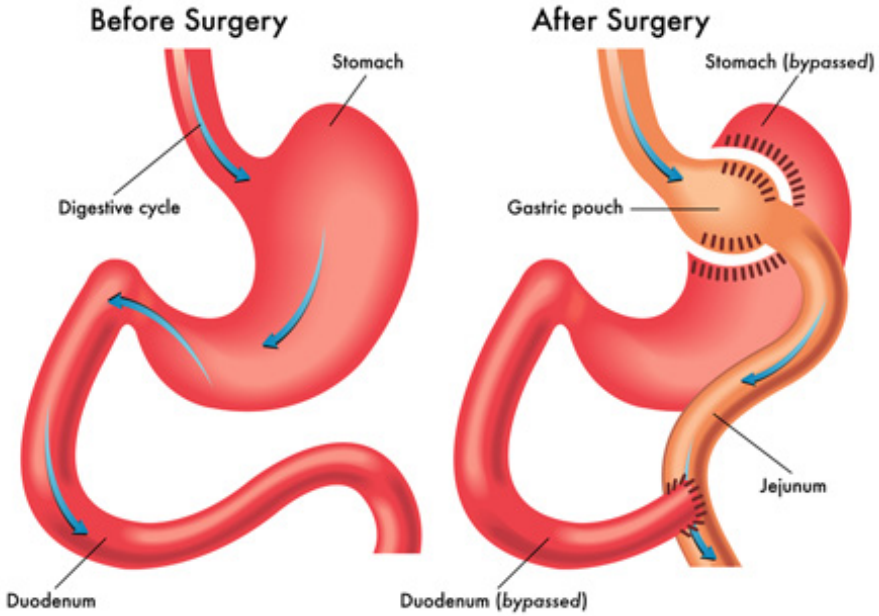
Post-Bariatric Sugery Hypoglycemia in Patients with Diabetes

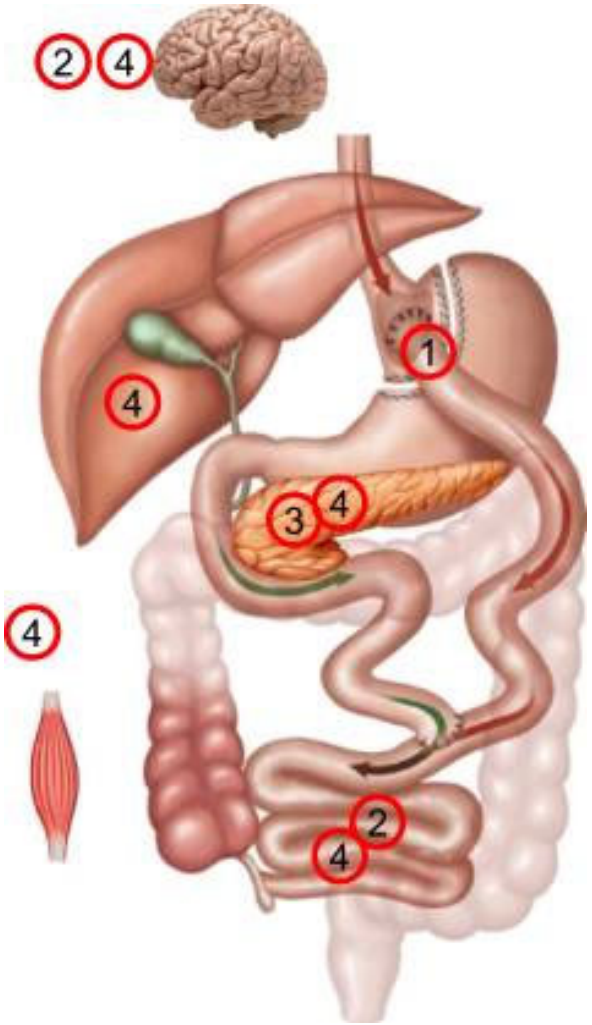
Tribal Diabetes ECHO

March 11,2021

Changes in Gastric Transit after RYGB

- Anatomic changes of Roux-en-Y gastric bypass (RYGB) →bypassing of the pylorus and proximal intestine → ***accelerated nutrient emptying*** from stomach pouch to intestine (roux limb)





Effects of Rapid Transit

- **Altered alcohol absorption**
  - Higher, sooner
- **Dumping Syndrome** (early-stage: 30-60 min)
  - Excessively concentrated food mass
  - Fluid & gut hormone shifts
  - Diarrhea, bloating, cramps, dizzy/faint, etc.
- **Post-Bariatric Hypoglycemia** (late-stage dumping syndrome: ~3hours))
  - Rapid & excessive glucose peak
  - Increased Insulin
  - Exaggerated Incretin (GLP-1)
  - Further increase in Insulin
  - Exaggerated glucose drop (→ low)
  - Abnormal glucagon responses
  - Autonomic & Neuroglycopenic symptoms

