Hypoglycemia After Bariatric Surgery: Diagnostic and Therapeutic Strategies

Mary-Elizabeth Patti MD
Investigator and Adult Endocrinologist
Research Division
Director, Hypoglycemia Clinic
Joslin Diabetes Center
Associate Professor of Medicine
Harvard Medical School
Eiger Pharmaceuticals – consultant

Medimmune – investigator-initiated research grant

Xeris Pharmaceuticals – collaborator on R44 NIH grant

Xoma – site investigator

Ethicon/Covidien – funding for multicenter ARMMS trial

Novo, Lifescan – support for ARMMS clinical trial

Janssen – investigator-initiated research grant
Thank you to...

**Joslin**
- Allison Goldfine
- CRC Nurses & Staff
- Kathy Foster
- Kristen Fowler
- Emilie Cloutier
- Christopher Mulla
- Ping Li
- Ali Bajwa
- Rohit Kulkarni
- Susan Bonner-Weir
- Gordon Weir
- Franco Folli
- Stefano La Rosa
- Jonathan Dreyfuss
- Hui Pan
- Emmy Suhl RD
- Joanne Rizzotto RD
- Patients!

**Harvard School of Engineering**
- Eyal Dassau
- Alejandro Laguna
- Frank Doyle

**Pathology**
- Jeffrey Goldsmith
- Eric Yee

**Radiology**
- Elisa Franquet
- Gerald Kolodny
- George Watts

**Surgery**
- Edward Mun
- Daniel Jones
- Ben Schneider
- Douglas Hanto
- Mark Callery
- David Lautz
- Jim Moser

**External Colleagues**
- Jens Holst
  - University of Copenhagen
- Jean-Claude Reubi
  - University of Geneva
- Clary Clish
  - Broad Institute

**Funding**
- NIH U01 – ARMMS
- NIDDK-SBIR (with Xeris)

**Harvard School of Engineering and Applied Sciences**
- John A. Paulson School of Engineering

**Veritas**
- American Society for Metabolic & Bariatric Surgery
- AZ/BMS/Amylin
- Medimmune
Common Bariatric Procedures in US

- Normal Anatomy
- Adjustable Gastric Band (AGB)
- Roux-en-Y Gastric Bypass (RYGB)
- Vertical Sleeve Gastrectomy (VSG)

ASMBS 2015: 193,000 procedures per year in US
Weight Loss is Sustained After Bariatric Surgery

Unadjusted Cumulative Mortality is Reduced After Bariatric Surgery

Prospective controlled study
What are the Effects on Glucose Metabolism?

Randomized controlled trials of surgery vs. intensive medical management for type 2 diabetes
SLIMM-T2D Randomized Trial: RYGB vs. Intensive Medical Management for T2D

Weight Loss Sustained

Improved A1c Sustained Only in RYGB

Why Wait Program*

RYGB

Why Wait

RYGB

A1c <6.5% and FPG <126 at 1 year: 58% of surgical patients (no meds) vs. 16% of intensive med Rx patients

Halperin...Osama Hamdy & WhyWait Team...Goldfine, JAMA Surgery 2014
Bariatric Surgery Improves Measures of Diabetes Control
5 Year Followup

Average 8.5 yrs of DM, 44% on insulin
Schauer PR et al., STAMPEDE, N Engl J Med 2017
Bariatric Surgery Improves Measures of Diabetes Control

5 Year Followup

Average 8.5 yrs of DM, 44% on insulin
Schauer PR et al., STAMPEDE, N Engl J Med 2017
5 Year Followup Shows Some Relapse of DM Despite Weight Maintenance

Sustained Weight Loss

Diabetes Remission*

* A1c <6.5% & 100-125 mg/dl on no Rx

Diabetes Medications

Mingrone et al Lancet 2015
Long-Term Observational Study Reveals Sustained Improvement in Diabetes Control & ↓ Complications

Prevalence of Diabetes Remission (FPG<110, no meds)

15 yrs

Microvascular

Macrovascular

SOS, Sjostrom et al. JAMA 2014
Multiple Mechanisms Contribute to Improvement in T2D Pathophysiology after RYGB

- ↓ hepatic glucose production
- ↓ ox glucose disp
- ↑ lipid oxidation
- ↑ GLP1 secretion
- ↑ β cell glc sensitivity
- ↑ insulin sensitivity
- ↑ nonox glc disposal
- ↓ adipose mass
- ↓ inflammation, ↑ signaling

All consequences of altered intestinal anatomy!
Complications of Bariatric Surgery

Perioperative morbidity

- Iron deficiency
- B12 deficiency
- Vitamin D deficiency
- Other nutrient deficiencies

- Hypoalbuminemia
- Osteopenia
- Osteoporosis
- Nephrolithiasis
- Neuropathy
- Cholelithiasis

- Marginal ulcers

- Weight regain

Hypoglycemia
Hypoglycemia is Increasingly Recognized After Bariatric Surgery
Post-Bariatric Hypoglycemia (PBH)

- **Hypoglycemia** is increasingly recognized in patients following bariatric surgery – especially gastric bypass but also sleeve gastrectomy.

