

# Glycemic Control

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## I. Introduction

Glycemic control is a subject which has drawn intense interest over the last decade due to several factors.

- A. Currently 10% of U.S. population and 1/3 of cardiac surgical patients have a diagnosis of diabetes mellitus (D.M.).
- B. Recent trends show an increasing incidence of obesity and type 2 D.M.
- C. Results of recent clinical investigations have led to an increased awareness of the hazards of hyperglycemia.
- D. There is increased awareness of states other than DM that predisposes patients for perioperative hyperglycemia (e.g. metabolic syndrome, stress hyperglycemia).
- E. There is a rapidly evolving body of literature examining the topic of glycemic control and its impact on perioperative outcomes.

## II. Pathophysiology

### A. Diabetes.

-Can be described as a group of heterogeneous disorders characterized by glucose intolerance. As many as one third of diabetics may be undiagnosed.

#### 1. Type 1 Diabetes

- a. Accounts for 10% of cases of diabetes.
- b. The result of autoimmune destruction of beta cells of the islets of Langerhans.
- c. Pancreas produces little or no insulin.

#### 2. Type 2 diabetes

- a. Accounts for 90% of cases of diabetes. Expected to affect 300 million worldwide by 2025.
- b. Characterized by variable degrees of insulin resistance and deficiency
- c. Subtypes include drug and chemically induced (e.g. corticosteroids) as well as gestational.

### B. Other conditions of concern.

-Conditions which predispose patients to perioperative hyperglycemia..

#### 1. Metabolic syndrome

- a. 34% of U.S. adults meet criteria for metabolic syndrome.
- b. A syndrome including central (visceral) obesity, insulin resistance, atherogenic lipid profile (elevated triglycerides, reduced HDL) and hypertension, proinflammatory state, prothrombotic state.

#### 2. Stress hyperglycemia

- a. Transient hyperglycemia during illness in patients without previous evidence of diabetes.
- b. Associated with elevated counterregulatory hormones and increased cytokines.
- c. May be reflection of prediabetic state or undiagnosed T2 DM.

### C. Insulin resistance.

-a state where there is a reduced biologic effect for any given concentration of insulin.

- a. Hyperinsulinemia, hyperglycemia and dyslipidemia resulting from insulin resistance promote and sustain insulin resistance.
- b. Glucose transport proteins. Defect in GLUT-4 transport probably plays an important role in insulin resistance.

### III. Acute hyperglycemia

-Chronic hyperglycemia can lead to microvascular complications (nephropathy, neuropathy, retinopathy, etc.) and/or macrovascular complications (CAD, carotid artery disease, etc.).

-In the past acute mild/moderate hyperglycemia under physiological stress was considered adaptational, permissive hyperglycemia benign. Due to its immediate threat to patient survival severe hyperglycemia always been avoided and/or treated aggressively.

#### A. "Severe" acute hyperglycemia

##### 1. Diabetic ketoacidosis (DKA)

- a. Characterized by hyperglycemia, metabolic acidosis & ketosis.
- b. Principle treatment is insulin & potassium.
- c. Seen in T1 DM.

##### 2. Non ketotic hyperosmolar syndrome (NKHS)

- a. Characterized by profound dehydration, extreme hyperglycemia (can exceed 600 mg/dL). Ketosis is absent, metabolic acidosis unusual.
- b. Principle treatment is fluids.
- c. Seen in T2 DM.

#### B. "Mild/moderate" acute hyperglycemia

-Hyperglycemia not severe enough to provoke DKA or NKHS is associated with increased in-hospital mortality, longer hospital length of stay and increased morbidity.

1. Cardiovascular system effects: Ischemic preconditioning impaired, ischemic-reperfusion injury exaggerated, oxidative stress increased (due to free fatty acid metabolism, endothelial function impaired (resulting in impaired vasodilation & capillary leakage).
2. Hematologic effects: fibrinolytic activity is decreased while platelet activity is hyperactive leading to increased thrombosis. Erythropoiesis is impaired by hyperglycemia.
3. Inflammatory effects: cytokines such as interleukins and tumor necrosis factor are released in response to moderate hypoglycemia and promote systemic inflammation. Graft rejection is increased in hyperglycemic patients.
4. Neurological effects: Hyperglycemic states aggravate cerebral ischemic damage due to increased tissue acidosis and lactate levels.
5. Infection: Responsiveness of leukocytes is inversely correlated with the extent of hyperglycemia. Incidence of post operative infection in patients with poor glycemic control increased.
6. Wound healing: Collagen formation impaired by hyperglycemia.
7. Effects of acute hyperglycemia tolerated better by diabetics than non diabetics.