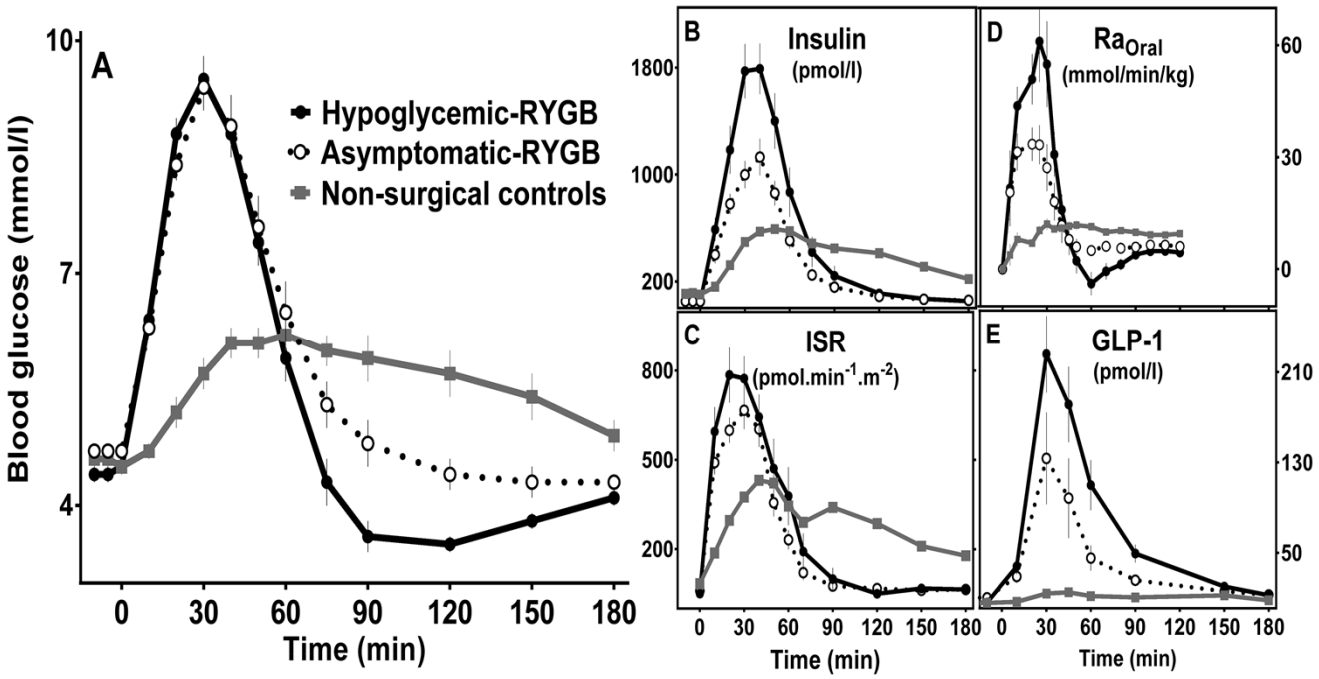
Changes in Glycemic Pattern after RYGB

- Accelerated nutrient emptying from stomach pouch to intestine (roux limb) → *wider glycemic excursion* after food intake, with an *earlier and greater peak* of glucose, as well as a *lower glucose nadir*

- As a result of the rapid delivery of nutrients to the proximal foregut, early postprandial ***secretion of insulin and GLP-1*** **is** ***exaggerated*** after RYGB.
  - Meal-induced GLP-1 response increases by 10-fold
  - The **postprandial hyperinsulinemia** after RYGB is typically attributed to the combined effects of more rapid nutrient transit from the gastric pouch to the gut, as well as an enhanced incretin effect

- Plausible that post-RYGB hypoglycemia simply reflects extreme glycemic effects of RYGB in a subgroup of susceptible individuals.

Figure 1. Typical glycemic and hormonal patterns in the fasting state and after mixed meal. (A) Blood glucose, (B) ...



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Abnormal Glucagon Responses after RYGB

- In addition to altered β-cell function after RYGB, ***α-cell*** responses are changed
  - **Food intake *enhances* glucagon response after RYGB** compared with nonsurgical controls via unknown mechanisms (normal response is suppression of glucagon with food)
    - **meal-induced glucagon secretion** in post-RYGB patients, with and without hypoglycemia, is similar
  - By contrast, there is a substantial ***reduction in glucagon response to hypoglycemia*** after RYGB.
    - Diminished counter-regulatory responses after RYGB may perpetuate recurrent hypoglycemia and unawareness in affected individuals

Hypoglycemia After Gastric Bypass Surgery: Current Concepts and Controversies

Marzieh Salehi, Adrian Vella, Tracey McLaughlin, Mary-Elizabeth Patti
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- Hypoglycemia, occurring after bariatric and other forms of upper gastrointestinal surgery, is increasingly encountered.
- The true frequency of this condition remains uncertain, due to
  - differences in the diagnostic criteria
  - differences in the affected populations
  - relative lack of patient and physician awareness and understanding of this condition
- Postbariatric hypoglycemia can be severe and disabling for some patients, with ***neuroglycopenia*** (altered cognition, seizures, and loss of consciousness) leading to falls, motor vehicle accidents, and job and income loss.
  - Repeated episodes of hypoglycemia can result in ***hypoglycemia unawareness***, further impairing safety and requiring the assistance of others to treat hypoglycemia.

Establish if Hypoglycemia is the Cause of Symptoms & If so – Is the Hypoglycemia related to RYGB or another Cause

- Details of the episodes (history) is a critical first step in the evaluation & should include
  - severity (frequency, presence of neuroglycopenia, whether assistance is required)
  - timing (relationships to fasting, meals, specific provocative foods, activity, and presence of nocturnal symptoms).
  - detailed records of symptoms, food, and activity can be helpful in identification of patterns linked to symptoms.
- "*Although continuous glucose monitoring (CGM) is less accurate in the hypoglycemic range, blinded monitoring may be helpful to identify patterns of glycemic excursions but should not be used for diagnostic purposes.*"
- Typically, presentation with post-bariatric hypoglycemia (PBH)
  - **First occurs >1 year after surgery**
  - Symptoms usually occur **1 to 3 hours after eating.**
  - Hypoglycemia *with activity and during overnight hours (e.g., 2 to 4 AM)* is occasionally reported by patients

Establish if Hypoglycemia is the Cause of Symptoms & If so – Is the Hypoglycemia related to RYGB or another Cause

- Not typical of PBH (raises concern of for other causes) is hypoglycemia occurring
  - very early in the postoperative period (<6 to 12 months),
  - in the fasting state
  - >4 hours after caloric intake
  - with activity and during overnight hours (e.g., 2 to 4 AM) is occasionally reported by PBH patients, but these patterns should also prompt consideration of alternative diagnoses.
- If hypoglycemia in well-appearing individuals occurs in the ***fasting*** state, then an additional workup should be performed to rule out ***insulinoma***.
- Consider ***additional causes of hypoglycemia***, such as malnutrition, side effects of medications or supplements, critical illness, hormone deficiencies, autoimmune hypoglycemia, or nonislet cell tumors.

