *Anesth Analg* 2010; 111:1056-65

- “Close glucose control... demands frequent measurement of blood glucose, which makes the rapid results and bedside convenience of POC devices highly attractive to the clinician.”
- “...devices now used in the perioperative and critical care settings where many users simply do not appreciate their lack of accuracy compared with laboratory glucose results.”
- “In August 2009, the FDA issued an alert to warn healthcare practitioners of potential for serious clinical errors...”

Glucose measurement in the operating room: more complicated than it seems

Rice MJ, Pitkin AD, Coursin DB. *Anesth Analg* 2010; 111:1056-65

Fahy BG, Coursin DB. *Mayo Clin Proc* 2008;83:394

- POC - whole blood; lab - venous plasma
- Plasma concentration = 110% blood concentration
 - POC devices “correct” by assuming nl Hct
 - Anemia ↑'s (POC overestimates)
 - Polycythemia ↓'s (POC underestimates)
 - Δ increases with arterial & capillary (finger stick) vs venous
 - Δ ↑'s with capillary blood in **hypotensive** patients
 - Δ ↑'s with decreasing temperature of sampling site
 - Δ : low PO_2 (< 50 mmHg) ↑'s; O_2 therapy ↓'s

Glucose measurement in the operating room: more complicated than it seems

Rice MJ, Pitkin AD, Coursin DB: *Anesth Analg* 2010; 111:1056-65

- FDA expects
 - Accuracy
 - BG \geq 75 mg/dL: 95% within 20% of reference
 - BG < 75: 95% within 15 mg/dL
 - Warning
 - “Critically ill patients should not be tested with blood glucose meters because inaccurate results may occur.”
- Advice: keep BG > 75 mg/dL if using POC

DM – End-organ Disease

- Vascular: PVD, retinopathy, CVA
- **Cardiac: small vessel CAD, silent ischemia, CHF**
- **Renal: CRI, CRF**
- Nervous system: peripheral neuropathy, CVA
- GI: ↓gastric emptying (?clinical relevance?)
 - Routine RSI in elective cases **not** indicated
 - Jellish WS, et al: *Anesth Analg* 2005; 102:904

Discontinue Oral Hypoglycemics

“Consensus of Experts”

But Girish Joshi (and SAMBA) say continue (2012)

- Theory
 - Harm extrapolated from animal experiments
 - Harm extrapolated from chronic administration to humans
- Philosophy
 - Use just one drug (insulin) to control BG perioperatively
 - Side-effects may complicate medical management
- Medical legal
 - FDA black box warnings & precautions
- Clinical studies
 - No well-designed, sufficiently powered clinical studies addressing decision re hold or continue

Kersten, Warltier, Pagel: Aggressive control of intraoperative glucose concentration. A shifting paradigm? *Anesthesiology* 2005; 103:677-8 (Editorial)

- “...strong evidence exists to indicate hyperglycemia alone, with or without diabetes, contributes to M & M in patients at risk for myocardial ischemia and reperfusion injury...”
- Speculated: “...thiazolidinedione insulin sensitizing agents may improve patient outcome by enhancing degree to which tight control of blood glucose concentrations may be achieved with exogenous insulin.” [Actos, Avandia]
- [FDA 2010: severely restricts use of thiazolidinediones: ↑risk of MACE]

Withhold Oral Hypoglycemics on DOS

Chen D, et al: *Anesth Analg* 2009; 108:1803

- Sulfonylureas – “↓BG intra-op if npo”
- Metformin – lactic acidosis
- Thiazolidediones (“glitazones”)– fluid retention, MI
- GLP-1 agonists – delay gastric emptying
- DPP-4 inhibitors (incretin enhancers) – only effective if oral intake

Unanswered Question: take any day before surgery?

Metformin and the FDA

Black box warning

“GLUCOPHAGE...should be temporarily discontinued prior to any vascular procedure, prior to any intravascular radiocontrast study and for any surgical procedure (see also Precautions)” [2000, 2006, 2008]

Precautions

“GLUCOPHAGE...should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and liquids) and should not be restarted until the patient’s oral intake has resumed and renal function has been evaluated as normal.” [2000, 2006, 2008]

Preoperative Metformin - Comments

FDA warnings and precautions

- Δ “should” vs “must”

Exceptions beyond your control – urgent/emergent surgery

- Δ “relative” vs “absolute” contraindications

Elective surgery

- Patient took metformin; you were not involved in decision
- **Proceed or cancel???**

- Time of last dose prior to surgery not stated by FDA

Reasonable to assume $\geq 4 \times (t_{1/2\beta} = 6 \text{ h})$ or $\geq 24 \text{ h}$

