



CARDIOMETABOLIC HEALTH CONGRESS

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# Shifting the Paradigm to Bariatric and Metabolic Surgery: The Solution for Obesity and Diabetes?

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# Case

**50-year-old woman seen following RYGB –  
has lost 30 kg in 6 months and is no longer hungry.  
Which gut hormone changes might be helping  
reduce hunger?**

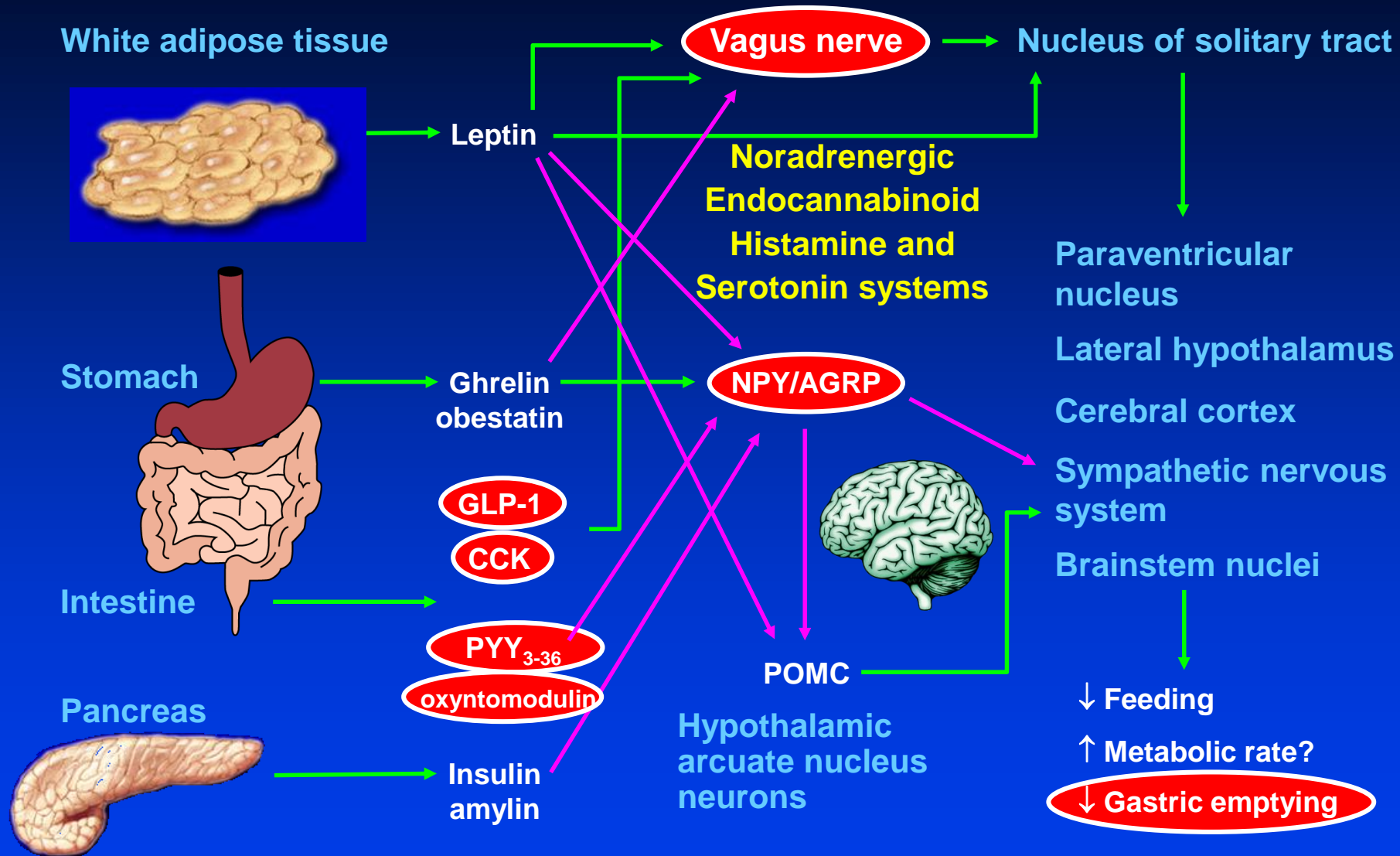
**1) Ghrelin**

**2) GLP-1**

**3) Oxyntomodulin**

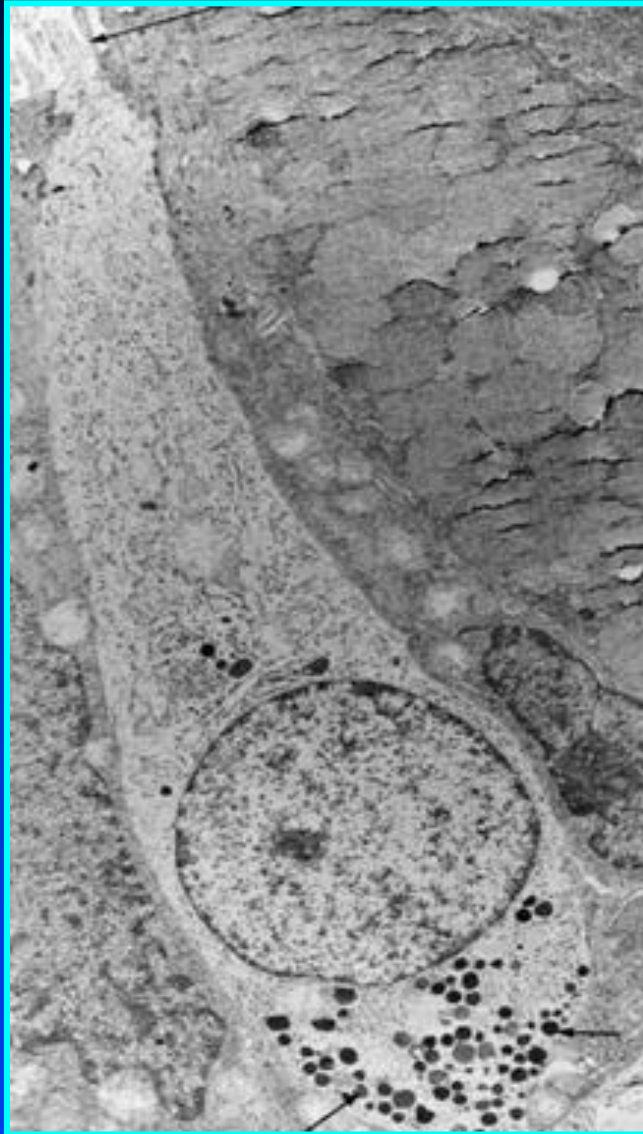
**4) What the heck is oxyntomodulin?**

# Appetite Regulation



Adapted from Neary et al. *Clin Endocrinol.* 2004;60:153-160.