Need to Confirm Symptoms are due to Hypoglycemia

- Glucose patterns alone cannot define who has hypoglycemia – integration with symptom profiles is essential
  - *The typical* glycemia post-RYGB include normal fasting glucose but ***exaggerated postprandial excursions*** with a rapid rise in glucose shortly after food intake and a fast decline thereafter
- Postbariatric patients have ***postprandial autonomic symptoms***, such as lightheadedness, palpitations, and fatigue, which may represent manifestations of the ***dumping syndrome*** but also *overlap* significantly with autonomic symptoms of ***hypoglycemia***.
- Given the complexity of distinguishing between symptoms of hypoglycemia and dumping syndrome, researchers propose that a strict definition of hypoglycemia be used in the postbariatric population
  - Whipple's Triad = **symptoms** with **concomitant low plasma glucose** with **symptoms relieved by correction of the hypoglycemia**, typically within a few minutes
  - Some require BG <70 or < 60, some require <50 (54) with neuroglycopenia symptoms

Confirming Hypoglycemia & Whipple's Triad

- If the history is typical for PBH syndrome, then the next step is to determine whether symptoms are caused by hypoglycemia and relieved by carbohydrate ingestion (Whipple's triad).
- In an ideal world, an analysis of *venous glucose at the time of a spontaneous episode of hypoglycemia* would be optimal.
  - However, this is often not practical; patients may not be able to predict when they will develop symptoms as a result of day-to-day variability and may not be able to get to a laboratory safely to have blood sampling at the time they are experiencing symptoms.

Therapy of Post-Bariatric Hypoglycemia

- The goal of therapy in post-RYGB hypoglycemia is to reduce the frequency and severity of hypoglycemia, thus improving safety and allowing resumption of activities of daily living.
  - With currently available therapies, the complete elimination of hypoglycemia in severely affected patients is unlikely, and ongoing vigilance to safety is essential.

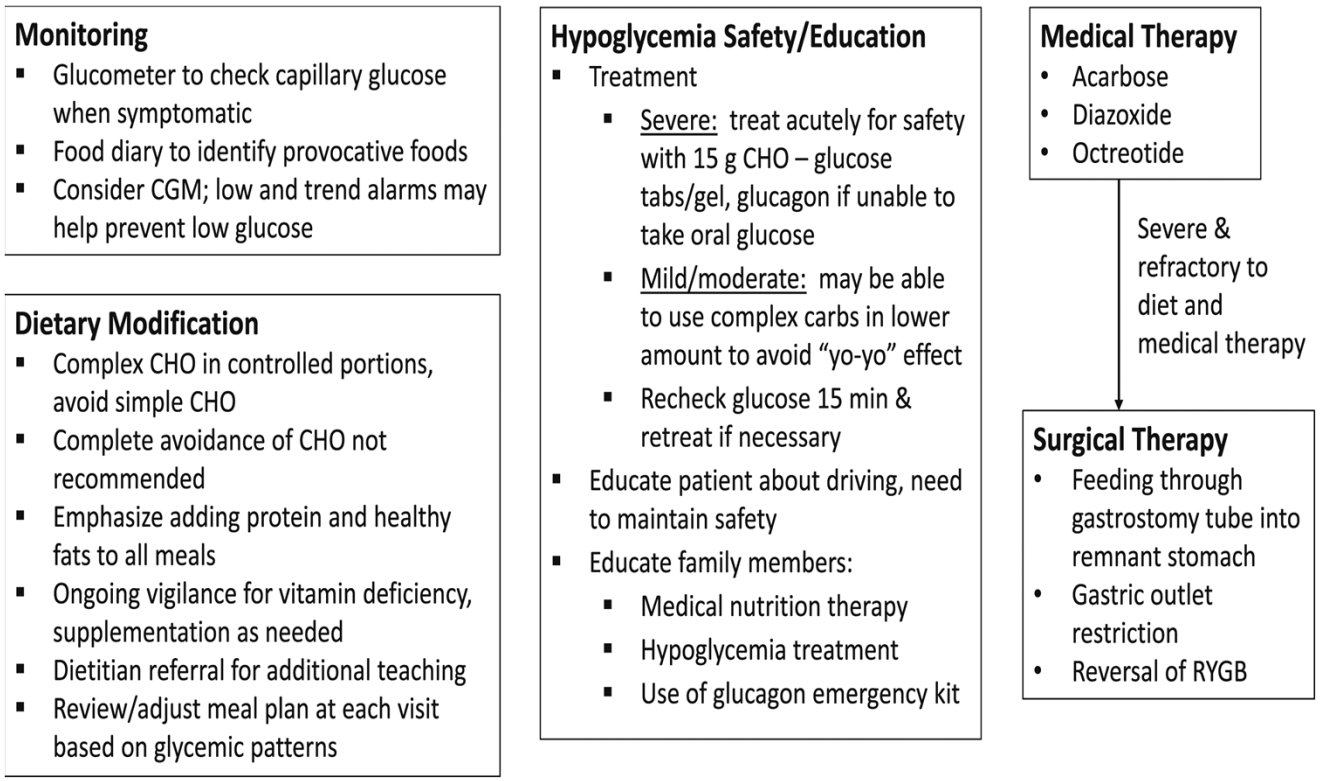
Medical nutrition therapy

- Diet is the cornerstone of therapy for post-RYGB hypoglycemia and is aimed at reducing the stimulus for glycemic spikes and insulin secretion.
  - Unfortunately, there are no well-designed studies comparing the long-term impact of meal plans with different nutrients and/or macronutrient composition.
  - In counseling patients, we emphasize that diet is not the cause of post-RYGB hypoglycemia but is an essential component of treatment