You saw patient $\geq 24 \text{ h}$ prior to surgery

- Last dose 36-48 h prior to surgery

Patient took metformin; you were not involved in the decision

- Last dose 24-48 h prior to surgery
 - Usually proceed unless
 - Recent (≤ 4 d) radiocontrast study & no BUN/Cr
 - Unresolved nephropathy
- Last dose < 24 h before surgery
 - Discuss
 - Usually proceed if “everything else is in order”
 - Reschedule if
 - Recent contrast study, nephropathy, severe diarrhea, colon prep

Recent metformin ingestion does not increase in-hospital morbidity or mortality after cardiac surgery

Duncan AI, et al: *Anesth Analg* 2007; 104:42 (Cleveland Clinic)

- 443 diabetics took metformin 8-24 h preop before cardiac surgery matched with 443 diabetics not-taking metformin
- No Δ in mortality or cardiac, renal, or neurologic morbidity; no lactic acidosis
- \downarrow intubation time, \downarrow infection, \downarrow overall M&M in metformin group

Key Preop Questions for Patients with Insulin-Treated Diabetes

- Do you recognize when your BG is low?
 - How frequently does this occur?
- Do you have a basal insulin dose regimen?
 - Continue usual basal insulin doses in type 1 DM
- What is your “usual” morning BG?
- Do you have an insulin pump?

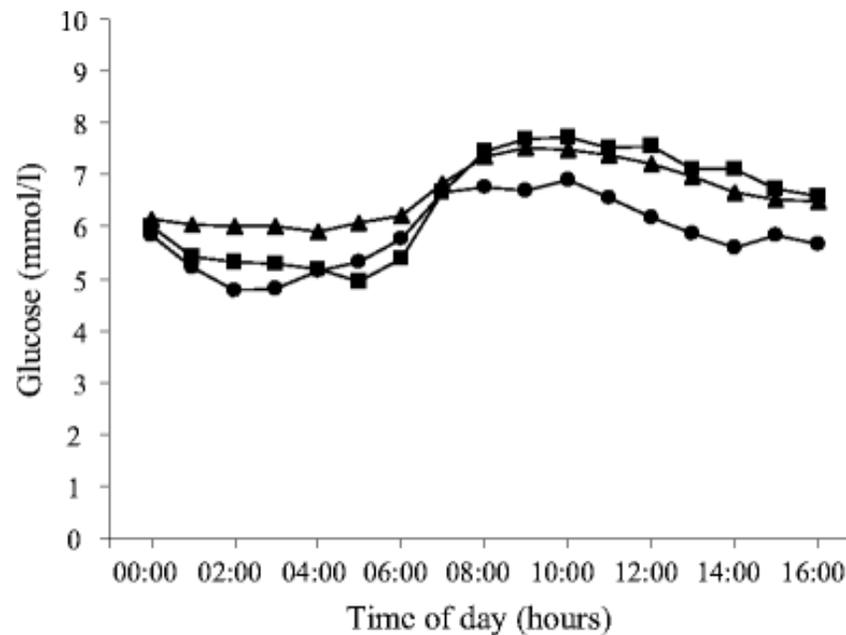
What is your “usual” morning BG?

Use answer to adjust dose of night-before and morning-of long-acting insulin

BG < 75 mg/dL	hold pm + hold am
BG < 100	½ pm + hold am
BG 100-150	full pm + hold am
BG > 150	full pm + hold am
BG > 180	full pm + reduced am

Omitting breakfast and lunch after injection of different long-acting insulin preparations at bedtime: a prospective study in patients with type 2 diabetes

Weisli P, et al: *Diabetologia* 2009; 52:1816



Mean glucose concentrations in 20 patients with type 2 DM during the fasting. Long-acting insulins (NPH, circles; detemir, squares; glargine, triangles) were injected at 22:45 hours; breakfast and lunch were not consumed the following day. Bars indicating SDs (20–35% of mean values) have been removed. To convert mmol/l to mg/dl multiply by 18.

Do you have an insulin pump?