- Hypoglycemia patterns similar to that of patients following gastrectomy and fundoplication.
OVERVIEW

• Clinical presentation of post-bypass hypoglycemia syndrome
• What are the metabolic profiles in affected patients?
• Potential mechanisms?
• Current research efforts
• Practical diagnostic and management strategies
What is Hypoglycemia?

Whipple’s triad required to diagnose hypoglycemia:

- Symptoms of hypoglycemia
- Low plasma glucose at time of symptoms
- Relief of symptoms by raising glucose

Allen O. Whipple
surgeon
Hypoglycemia Symptoms

<table>
<thead>
<tr>
<th>Adrenergic</th>
<th>Cholinergic</th>
<th>Neuroglycopenia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>Sweating</td>
<td>Impaired cognition</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Hunger</td>
<td>Seizures</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Paresthesias</td>
<td>↓ Consciousness</td>
</tr>
</tbody>
</table>

These symptoms are often nonspecific!

Overlap with dumping syndrome occurring after meals in bariatric patients
Hypoglycemia Symptoms

<table>
<thead>
<tr>
<th>Adrenergic</th>
<th>Cholinergic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>Sweating</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Hunger</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Paresthesias</td>
</tr>
</tbody>
</table>

Neuroglycopenia
- Impaired cognition
- Seizures
- ↓ Consciousness

**Hypoglycemia Unawareness:** A Threat to Safety

- loss of adrenergic or cholinergic warning symptoms
- abrupt onset of neuroglycopenia
- can result in serious falls, motor vehicle accidents, seizures, loss of consciousness
Representative Case - I

- 66 year old female with obesity since adolescence (BMI 48 kg/m²)
- No personal or family history of DM or hypoglycemia
- Roux-en-Y gastric bypass without complications
- Symptoms of dumping syndrome immediately postoperatively, resolved with dietary modification
- Presented at 24 months postop (BMI 35 kg/m², stable) with palpitations, sweating, and confusion
- Capillary glucose as low as 25 mg/dl (1.4 mM), typically 2-3 hours postprandial and in association with symptoms
- No fasting hypoglycemia, but more frequent with activity or stress
Hypoglycemia in Adults

Ill-Appearing
- Medications and OTC
- Insulin
- Insulin secretagogue
- EtOH
- Medication errors
- Others

Critical illness
- Hepatic, renal, cardiac failure
- Sepsis
- Malaria

Hormone deficiency
- Cortisol
- Glucagon/epi (in DM1)

Nonislet cell tumor – IGFII, IGF1

Malnutrition

Healthy-Appearing

Endogenous hyperinsulinism
- Insulinoma
- Functional β-cell disorders
  - NIPHS (noninsulinoma pancreatogenous hyperinsulinemia syndrome)
  - post-GI surgery

Autoimmune hypoglycemia
- antibodies to insulin
- antibodies to IR

Insulin secretagogue medicines & OTC
- EtOH

Surreptitious

Congenital Disorders
- hyperinsulinism
- other metabolic disorders
Hypoglycemia and Medications

Insulin
SFU
Meglitindes
EtOH
Tramadol
Quinolones
Pentamidine
Quinine
β-blockers
ACE-I
IGF1
Gleevec

Herbal supplements
SFU contaminants

Ackee, lychee fruit

<table>
<thead>
<tr>
<th>Drugs other than antihyperglycemic agents and alcohol reported to cause hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Moderate quality of evidence</strong></td>
</tr>
<tr>
<td>Cibenzoline</td>
</tr>
<tr>
<td>Gatifloxacin</td>
</tr>
<tr>
<td>Pentamidine</td>
</tr>
<tr>
<td>Quinine</td>
</tr>
<tr>
<td>Indomethacin</td>
</tr>
<tr>
<td>Glucagon (during endoscopy)</td>
</tr>
<tr>
<td><strong>Low quality of evidence</strong></td>
</tr>
<tr>
<td>Chloroquine oxalate sulfonamide</td>
</tr>
<tr>
<td>Artesunate/artesimin/artemether</td>
</tr>
<tr>
<td>IGF-1</td>
</tr>
<tr>
<td>Lithium</td>
</tr>
<tr>
<td>Propoxyphene/dextropropoxyphene</td>
</tr>
<tr>
<td><strong>Very low quality of evidence</strong></td>
</tr>
<tr>
<td>Drugs with &gt;25 cases of hypoglycemia identified</td>
</tr>
<tr>
<td>Angiotensin converting enzyme inhibitors</td>
</tr>
<tr>
<td>Angiotensin receptor antagonists</td>
</tr>
<tr>
<td>β-Adrenergic receptor antagonists</td>
</tr>
<tr>
<td>Levofloxacin</td>
</tr>
<tr>
<td>Mifepristone</td>
</tr>
<tr>
<td>Disopyramide</td>
</tr>
<tr>
<td>Trimethoprim-sulfamethoxazole</td>
</tr>
<tr>
<td>Heparin</td>
</tr>
<tr>
<td>6-Mercaptopurine</td>
</tr>
</tbody>
</table>