Acute treatment of hypoglycemia

- Immediate treatment with glucose tablets or gels is recommended when post-bariatric patients experience hypoglycemia, to optimize safety.
  - Treatment is recommended if the glucose is under 70 mg/dL according to the "rule of 15":
    - consume 15 grams of glucose, such as 4 glucose tablets or 1 tube of glucose gel, then wait 15 minutes to recheck blood glucose. If glucose is not at least 80 mg/dl, repeat treatment with 15 grams of glucose.
  - BG less than 50 mg/dL typically requires treatment with 30 grams of glucose.
  - Gels can be swallowed, but for faster glucose absorption, *glucose gels can be held between gum and cheek for absorption via the buccal mucosa.*
- While this treatment protocol is designed to rapidly increase the patient's glucose level, thus improving safety, ***rapid spikes in blood glucose may also trigger later hypoglycemia in PBH patients***.
  - If this is a consistent pattern, a lower initial glucose treatment dose e.g., 8–12 g, may be suggested, with careful testing to ensure adequate treatment of hypoglycemia.
  - In addition, we recommend that patients ***eat a low glycemic index snack after treating hypoglycemia to avoid repeated hypoglycemia***.
- ***Glucagon*** for severe hypoglycemia

Figure 4. Suggested approach to the treatment of established post-RYGB hypoglycemia.



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Medical Nutrition Therapy for Post-Bariatric Hypoglycemia: Practical Insights
Emmy Suhl,a Sue-Ellen Anderson-Haynes,a Christopher Mulla,a,b and Mary-Elizabeth Pattia,b

- https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5469688/

Additional Helpful Recommendations

- Proteins and fats are not only essential for a balanced meal plan but can also slow nutrient absorption, reducing glucose spikes and subsequent hypoglycemia. Adequate intake of protein and healthy fats should be guided by the team dietitian.

- Additional recommendations include
  - fully chewing food and eating slowly,
  - avoiding liquids with meals to prevent dumping symptoms and instead drinking between meals,
  - portion control to avoid weight regain,
  - avoidance of excessive caffeine and alcohol, which can cause hypoglycemia via inhibition of hepatic glucose release.

- CGM - Although there are no data addressing the value of CGM in post-RYGB hypoglycemia at present, and accuracy of sensor glucose values is reduced in the hypoglycemic range, many patients find CGM to be a valuable tool in detecting patterns of dropping glucose, particularly in patients with hypoglycemia unawareness.
  - Trend curves and alarms, available on some but not all CGM, can enable early treatment and prevention of severe hypoglycemia.
  - The attainment of insurance coverage for patients with post-RYGB hypoglycemia can be very challenging; preauthorization letters and appeals are typically required.

Pharmacotherapy

Medications are an important adjunct to medical nutrition therapy.

- **Acarbose** delays and reduces absorption of glucose by inhibition of intestinal α-glucosidase, which is required to break down luminal carbohydrates into monosaccharides.
  - This has the effect of reducing postprandial glycemic excursions.
  - Gastrointestinal side-effects of gas and abdominal cramping can limit tolerance,
    - introduction of low doses (e.g., 25 mg before each meal) and slow escalation to the maximal tolerated dose can be effective in limiting side-effects

Surgery (Partial Pancreatectomy)??

- Initial reports indicated that ***increased β-cell mass*** might contribute to increased insulin secretion in post-RYGB hypoglycemia when compared with surgical controls.
  - Subsequent analyses revealed no differences in overall β-cell mass when the same samples were compared with autopsy specimens.
- Regardless, the finding that reduction in β-cell mass by ***partial pancreatectomy*** has ***not*** been ***effective*** in fully resolving hypoglycemia over time in post-RYGB patients also suggests that increased β-cell mass is not the dominant contributor to PBH.

Extra Slides

Uncooked Cornstarch

- Uncooked cornstarch is not readily absorbed by the small intestine but is slowly hydrolyzed by pancreatic amylase and intestinal glucoamylase to provide a steady supply of exogenous glucose.
- Cornstarch has been successfully used to treat hypoglycemia in glycogen storage disease, hyperinsulinemic hypoglycemia of infancy, and insulin–antibody-mediated hypoglycemia.
- It has not been studied in the PBH population but may be an option for preventing hypoglycemia.
  - Commercial products containing cornstarch are reported by some to be helpful, especially for hypoglycemia occurring at night and during physical activity.

What is dumping syndrome after gastric bypass surgery?

- Dumping syndrome after gastric bypass surgery is when food gets “dumped” directly from your stomach pouch into your small intestine without being digested. There are 2 types of dumping syndrome: early and late. Early dumping happens 10 to 30 minutes after a meal. Late dumping happens 1 to 3 hours after eating. Each has slightly different symptoms, such as abdominal cramping, fast heartbeat, lightheadedness, and diarrhea.

- What causes dumping syndrome after gastric bypass surgery?
- Early dumping syndrome can occur because of the dense mass of food that gets dumped into your small intestine at an earlier stage of digestion. The intestines sense that this food mass is too concentrated, and release gut hormones. Your body reacts by shifting fluid circulating in your bloodstream to the inside of your intestine. As a result, your intestines become fuller and bloated. Diarrhea often occurs 30 to 60 minutes later. In addition, certain substances are released by your intestine that affect heart rate and often blood pressure, causing many of the symptoms of early dumping. This can lead to lightheadedness or even fainting.

- Symptoms of late dumping happen because of a decrease in blood sugar level (reactive hypoglycemia). Reactive hypoglycemia is low blood sugar caused 1 to 3 hours after a large surge of insulin. You are more likely to have dumping syndrome if you eat a meal heavy in starches or sugars. The sugars can be either fructose or table sugar (sucrose). Insulin levels can increase to high levels, then lower your blood sugar too much.

- Who is at risk for dumping syndrome after gastric bypass surgery?
- Dumping syndrome can happen in at least 3 out of 20 people who have had a part of their stomach removed for any reason.