Set to deliver subcutaneous basal infusion intraop

- Shorter surgery in healthy patients
- Position to avoid kinking insulin infusion catheter
- BG pre- & post-op; administer insulin/dextrose prn

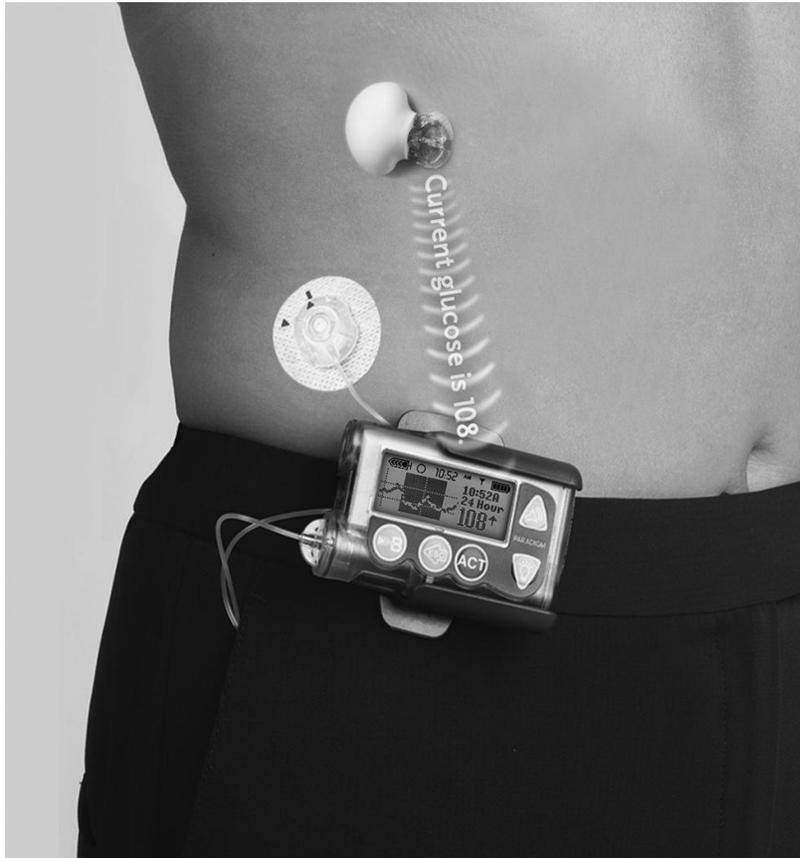
Stop immediately prior to longer duration surgery, especially if

- Major, urgent or emergent surgery
- Severe medical illness

Insulin Pumps & a Glucose Monitoring System

Mastrototaro J, et al: *Diabetes Technol Ther* 2009; 11:S-37

Potti LG, et al: *J Am Pharm Assoc* 2009; 49:e1



Must, Should, or Potentially Useful if Order HbA1c Preoperatively?

Assume no HbA1c \geq 120 days

- Patients whose BG will increase intraop (\leq 100%)?
- Patients with non-surgical risk of hyperglycemia (35%)
- Patients with DM types 1 & 2 (15%)?
- Select patients with DM type 2 (5%)?
- Patients with DM type 1 ($<$ 1%)?
- No patients (0%)?

How I Use of HbA1c

Compare current blood glucose (BG) to pre-admission/admission HbA1c

↑BG + low HbA1c

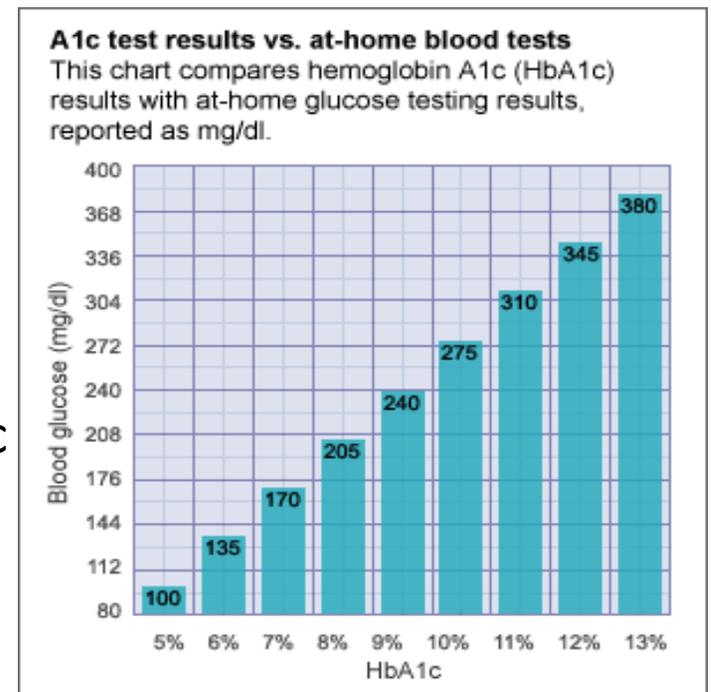
Search for cause of ↑ RBC turnover (e.g., hemolysis) or atypical hemoglobin

↑BG + normal HbA1c

Treat BG \geq 180 mg/dL
Search for infection

↑BG + ↑HbA1c

Calculate BG associated with HbA1c
Treat Δ (actual BG - calculated BG)



Preop Testing for Diabetic Patient Taking Insulin

- Minimum outpatient: BG prior to surgery
- Usual inpatient: K⁺
- End-organ disease: ECG, BUN, Cr
- Recommended: HbA1c < 90 d
- Symptomatic: anion gap, ketones, ABG

Proceed with elective surgery if
preop BG ? mg/dL?
(Assume no ketosis or acidosis)

600

500

400

300

200

Definition of “proceed”?