JCEM March 2009 Endocrine Society Clinical Practice Guidelines
Clinical Evaluation of Hypoglycemia

History of episodes
- symptoms, timing, duration
- examine all medications!
- MEN family history?
- neuroglycopenia – mandates full workup

Aggravating & relieving factors
- fasting?
- insulinoma
- meal-related symptoms?
- NIPHS, gastric surgery
- insulinoma
- anti-insulin antibodies
- anti-IR Ab – activation of IR
- post-GI surgery: functional defect or insulinoma
- exercise-induced?
- rare mutations in MCT1

Healthy-Appearing

Endogenous hyperinsulinism
- Insulinoma
- Functional β-cell disorders
  - NIPHS
  - post-gastric surgery

Autoimmune hypoglycemia
- antibodies to insulin
- antibodies to IR

Insulin secretagogue

Surreptitious or med errors

Rare: mutations in IR, MCT1
Clinical Evaluation of Hypoglycemia

Physical Exam

Laboratory Evaluation
  general
  anti-insulin Ab

Key questions:
  1. What is glucose at time of Sx?
  2. What are insulin and C-peptide at time of hypoglycemia?
  3. Does insulin secretion suppress appropriately, or
  4. Fail to suppress?
Diagnostic Evaluation of Hypoglycemia

Best option:

Try to “catch” symptoms.

Draw blood:
- venous glucose

If low, measure:
- insulin
- C-peptide
- proinsulin
- β-hydroxybutyrate
- drug screen
- ± cortisol
- urinary ketones

What if you can’t “catch” spell?

Try to recapitulate factors causing symptoms.

- fast
  - overnight vs. 72 hour in hospital?
- meal (mixed meal)

Same labs

NOT OGTT!
- Provoke dumping
- Not physiologic
- Lacks specificity
Postprandial Hypoglycemia?
Analyze Response to Meals: Mixed Meal Testing

- not OGTT!
- 10% of pts have glc <50 on OGTT, normal on MMTT, no EEG changes
- assess whether symptomatic hypoglycemia develops
- often lack of correlation between glucose and Sx
- what is insulin/C-peptide response?
- no standards for interpretation
Representative Case - II

- Symptoms ↑ in frequency and severity (3 per day),
  - falls
  - loss of consciousness
  - witnessed seizures with documented glucose 36 mg/dl (2 mM)

- Unprovoked symptomatic episode:
  - glucose 48 mg/dl (3.0 mM)
  - insulin 11 μU/ml (2-30), C-peptide 2.9 ng/ml (1.1-3.2)
  - insulin level inappropriately high in face of hypoglycemia
  - negative sulfonylurea screen, negative anti-insulin Ab
  - normal adrenal function

Documented Hypoglycemia in Post-Bariatric Patient
Assess Frequency, Severity, Timing?
Frequent hypoglycemia with symptoms (red) Minimum 41 mg/dl (2.3 mM), peak 213 Most 1-3 hours after meals

Confirmed by low venous glucose
The Roller Coaster of Post-Bypass Glycemia

Postprandial spikes
Nocturnal lows
Postprandial lows

Range: 40-203; 15% of readings under 70 (0-25%)
Continuous Glucose Monitoring Reveals Spikes and Troughs of Glucose Values

Rapid rise in glucose after eating
“Spike”

Hypoglycemia: Adrenergic Sx
Capillary glucose 61 mg/dl
Treatment with glucose tablets

Neuroglycopenia
Confusion, fall
Capillary glucose 51
Representative Case - III

- Initial treatment aimed to reduce stimulus for meal insulin secretion:
  - dietary modification – low glycemic index
  - acarbose

- Ongoing severe hypoglycemia with seizures
  - Concern for safety
  - ? Some nocturnal & early AM hypoglycemia by history and diagnostic CGM

- Insulinomas can present with postprandial hypoglycemia
  - Important to r/o as Rx would be surgical
  - Proceeded with inpatient fast
Normal Suppression of Insulin Secretion During 72-Hour Fast

End-of-test glucagon stimulation: normal (<25 mg/dl increase), reflecting glycogen depletion with fast
• No evidence for autonomous insulin secretion
  • Insulinoma unlikely

• No need for imaging
  • CT/MRI, endoscopic ultrasound, arteriography

Dx: Post-Bariatric Hypoglycemia
Characteristics of Patients with Severe Post-Bypass Hypoglycemia (Neuroglycopenia)