What are Symptoms of Dumping Syndrome?

Most people have early dumping symptoms

- Bloating
- Sweating
- Abdominal cramps and pain
- Nausea
- Facial flushing
- Stomach growling or rumbling
- An urge to lie down after the meal
- Heart palpitations and fast heartbeat
- Dizziness or fainting
- Diarrhea

About 1 in 4 people have late dumping symptoms

- Heart palpitations
- Sweating
- Hunger
- Confusion
- Fatigue
- Aggression
- Tremors
- Fainting

How is dumping syndrome after gastric bypass surgery treated?

- The main treatment for dumping syndrome is changes in your diet. These include
  - Don’t drink liquids until at least 30 minutes after a meal.
  - Divide your daily calories into 6 small meals.
  - Lie down for 30 minutes after a meal to help control the symptoms.
  - Choose complex carbohydrates such as whole grains.
  - Avoid foods high in simple carbohydrates, such as those made white flour or sugar.
  - Add more protein and healthy fat to your meals.

Natural History of PBH

- The natural history of post-RYGB remains uncertain.
  - One series that identified hypoglycemia based on clinical and billing data found that the median time from surgery to the hypoglycemic event was 41 months; 79% of cases identified eventually resolved.
  - Dumping syndrome-related symptoms generally improve over time by avoiding triggers, whereas severe hypoglycemia does not.
    - Given that recurrent hypoglycemia can also be associated with hypoglycemia unawareness, continued vigilance for asymptomatic hypoglycemia is suggested. Additional longitudinal studies will be required to address fully the natural history of both asymptomatic and symptomatic hypoglycemia.

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Medical Nutrition Therapy for Post-Bariatric Hypoglycemia: Practical Insights
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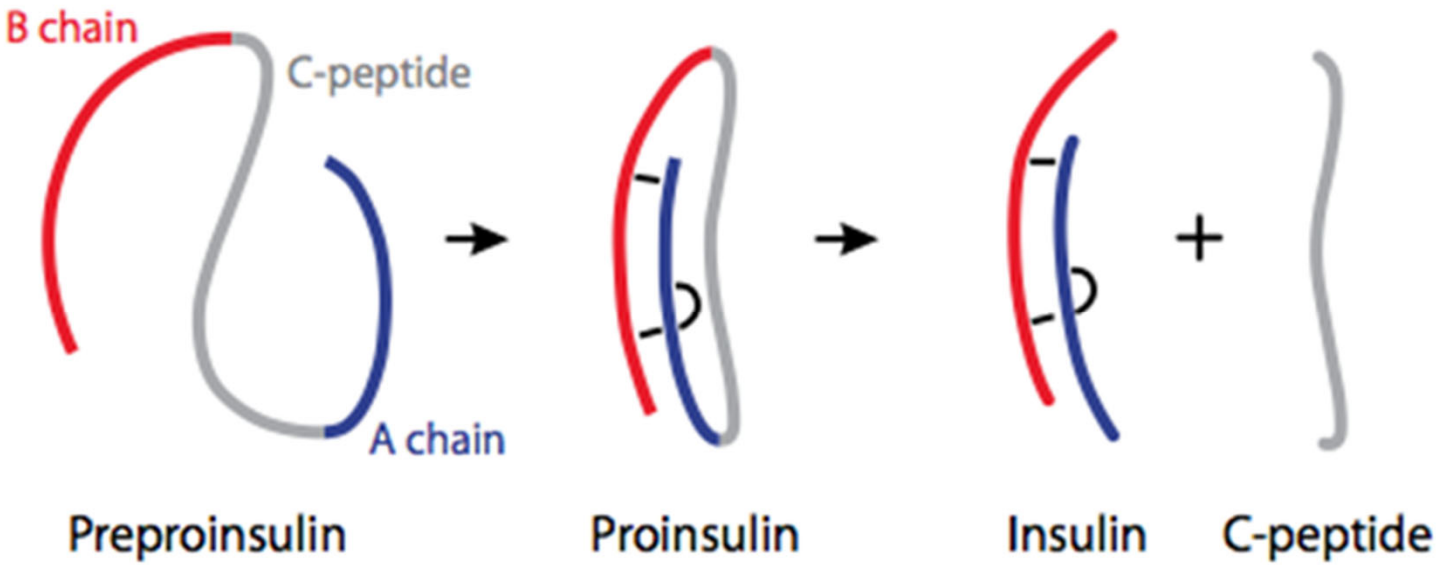
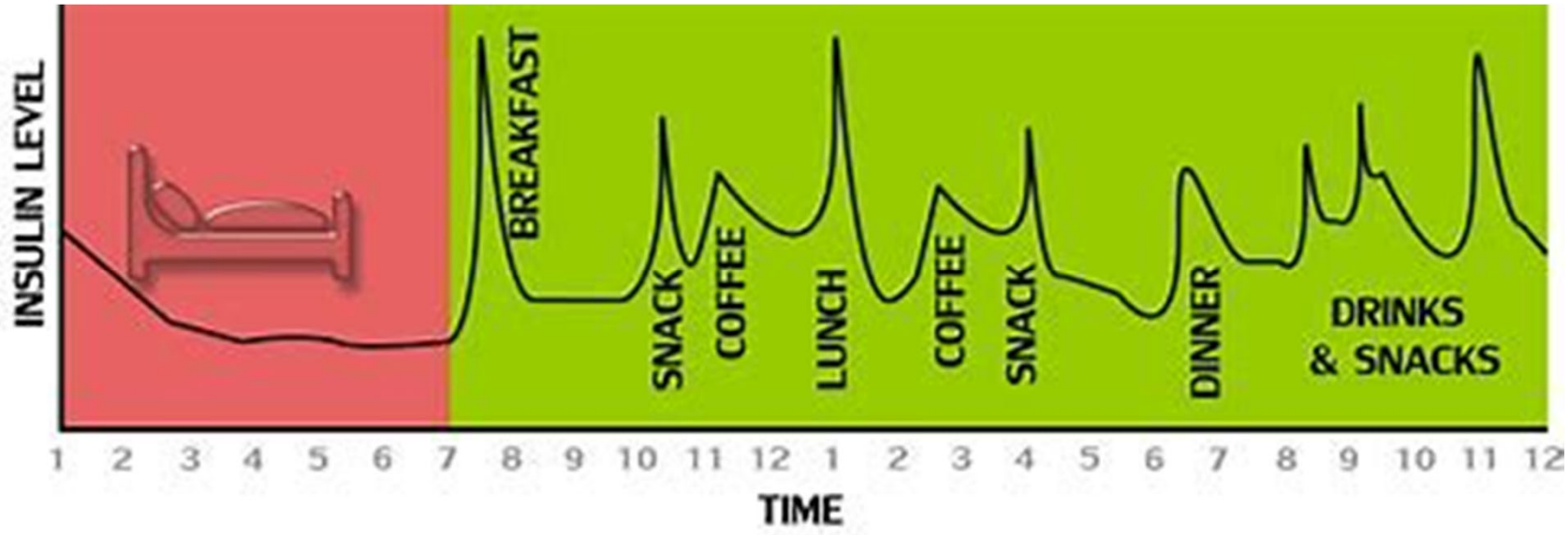
C-peptide