IV Randomized controlled trials of tight glucose control (TGC).

Reference	Study Design	N	Population	Protocol	Outcomes	Notes
Malmberg, et al, 1999	RCT	620	AMI pts w/DM	I=126-96 mg/dL C=NS D=ICU admit.	11% reduction in mortality w TGC. NNT 9 for survival 3yr p MI	DIGAMI study.
Furnary, et al, 1999	Quasi-experimental	2467	CABG pts w DM	I=150-200 mg/dL C= < 200 mg/dL D=SICU admit	0.8 % DSW w TGC, 2.0% DSW in control NNT 83 for prevention of DSW	Portland group. Historical controls.
Van Den Berghie et al, 2001	RCT	1548	SICU pts w, w/o DM	I=80-110 mg/dL C=180-200 mg/dL D=SICU admit	3.4 % reduction in mortality w TGC. NNT 29 for survival in SICU	First Leuven study.
Furnary, et al, 2003	Quasi-experimental	3554	CABG pts w DM	I=100-150 mg/dL C= <200 mg/dL D= 3 <sup>rd</sup> POD	2.8% decrease in mortality w TGC. NNT 36 for survival during hospitalization.	Portland group. Historical controls
Van Den Berghie et al, 2006	RCT	1200	MICU pts w, w/o DM	I=80-110 mg/dL C=180-200 mg/dL D=MICU admit	9.5% decrease in mortality if pt treated >3days otherwise results NS. NNT 11.	Second Leuven study.
Gandhi, et al, 2007	RCT	400	CABG pts w, w/o DM	I=80-100 mg/dL C= <200 D= Intraop period	Results NS. Cannot rule out increased mortality with TGC	Mayo Clinic. Intervention only during surgery.
Preiser, et al. 2009	RCT	1101	M&SICU pts w, w/o DM	I=80-110 mg/dL C=140-180 mg/dL D=ICU admission	ICU mortality similar in 2 groups. Results NS due to early halting of study.	Glucose control study. Study halted for protocol violations.
Finfer, et al, 2009	RCT	6104	M&SICU pts w, w/o DM	I=81-108 mg/dL C= <180 mg/dL D=ICU admission	2.6% increase of risk of death In TGC group. NNH 38.	NICE-STUGAR study.

N=Number of patients. RCT=Randomized controlled trial. AMI=Acute myocardial infarction. w=with. w/o= without. DM=Diabetes mellitus. CABG=Coronary artery bypass graft. SICU=Surgical intensive care unit. MICU=Medical intensive care unit. I=Intervention group blood glucose goal. C=Control group blood glucose goal. D=Duration of study treatment protocol. POD=postoperative day. TGC=tight glucose control. DSW=Deep sterna wound. NNT= number needed to treat. NS= not statistically significant.

## V. Theories/explanations for variations among studies.

### A. Specifics of protocol.

1. Better results if TGC for 3 or more days.
2. Control group blood glucose parameters vary among studies.
3. Staffing patterns variable.
4. Differences in electrolyte, nutritional management.
5. Testing of blood glucose varies: Instrumentation includes laboratory testing vs. point of care testing, specimens include arterial, venous and capillary samples.

### B. Population

1. Outcomes vary between surgical and medical populations, non-diabetic and diabetic populations.

### C. Blood glucose variability

1. Variability of blood glucose, not just mean value demonstrated affect morbidity and mortality.

### D. Methodological. Studies vary depending on:

1. Blinding
2. Sample size
3. Setting (single vs. multicenter)

## VI. Treatment of hyperglycemia

### A. Basal/bolus principle

1. Proactive, mimics normal physiology. Used to effectively manage Type 1 & 2 diabetes.

### B. Sliding scale

1. Reactive. Efficacy not demonstrated in clinical studies.

### C. Infusion protocols

1. Characteristics of good protocol
  - a. Dynamic, accounts for variation in insulin sensitivity, blood glucose levels and rate of change in blood glucose.
2. Pharmacokinetics of IV insulin
  - a. Very short half life.
3. Route of administration
  - a. I.V. preferred in critically ill.
4. Testing (frequency, instrumentation, and specimen source)
5. Blood glucose parameters
  - a. Area of intense investigation & debate.

### D. Hypoglycemia

1. Incidence in TGC
2. Complications of hypoglycemia.
  - a. Animal studies
  - b. Clinical studies
3. Spontaneous vs. iatrogenic hypoglycemia.

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