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Pre-Op BMI</th>
<th>Post-Op BMI</th>
<th>Time Postop (yr)*</th>
<th>Clinical Description</th>
<th>Timing (hour)</th>
<th>Glucose (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>46</td>
<td>M</td>
<td>40.6</td>
<td>23.1</td>
<td>1.6</td>
<td>Motor vehicle accident</td>
<td>1-1.5 hr</td>
<td>29</td>
</tr>
<tr>
<td>69</td>
<td>F</td>
<td>48.4</td>
<td>35.2</td>
<td>1.8</td>
<td>Loss of consciousness</td>
<td>1 hr</td>
<td>50</td>
</tr>
<tr>
<td>62</td>
<td>F</td>
<td>49.7</td>
<td>24.5</td>
<td>2.4</td>
<td>Presyncope, confusion</td>
<td>3 hr</td>
<td>low*</td>
</tr>
<tr>
<td>37</td>
<td>F</td>
<td>49.7</td>
<td>26.8</td>
<td>2.8</td>
<td>Unresponsive</td>
<td>2 hr</td>
<td>58</td>
</tr>
<tr>
<td>42</td>
<td>F</td>
<td>65.1</td>
<td>37.1</td>
<td>0.8</td>
<td>Syncope, blurred vision</td>
<td>1 hr</td>
<td>24**</td>
</tr>
<tr>
<td>41</td>
<td>F</td>
<td>42.0</td>
<td>27.7</td>
<td>3.3</td>
<td>Confusion, blurred vision</td>
<td>1 hr</td>
<td>47</td>
</tr>
<tr>
<td>52</td>
<td>F</td>
<td>54.0</td>
<td>28.7</td>
<td>1.7</td>
<td>Confusion</td>
<td>1-1.5 hr</td>
<td>25</td>
</tr>
<tr>
<td>56</td>
<td>F</td>
<td>65.3</td>
<td>37.6</td>
<td>1.3</td>
<td>Confusion</td>
<td>1.5 hr</td>
<td>39</td>
</tr>
<tr>
<td>36</td>
<td>F</td>
<td>44.8</td>
<td>28.1</td>
<td>2.7</td>
<td>Confusion</td>
<td>1 hr</td>
<td>23</td>
</tr>
<tr>
<td>31</td>
<td>F</td>
<td>42.8</td>
<td>31.1</td>
<td>2.0</td>
<td>Presyncope, confusion</td>
<td>3-4 hr</td>
<td>40’s</td>
</tr>
<tr>
<td>51</td>
<td>M</td>
<td>37.0</td>
<td>32.4</td>
<td>1.3</td>
<td>Syncope</td>
<td>2-3 hr</td>
<td>low*</td>
</tr>
<tr>
<td>56</td>
<td>F</td>
<td>73.6</td>
<td>35.4</td>
<td>3.8</td>
<td>Grand mal seizure</td>
<td>1.5</td>
<td>48</td>
</tr>
</tbody>
</table>

* First neuroglycopenic episode
Take Home Messages About Severe Post-Bariatric Hypoglycemia

- A subset of patients have severe hypoglycemia with neuroglycopenia and unawareness:
  - Documented low plasma venous glucose levels at time of neuroglycopenia, with inappropriately high insulin levels
  - Symptoms resolve with glucose administration
  - Typical onset 2-3+ years after surgery
  - Usually 1-3 hours after meals
  - Normal glucose and insulin response to prolonged fasting
Hypoglycemic Disorder

*Symptoms*
Adrenergic, Cholinergic, or Neuroglycopenic

Glucose Level During Symptoms?

- **<70 mg/dl**
  - Possible Hypoglycemia
    - Is Whipple’s triad* present?
      - Hypoglycemic Sx
      - VENOUS glc <50
      - Relief with CHO
    - YES
      - Hypoglycemic Disorder
        - Assess Patterns, R/O Other Causes of Hypo
          - Reactive pattern? >6 mo after surgery?
          - Fasting or nocturnal hypo?
          - Started <6 mo after bariatric surgery?
            - Likely Post-Bariatric Hypoglycemia Syndrome
            - Initial Treatment Nutrition, Acarbose
            - Incomplete Response
            - Not Typical Post-Bariatric Hypoglycemia!
              - Could This Be Insulinoma?
            - Assess fasting insulin (overnight or prolonged inpatient fasting)
              - If inappropriately ↑, imaging or SACST
        - NO
          - Unlikely Hypoglycemia
            - Consider Dumping Syndrome, CV Disorders

- **>70 mg/dl**
OVERVIEW

• Clinical presentation of post-bypass hypoglycemia syndrome
• What are the metabolic profiles in affected patients?
• Potential mechanisms?
• Current research efforts
• Practical diagnostic and management strategies
Postprandial Glucose Patterns Differ in Post-GB Patients

Mixed meal tolerance test after overnight fast, 40g CHO
Goldfine and Patti, JCEM 2007
Postprandial Glucose Patterns Differ in Post-GB Patients

Goldfine & Patti, JCEM 2007
Postprandial Glucose Patterns Differ in Post-GB Patients

Goldfine & Patti, JCEM 2007
Postprandial Glucose Patterns Differ in Post-GB Patients

Goldfine & Patti, JCEM 2007
What about fundoplication or sleeve?