Presented by:
Carol Greenlee, MD MACP

C-peptide – utilized for indication of endogenous insulin secretion



Normal Insulin & C-peptide Levels



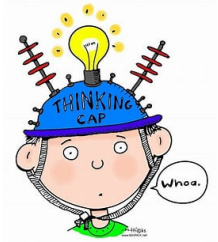
Insulin vs C-peptide

- Insulin is cleared by the liver (first pass through the liver after secretion from the pancreas), thus the measurement of insulin in peripheral blood does not accurately reflect secretion from pancreas
- C-peptide is not cleared by the liver and thus can be measured in the blood peripherally to provide an indication of insulin release from pancreas
- C-peptide has a longer half-life than insulin (30 minutes compared to 4 minutes for insulin).
- Renal failure, with a creatinine clearance of less than 50 mL/min, has been shown to increase fasting insulin levels by approximately 20% and fasting ***C-peptide levels increase by 100% (****due to reduced clearance – no longer indicative of beta-cell capacity)*

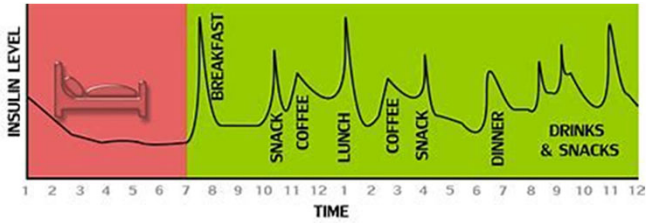
What *should* we see in lab results with:

- Normal fasting state
  - Low insulin & low C-peptide
- Hypoglycemia (low BG) (fasting levels)
  - Due to starvation?
    - Low insulin level, low C-peptide level
  - Due to taking too much exogenous insulin?
    - High insulin level, *low* c-peptide level
  - Due to a tumor making to much insulin (insulinoma)?
    - Inappropriately *high* insulin level, inappropriately *high* c-peptide level
  - Due to too much sulfonylurea (glipizide, etc.)?
    - High Insulin, high c-peptide
  - Due to Post Bariatric changes?
    - Should not be *fasting* hypoglycemia – if so consider "other" cause
    - Not recommended to measure insulin/C-peptide – research studies show incompletely suppressed insulin/C-peptide (residual from exaggerated release)

What *should* we see in lab results with:



- Hyperglycemia (high BG)
  - Due to a glucose load / meal?
    - Increase in/ high insulin and increase in/high c-peptide



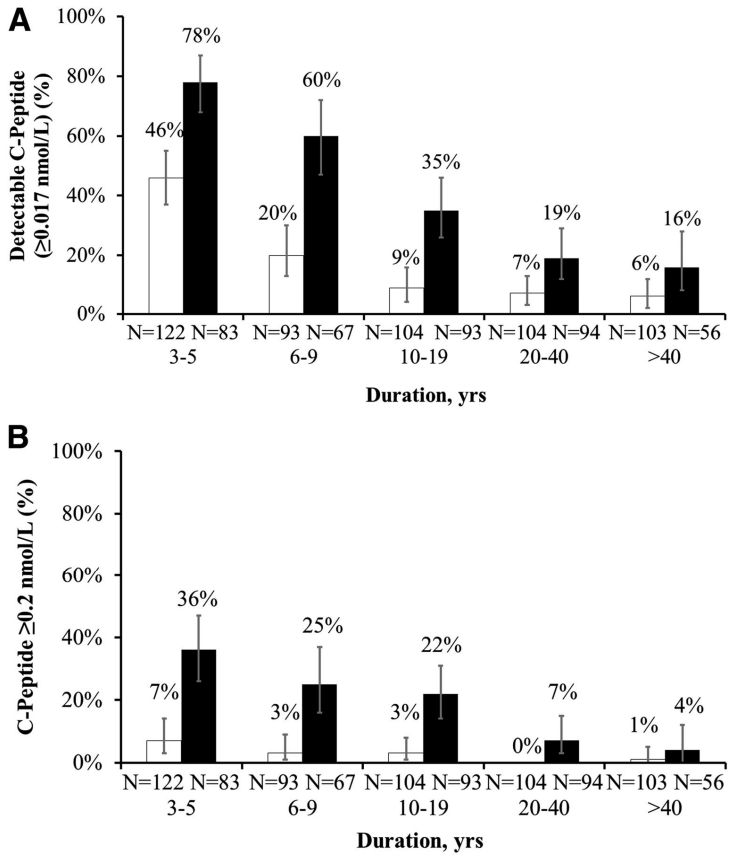
  - Type 1 Diabetes?
    - You would think undetectable insulin & c-peptide *BUT* it depends
  - Type 2 Diabetes ?
    - You would think detectable to high insulin & c-peptide *BUT* it depends