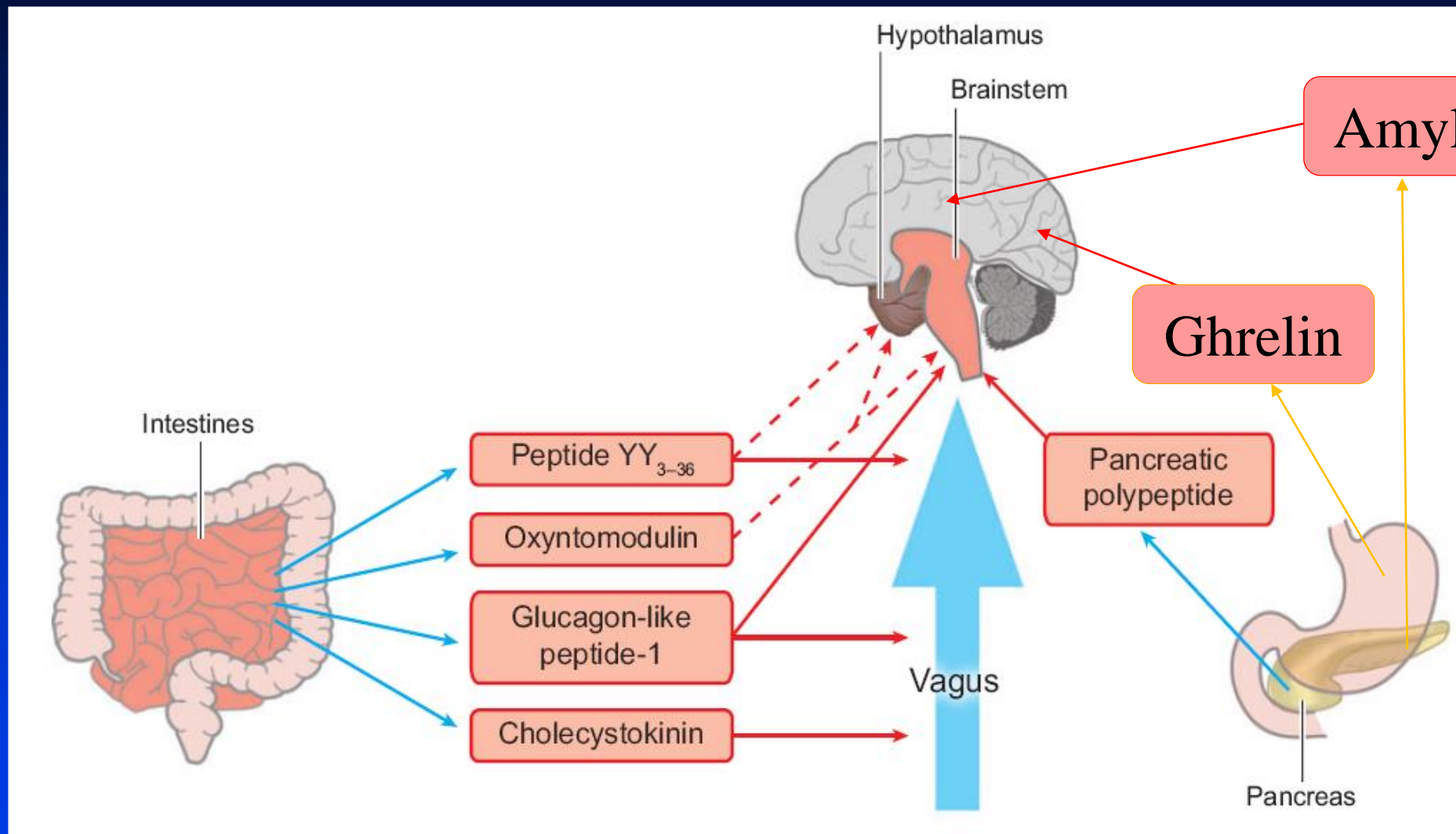
# The Gut as an Endocrine Organ



- The gut is not a monolithic organ and comprises multiple cell types (neural, muscle, exocrine, endocrine)