Hypoglycemia also observed:
- fundoplication (for reflux)
- sleeve gastrectomy

OGTT in patients after SG:

Hypoglycemia:
- PG <60 mg/dl at 90 or 120 min
  - 6 mo: 25% of SG pts
  - 12 mo: 33% of SG pts
- Distinct patterns

Papamargaritis D et al. Obesity Surgery 2012
OVERVIEW

• Clinical presentation of post-bypass hypoglycemia syndrome
• What are the metabolic profiles in affected patients?
• Potential mechanisms?
• Current research efforts
• Practical diagnostic and management strategies
Potential Mechanisms Contributing to Post-Bariatric Hypoglycemia

Increased secretion?  
Increased islet mass?
Glucose Lower and Insulin Higher in Post-GB Patients with Neuroglycopenia

Goldfine & Patti, JCEM 2007
Increased Insulin to Glucose Molar Ratio Following Mixed Meal

![Graph showing the increased insulin to glucose molar ratio following a mixed meal. The graph includes data points for GB+NG, GB, OW, and MOB conditions.]

\[ p \text{ (ANOVA)} = 0.001 \]

Goldfine & Patti, JCEM 2007

Similar results for C-peptide
Surgical Pathology in Patients with Severe Post-GB Hyperinsulinemic Hypoglycemia

Anti-Glucagon Stain

- Partial pancreatectomy for refractory hypoglycemia
  - Not performed any longer as not curative
- No insulinoma
- Diffuse increase in islet number
- Islets of varying size & shape

Patti et al Diabetologia, 2005; Service NEJM 2005
*Increased Islet Size in Severely Affected Post-Bypass Hypoglycemia Patients*

**RYGB:** Patients requiring pancreatectomy for severe hypoglycemia (n=6)

**Controls:** Organ donors or benign tumors (n=10)

Reubi & Patti, Diabetologia 2010; increased size/number not consistently observed (Butler et al)
Increased Islet Area & Markers of Proliferation in Severely Affected PBH Patients

Patti...Kulkarni. Acta Diabetologia 2017
N=6 controls, n=9 PBH
No difference in apoptosis markers
Potential Mechanisms Contributing to Post-Bariatric Hypoglycemia

- Increased secretion
- Increased islet size
- Altered clearance

Why is prandial insulin secretion high??
Role of incretin hormones?

Adapted from Patti, Gastroenterology 2014
Incretin Responses to Mixed Meal are Enhanced Post-GB

**GLP-1**

- GB+NG
- GB
- OW
- MOb

**GIP**

- GB+NG
- GB
- OW
- MOb

**Fasting GLP-1**

- GB+NG
- GB
- OW
- MOb

* p (ANOVA) = 0.03

* * * p (ANOVA) = 0.0005

Goldfine & Patti, JCEM 2007
High levels of GLP1 in fasting and post-meal state

GLP1 inhibitory peptide infused *in vivo* reduces insulin secretion (Salehi et al)

Infusion of nutrients into the bypassed duodenum via G tube reduces incretin & insulin secretion in parallel & can improve hypoglycemia

BUT…hypoglycemia not always after eating – can occur with stress, activity
Do Additional Mechanisms Contribute to Hypoglycemia Beyond Postprandial Incretin and Insulin Secretion?

YES!

Are these incretin-independent?
Analyze insulin secretion in response to IV glucose
↑ Insulin Secretion & ↑ Glucose Effectiveness in Response to IV Glucose in Patients with Severe Post-Bariatric Hypoglycemia

↑ Acute Ins Response to IV Glucose

Trend to ↓ Insulin Sensitivity (SI)

↑ Glucose Effectiveness (Insulin-Independent Glucose Disposal)

IVGTT with minimal model analysis
Patti & Goldfine, Obesity (Silver Spring) 2015
Role of Altered Counterregulation?
Glucagon Levels Do Not Differ in Patients with Neuroglycopenia but are Increased in Both Groups of Post-GB Patients vs. Controls

No differences in cortisol, leptin, adiponectin

Goldfine & Patti, JCEM 2007
Reduced Counterregulatory Responses during Hypoglycemic Clamp after RYGB

Abrahamsson et al. Diabetes 2016

- Glucagon
- Cortisol
- Epi
- Norepi
- GH
- GLP1
- GIP
- HR Var

*Values are reported as the mean (SEM) for counterregulatory hormones, incretin hormones, and HRV during clamp preoperatively and postoperatively. *Significant difference. Target glucose levels during clamp are shown on top. Insets: AUC, *p<0.05, **p<0.01, ***p<0.001.
Potential Mechanisms Contributing to Post-Bariatric Hypoglycemia