C-peptide is not a reliable indicator of the type of diabetes

Residual Insulin Secretion (+ C-peptide levels) in T1DM

- The American Diabetes Association 2014 Standards of Care describe **type 1 diabetes** as *"β-cell destruction, usually leading to absolute insulin deficiency"*. -- This statement has led to the ***belief that the presence*** of ***residual insulin secretion is unexpected*** in this population.
- A study of more than 900 participants with ***type 1 diabetes*** ranging from 3 to 81 years from diagnosis *demonstrated otherwise*:
  - **78%** of participants diagnosed at >18 years of age and **46%** of those diagnosed at ≤18 had **residual C-peptide** 3–5 years from diagnosis
  - **16%** of adult-onset and **6%** of childhood-onset cases had residual C-peptide even >40 years from diagnosis.

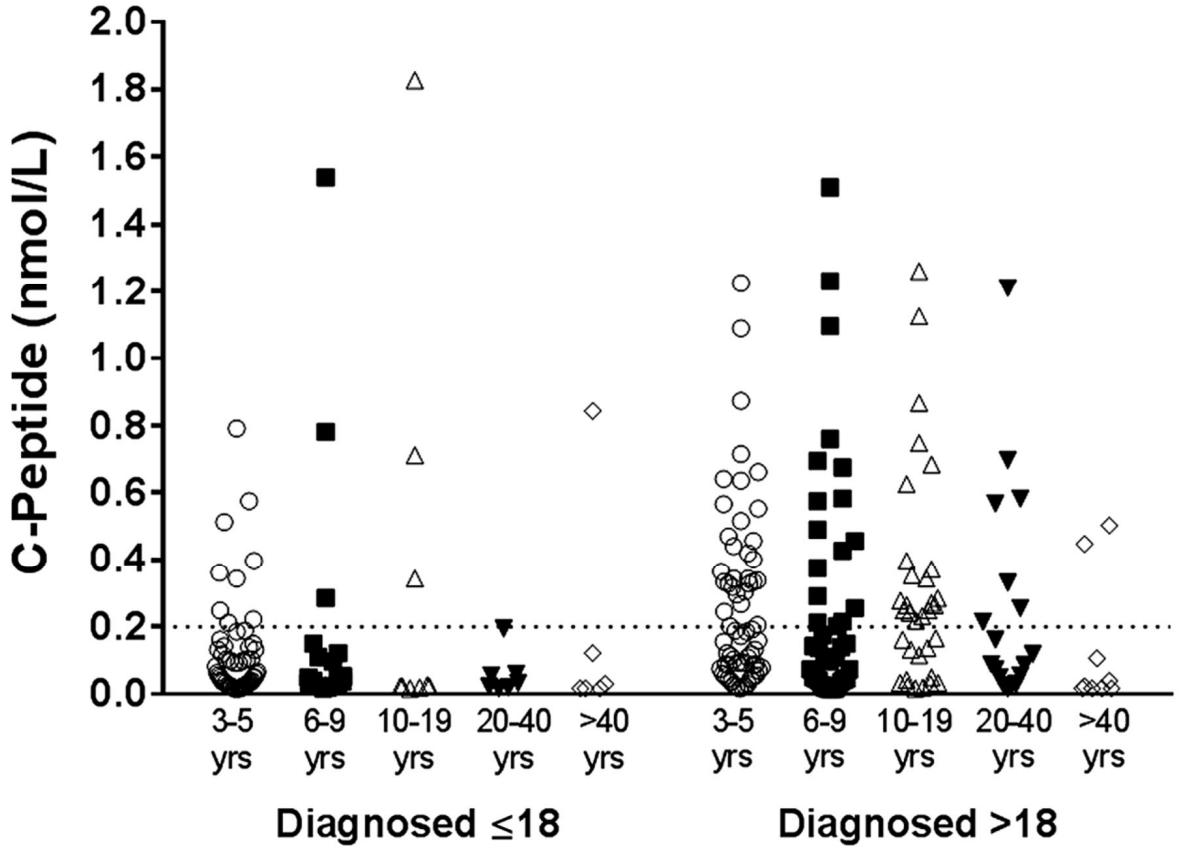
A: Proportion of participants with detectable (≥0.017 nmol/L) nonfasting C-peptide, according to age at diagnosis and duration of type 1 diabetes.



Asa K. Davis et al. Dia Care 2015;38:476-481

American Diabetes Association.

Nonfasting C-peptide values by diagnosis age and duration bins for participants with detectable levels.