- What does “not proceed” mean?
- What does “proceed” mean?
- Who makes decision?
 - Patient
 - You
 - Surgeon
 - Joint [(patient), you, surgeon]
 - Hospital policy

What does “not proceed” mean?

- Determine likely cause of hyperglycemia
 - Reschedule if HbA1c ↑↑ (e.g., > 12)
 - Poor compliance vs poor control despite compliance
 - Reschedule if HbA1c ↑ (e.g., 8-12)
 - AND if hyperglycemia not due to infection or recent steroids
 - Delay until later in day & treat if HbA1c ↑ and:
 - Hyperglycemia due to preop medical management
 - Withholding oral hypoglycemics and insulin
 - Adding glycemia-disturbing medications, e.g., steroids
 - Hyperglycemia not “too high” (? < 450 mg/dL ?)
 - No acidosis or ketosis; no ECG Δ’s

What does “proceed” mean?

- Administer anesthesia without treating BG
 - “If the BG required treatment, then case would have been delayed or rescheduled” vs.
- Treat BG while administering anesthesia
 - Increase rate of fluid administration
 - Can patient tolerate (CHF, diastolic dysfunction)?
 - Administer regular insulin
 - *sc* (SAMBA) vs. *im* vs. *iv* (inpatient)
 - **iv infusion 1-2 units/h** vs. sliding scale bolus

How Sophisticated is Your DM Practice?

Increasing level of “sophistication” of perioperative glycemic control as descend scale

- Avoids ↓BG, DKA, HHS
 - Rarely checks BG; always cancels if BG > 300 mg/dL
 - Considers potential DM-related end-organ damage
 - Selectively checks BG; treats BG > 200 mg/dL
-
- Selectively checks BG, HbA1c; “individualizes” BG Rx
 - Frequently checks BG; maintains BG 140-180 mg/dL

Keegan MT, Coursin DB: Breathe deeply the sweet air: ruminations on glycemic control.

Anesth Analg 2010; 110;296 [editorial]

“For now, the best advice is to individualize glucose control based on the patient’s characteristics, comorbidities, procedural duration, location, and potential impact of hypoglycemia or hyperglycemia on outcome.”

AACE and ADA Consensus Statement on Inpatient Glycemic Control

Moghissi ES, et al: *Diabetes Care* **2009**; 32:1119

- Critically ill
 - Insulin infusion if BG > 180 mg/dL
 - BG goal: 140-180 mg/dL
- Significant backing off from tight control
- Does not specifically address management of anesthetized patients

SAMBA Consensus Statement

Joshi, et al: *Anesth Analg* 2010;111(6):1378-87

“There is insufficient data to....” recurring theme re
pertinent clinical issues

- Questions current state of “evidence-based medicine”

Although **IV** insulin infusion recommended for major
surgery, **SC** is preferred in ambulatory surgery

SAMBA Consensus Statement

Joshi, et al. *Anesth Analg* 2010;111(6):1378-87

Suggestions for diabetic patients

- Travel with clear juices for ↓BG during transit
- Avoid dehydration: consume H₂O ≥ 2hrs preop
- Aggressive PONV prophylaxis
 - Okay to use dexamethasone
- Check BG
 - Minimum of 3: preop, PACU arrival and discharge
 - More frequently if treat ↑ BG

“Glucometrics”- Assessing the Quality of Inpatient Glucose Management

Goldberg PA, et al. *Diabetes Technol Ther* 2006; 8:560

- BG determinations: # per patient per shift
- % BGs in range (80-139 mg/dL)
- % hypoglycemic events (BG < 60 mg/dL)
- % hyperglycemic events (BG > 300 mg/dL)

“Glucometrics for Anesthesia”

Assessing the Quality of Perioperative Glucose Management

**Coming soon to an operating theater
near you!**

Not here yet

Predict:

Proposals < 5 yrs

“Accepted” quality metrics < 10 yrs