**Insulin-Dependent Mechanisms**
- Increased postprandial insulin secretion
- Postprandial hypoglycemia

**Insulin-Independent Mechanisms**
- Increased GLP-1 secretion from L-cells

**Altered systemic metabolism & counterregulation**

**Role of gut control of metabolism**
- Increased rate of appearance of glucose after oral ingestion
- Gut as a glucose-consuming metabolic organ?
- ↑ Bile acids
- Gut flora
- Other components of the gut-liver-brain axis?
Both Insulin-Dependent and Independent Mechanisms Contribute to Hypoglycemia

- ↑ Intestinal hormones
- ↑ Bile acids
- Altered intestinal mucosa
- ↑ Intestinal glucose uptake
- Altered gut-liver-brain axis
- Altered counterregulation

?Genetic Susceptibility

Insulin-Dependent Mechanisms

Postprandial Hypoglycemia

Insulin-Dependent Mechanisms

Increased postprandial insulin secretion

Increased GLP-1 secretion from L-cells

Exendin 9-39

Islet
Summary: Post-Bariatric Hypoglycemia

Hypoglycemia after bariatric surgery is linked to both *insulin-dependent* and *insulin-independent* glucose disposal.

Need to define precise mechanisms responsible!

- Plasma proteomics & metabolomics analysis in patients with PBH
- Testing candidates in rodent models to assess impact on glycemia
- Are mechanisms similar to those responsible for T2D resolution after bariatric surgery?
Plasma Proteomics Analysis Reveals Peptides Significantly Altered in Both PBH and in T2D Treated with RYGB

Somalogic analysis

↑ in both hypoglycemia and in s/p RYGB

Hypo vs. No Hypo  RYGB vs. Medical Rx for T2D
OVERVIEW

• Clinical presentation of post-bypass hypoglycemia syndrome
• What are the metabolic profiles in affected patients?
• Potential mechanisms?
• Current research efforts
• Practical management strategies
Clinical Management Strategies

• **Safety:** Test glucose before driving, before bed, and in situations where hypoglycemia likely:
  – After meals, after exercise
  – Nocturnal, especially if AM headaches, vivid dreams, sweating

• Consider diagnostic or **personal CGMS** to detect trends early and determine frequency of asymptomatic hypoglycemia.

• Family instruction in glucagon use
  – It is effective as therapy!

• Wear medical ID bracelet.

• Correct nutrient deficiencies:
  • Fe, B12, vitamin D, Ca, B-complex, minerals
  • Cornstarch (grocery, Extend, UCAN)
Clinical Management Strategies

• **Dietary interventions** to reduce stimulus for insulin secretion:
  – frequent small meals
  – moderate intake of low glycemic index (complex) carbohydrates (<30 g/meal)
  – RD assessment (**Emmy Suhl, RD extraordinaire!**)
  – Emphasize adequate protein and macro/micronutrient intake.

• Cornstarch: grocery, Extend, UCAN

• Avoid EtOH, caffeine.
Medical Nutrition Therapy is the Cornerstone of Treatment of PBH

Prevention: reduce stimulus for insulin secretion

– Reduce intake of simple carbohydrates
– Controlled portions of complex carbs

Standard Diet

Controlled CHO Diet

Nielsen 2016
10-Point Nutrition Plan for Post-Bariatric Hypoglycemia

1. Control portions of carbohydrate – 30 g/meal, 15 g/snack.
2. Choose low-glycemic carbohydrates.
3. Avoid high-glycemic carbohydrates.
4. Include (heart-healthy) fats in each meal or snack – 15 g/meal, 5 g/snack.
5. Emphasize optimal protein intake.
7. Avoid consuming liquids with meals.
8. Avoid alcohol.
9. Avoid caffeine.
10. Maintain post-bariatric vitamin and mineral intake.
**Choose** Low Glycemic Index CHO (GOOD!)

- Steel-cut oats (regular, not quick-cook or instant)
- Oat bran cereal
- Beans/legumes (e.g., garbanzo, navy, kidney, lima, pinto, black-eyed and pea beans, edamame [soybeans], lentils)
- Bean products (e.g., hummus, tofu)
- Pearled barley, cooked al dente
- Yams
- Some fruits (e.g., grapefruit, apples, pears, berries, apricots, peaches)
- Some pasta (e.g., Barilla Plus pasta), cooked al dente
- Some whole grain breads (e.g., Ezekiel bread, Joseph’s Flax, Oat Bran & Whole Wheat Pita/Lavash/Tortillas)
- Some whole grain crackers (e.g., RyKrisp, RyVita, Wasa)

**Avoid** High Glycemic Index CHO (“BAD”)

- Refined breakfast cereals (e.g., Corn Flakes, Rice Krispies, Cream of Rice, instant oatmeal)
- Regular pasta
- Most starchy vegetables (e.g., white potatoes, corn, winter [orange] squash)
- White rice, rice cakes
- Popcorn, pretzels, chips
- Some fruits (e.g., ripe bananas, pineapple, mango, watermelon, grapes)
- All fruit juices and sweetened drinks (e.g., sodas, sweetened iced tea)
- Bread, rolls, bagels, English muffins, and crackers made with refined flour
- Sweets (e.g., candy, cake, cookies, ice cream, syrup)
## Don’t Forget Supplements!