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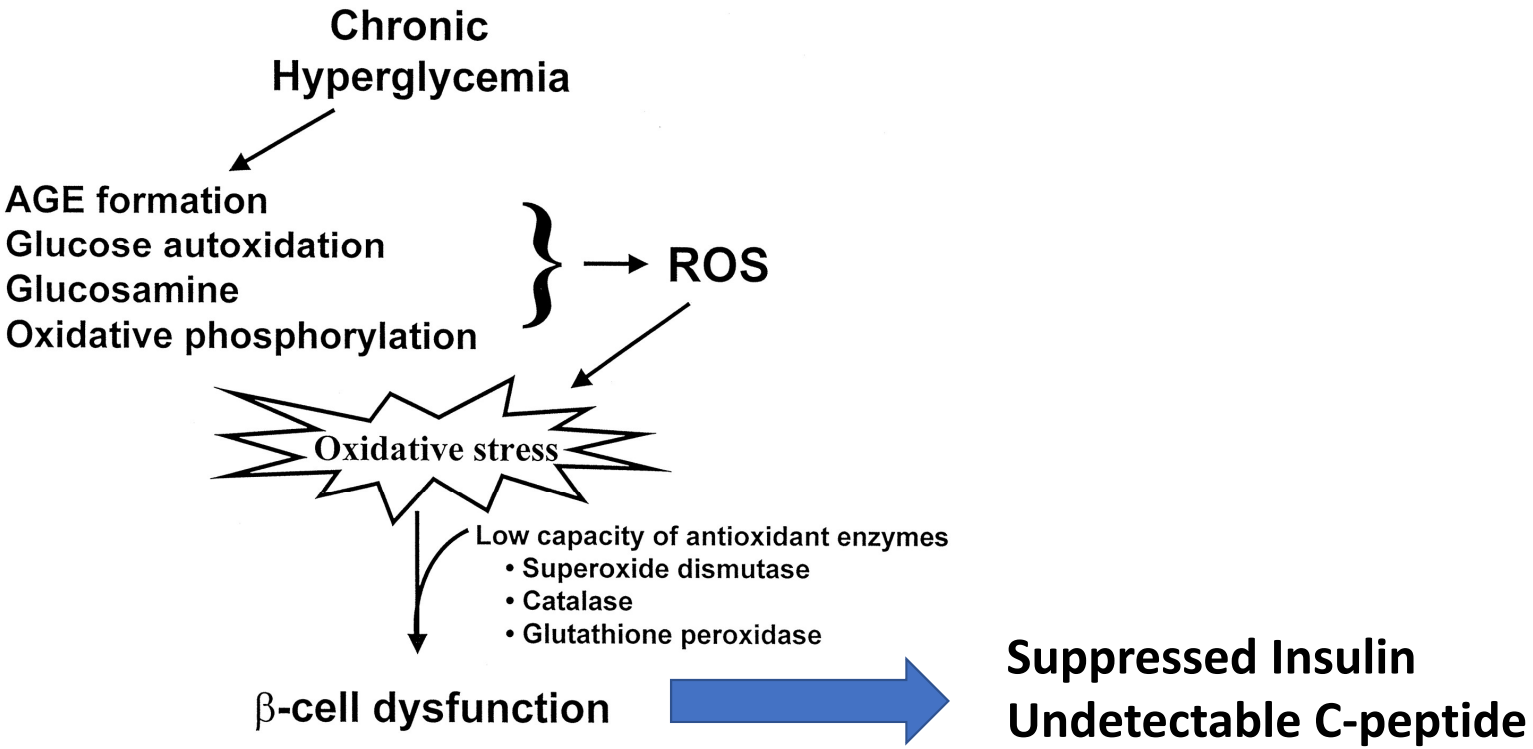
American Diabetes Association.

Can have undetectable C-peptide in T2DM

High glucose levels can cause *glucose toxicity to the ß-cell* and impair both blood levels of C-peptide and insulin

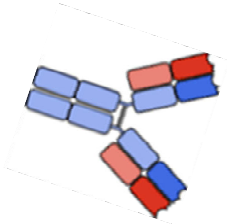


The broad clinical phenotype of type 1 diabetes at presentation

SR Merger, RD Leslie, BO Boehm - Diabetic medicine, 2013 - Wiley Online Library

- Immune-mediated (auto-immune) Type 1 diabetes mellitus is not a homogenous entity, but nonetheless has distinctive characteristics.
- In children, it may present with classical insulin deficiency and ketoacidosis at disease onset, whereas autoimmune diabetes in adults may not always be insulin dependent.
- Indeed, as the adult-onset form of autoimmune diabetes may resemble Type 2 diabetes, it is imperative to test for ***diabetes-associated autoantibodies to establish the correct diagnosis***.

DAA (Diabetes Auto-Antibodies)



- **IA-2A** (insulinoma-antigen2)(54-75%)
- IAA (Insulin autoantibody)
  - Highest sensitivity in children <10
  - Positive after 7-10 days of insulin therapy (so no longer useful for diagnosing)
- **GAD65 AB** –most common and persistent (80%)
  - Level >20 u/ml most significant
  - Weakly positive can be false + assay or general population
- ICA (islet cell antibody) (69-90% at dx)
- ZnT8A (more aggressive progression, loss of Beta cells/Insulin)

For the most part, IAA, GADA, IA-2A, & ZnT8A have replaced ICA

Age of Onset & BMI and Type 1 Diabetes

Demographics

- Increased in young children
  - Fewer with high-risk HLA genes
- Also, more ***adult onset***
  - Seen as late as 9th decade
- More LADA
  - Very slowly progressive loss of beta cells (some only partial loss)
  - 5-10% of T2DM in studies of T2DM meds found to have +DAA
    - More rapid progression to Insulin
    - If GAD >20, likely T1DM
- "Immune-mediated diabetes"

BMI at Diagnosis (2004-2007 data)

- **20% BMI >30**
- **45% BMI 25-29.9**
- 30% BMI 20-24.9
- 5% BMI <20
- Weight gain following Dx

- T1DM
  - 1:3000 for general population
  - 1:20 (15x) in family member

Stages of T1DM

- Stage 1: 2+ DAA, normal glucose levels
  - 35/100 go on to T1DM
- Stage 2: 2+ DAA, abnormal glucose levels, no sxs
- Stage 3: 2+ DAA, symptomatic hyperglycemia, dx
- Stage 4: longstanding T1DM

Rate of progression from +DAA to T1DM is highly variable

- Rapid under age 10
- Slower after age 20
  - Some are LADA, very slow, maybe never totally lose Beta cells

The broad clinical phenotype of type 1 diabetes at presentation

SR Merger, RD Leslie, BO Boehm - Diabetic medicine, 2013 - Wiley Online Library

- Latent autoimmune diabetes in adults (LADA) is a slowly progressing form of immune-mediated diabetes often misdiagnosed as type 2 diabetes because of its typical clinical presentation, i.e., an adult *without* weight loss or ketoacidosis not initially requiring insulin