<table>
<thead>
<tr>
<th>Supplement</th>
<th>Recommendations for the Post-bariatric Surgery Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Multivitamin-multimineral:</strong></td>
<td>200% of daily value (2 per d)</td>
</tr>
<tr>
<td>● Begin with chewable or liquid,</td>
<td></td>
</tr>
<tr>
<td>progress to whole tablet/capsule</td>
<td></td>
</tr>
<tr>
<td><strong>Vitamin B12:</strong></td>
<td>1000 µg/mo intramuscularly</td>
</tr>
<tr>
<td>● Sublingual tablets, liquid</td>
<td>Sublingual/oral tablet dose: 350-500 µg/day to start,</td>
</tr>
<tr>
<td>drops, or mouth spray; if</td>
<td>may need to increase dose</td>
</tr>
<tr>
<td>inadequate response, intramuscular</td>
<td></td>
</tr>
<tr>
<td>injection may be needed</td>
<td></td>
</tr>
<tr>
<td>● Note &gt;1000 mg of supplemental</td>
<td></td>
</tr>
<tr>
<td>folic acid combined with</td>
<td></td>
</tr>
<tr>
<td>multivitamin supplements may</td>
<td></td>
</tr>
<tr>
<td>mask B12 deficiency</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Calcium Citrate and Vitamin D3</strong></td>
<td>1500–2000 mg/d Calcium Citrate</td>
</tr>
<tr>
<td>● Begin with chewable or liquid,</td>
<td>1500–2000 IU/d Vit D3 (with dose adjustments guided</td>
</tr>
<tr>
<td>progress to whole tablet/capsule</td>
<td>by laboratory assessment of vitamin D levels)</td>
</tr>
<tr>
<td>● Split into 500–600 mg dose</td>
<td></td>
</tr>
<tr>
<td>● Do not combine with iron</td>
<td></td>
</tr>
<tr>
<td>containing supplements. Wait &gt;2 h</td>
<td></td>
</tr>
<tr>
<td>after taking multivitamin or iron</td>
<td></td>
</tr>
<tr>
<td>supplement</td>
<td></td>
</tr>
<tr>
<td><strong>Iron</strong></td>
<td>18–27 mg/d elemental iron</td>
</tr>
<tr>
<td>● Recommended for menstruating</td>
<td></td>
</tr>
<tr>
<td>women and those at risk for</td>
<td></td>
</tr>
<tr>
<td>anemia. Begin with chewable or</td>
<td></td>
</tr>
<tr>
<td>liquid, progress to tablet.</td>
<td></td>
</tr>
<tr>
<td><strong>B complex vitamins</strong></td>
<td>Vitamin B-50 complex 1 per d</td>
</tr>
<tr>
<td>● Liquid form, avoid time-released</td>
<td></td>
</tr>
<tr>
<td>tablets</td>
<td></td>
</tr>
</tbody>
</table>
Clinical Management Strategies

Stepped pharmacology:
- **Acarbose** – to slow CHO absorption, reduce postprandial hyperglycemia and stimulus for insulin secretion; may also slow gastric emptying and reduce glucagon secretion
  - usually limited by abdominal gas
Effects of Acarbose:
↓ Peak Glucose, ↑ Nadir Glucose, ↓ Insulin Peak, ↓ GLP1
Clinical Management Strategies

Stepped pharmacology:
- Acarbose
- Octreotide – to reduce incretin & insulin secretion
  - options: preprandial SQ and monthly IM
  - 50 μg pre-meal to start
  - Usually limited by diarrhea
  - Occasional worsening of hypoglycemia immediately after injection, presumably due to inhibition of glucagon secretion
- Diazoxide – to reduce insulin secretion, limited by edema
  - No response to calcium channel blockade, anticholinergics, β-blockade in our experience

Consider: G tube feeds into remnant stomach.
   Reversal of bypass when feasible.
Pancreatectomy not curative! - not a mass problem
G-Tube Delivery of Nutrients into the Bypassed Stomach in Post-GB Patient Yields Normal Insulin Secretion

McLaughlin T JCEM 2010
Symptom Recurrence is Nearly Universal after Partial Pancreatectomy

Figure 1.
Kaplan-Meier estimates of symptom-free survival after pancreatic resection for noninsulinoma pancreatogenous hypoglycemia.
Investigational Approaches

• Block GLP1 action
  • Clinical trial of investigational GLP1R antagonists

• Improve counterregulatory responses to prevent and treat hypoglycemia
  • Clinical trials of investigational stable glucagon
  • Guided by CGM data and computational prediction of hypoglycemia
  • Delivery by pump before hypoglycemia develops
Investigational GLP1R Inhibitor Exendin 9-39 Reduces Insulin Secretion and Alters Prandial Glucose in PBH
Investigational Approaches

• **Block GLP1 action**
  • Clinical trial of investigational GLP1R antagonists

• **Improve counterregulatory responses to prevent and treat hypoglycemia**
  • Clinical trials of investigational stable glucagon
  • Guided by CGM data and computational prediction of hypoglycemia
  • Delivery by pump before hypoglycemia develops
• Clinical trial of **stable investigational glucagon**
• Infusion via pump
• Delivery guided by CGM sensor and glucose data predictions

Rapid drop after meal
Predicted hypo
Trigger GCG delivery before hypo onset
## Prevalence of Hypoglycemia after Roux-en-Y Gastric Bypass Surgery

<table>
<thead>
<tr>
<th>Method of Ascertainment</th>
<th>Prevalence</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalization</td>
<td>0.1-1%</td>
<td>Marsk, Gribsholt, Sarwar, Lee</td>
</tr>
<tr>
<td>Clinical recognition</td>
<td>0.4-6.6%</td>
<td>Kellogg, Gribsholt</td>
</tr>
<tr>
<td>Symptoms (survey)</td>
<td>33%</td>
<td>Lee</td>
</tr>
<tr>
<td>OGGT glucose &lt;50mg/dl</td>
<td>10%-33%</td>
<td>Pigeyre, Goldfine, Papamargatis (sleeve)</td>
</tr>
<tr>
<td></td>
<td>55% &lt;60</td>
<td>Feichtinger (pregnancy, 75 g OGGT)</td>
</tr>
<tr>
<td>MMTT glucose &lt;55 mg/dl</td>
<td>29%</td>
<td>Kefurt*</td>
</tr>
<tr>
<td>CGMS (sensor glucose &lt;55 mg/dl)</td>
<td>75%</td>
<td>Kefurt*</td>
</tr>
<tr>
<td>CGMS (sensor glucose &lt;60 mg/dl)</td>
<td>30-71 minutes</td>
<td>Halperin, Abrahamsson, Kefurt **</td>
</tr>
</tbody>
</table>

*median duration postop 7.4 years; ** threshold <55 mg/dl
What is Different About These Patients?

- OGGT preop and 12 months postop in 222 patients
- Postop hypo defined by glucose at 120 minutes:
  - >50
  - <50

No Hypo  
N=199

Hypo  
N=23  
(10%)

No difference in preop insulin levels, BMI, wt loss  
Pigeyre M, SOARD 2015
What is Different About These Patients?

216 non-diabetic morbidly obese subjects undergoing bariatric surgery

163 treated by RYGB
34 enrolled

53 treated by LSG
51 enrolled

21 self-reporting PPHG symptoms and glucose ≤2.7 mmol/L on the OGTT (PPHG group)

13 not reporting PPHG symptoms and/or glucose ≤2.7 mmol/L on the OGTT (No-PPHG group)

11 self-reporting PPHG symptoms and/or glucose ≤2.7 mmol/L on the OGTT (PPHG group)

40 not reporting PPHG symptoms and/or glucose ≤2.7 mmol/L on the OGTT (No-PPHG group)

75 g OGTT pre and post op at 1-2 yr

14/21 had glu < 2.7 on OGTT preop
None of no-PPHG had glu < 4 mM preop

Nannipieri M JCEM 2016
What is Different About These Patients?

Preop evaluation of those patients developing hypo after RYGB:
- Lower BMI
- Lower fasting plasma glucose
- Lower nadir glucose
- Higher insulin sensitivity
- Higher \( \beta \)-cell glucose sensitivity
- Reduced insulin clearance

Not different:
- Fasting insulin similar
- Insulin secretion rates similar

Logistic regression model predictors (both RYGB& LSG): Insulin sensitivity, insulin clearance, nadir glucose during OGTT preop

_Nannipieri M JCEM 2016_
Patients Developing PBH Have Higher Insulin Secretion (Beta-Cell Glucose Sensitivity) Preoperatively.
Can We Predict Using Clinical Features?

**Preop**

- Female
- Lower A1c
- Lower BMI
- History of hypoglycemia
- Greater early weight loss (6 mo)

**Postop**

- Female
- Lower A1c
- Lower BMI
- History of hypoglycemia
- Greater early weight loss (6 mo)
Food Intake in Post-Bariatric Patient

- Accelerated Intestinal Delivery
- Rapid ↑ Plasma Glucose

Chronic Intestinal & Neural Adaptation
- Dysregulated Enteroendocrine Cell Secretion
  - ↑ GLP1, GIP, glucagon
  - Altered Gut Microbiota
  - ↑ Bile Acids
  - Altered Intestinal Metabolism
  - β-Cell Trophic Hormones

↑ Postprandial Insulin Secretion

↑ Insulin-Independent Glucose Disposal

? Genetic Variation

Severe Postprandial Hypoglycemia

Patti & Goldfine, Lancet Diab & Endo, 2016
Thank You!

Mary.elizabeth.patti@joslin.harvard.edu