- It is responsible for the integration of multiple peripheral and central signals necessary for the maintenance of body weight

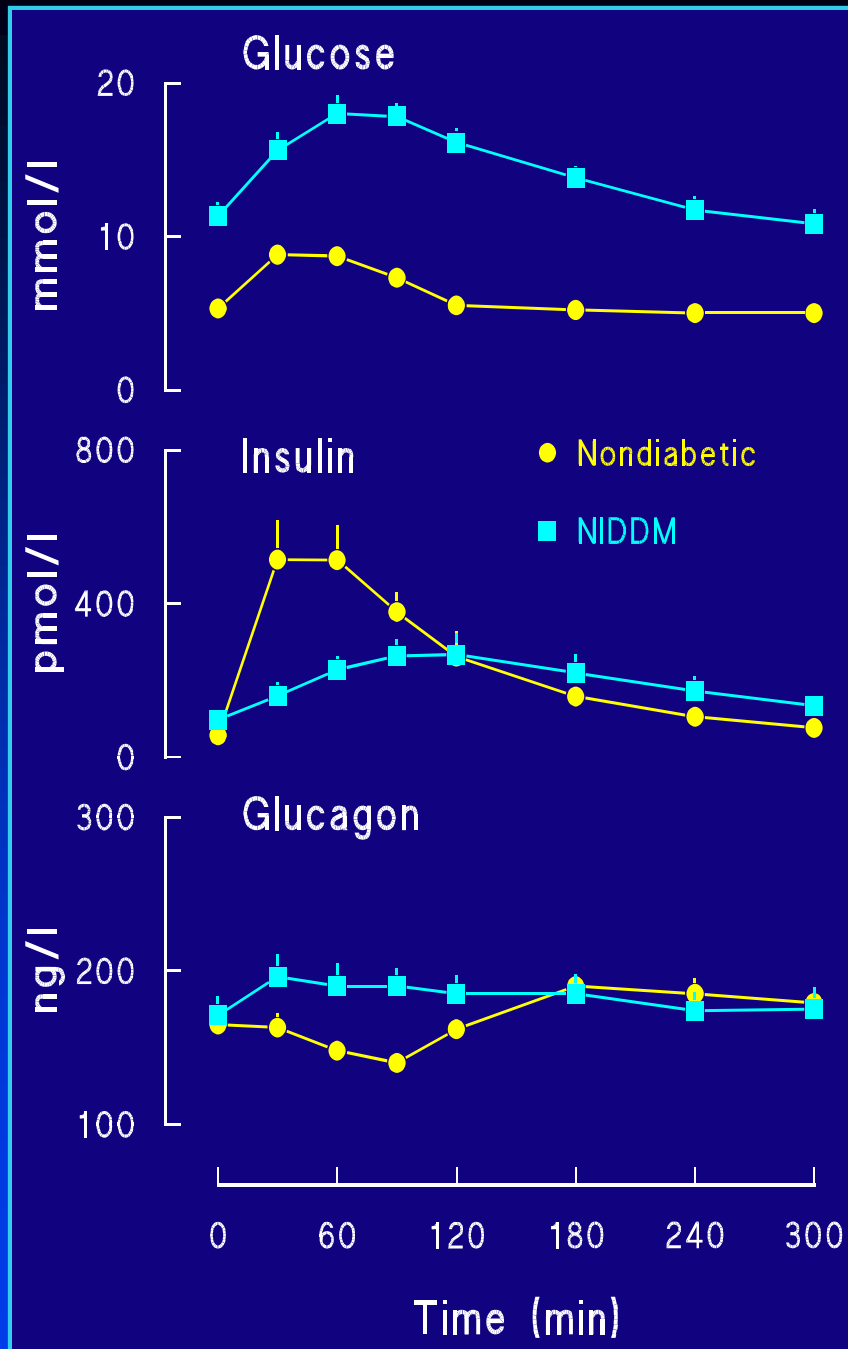


# Gut Hormones

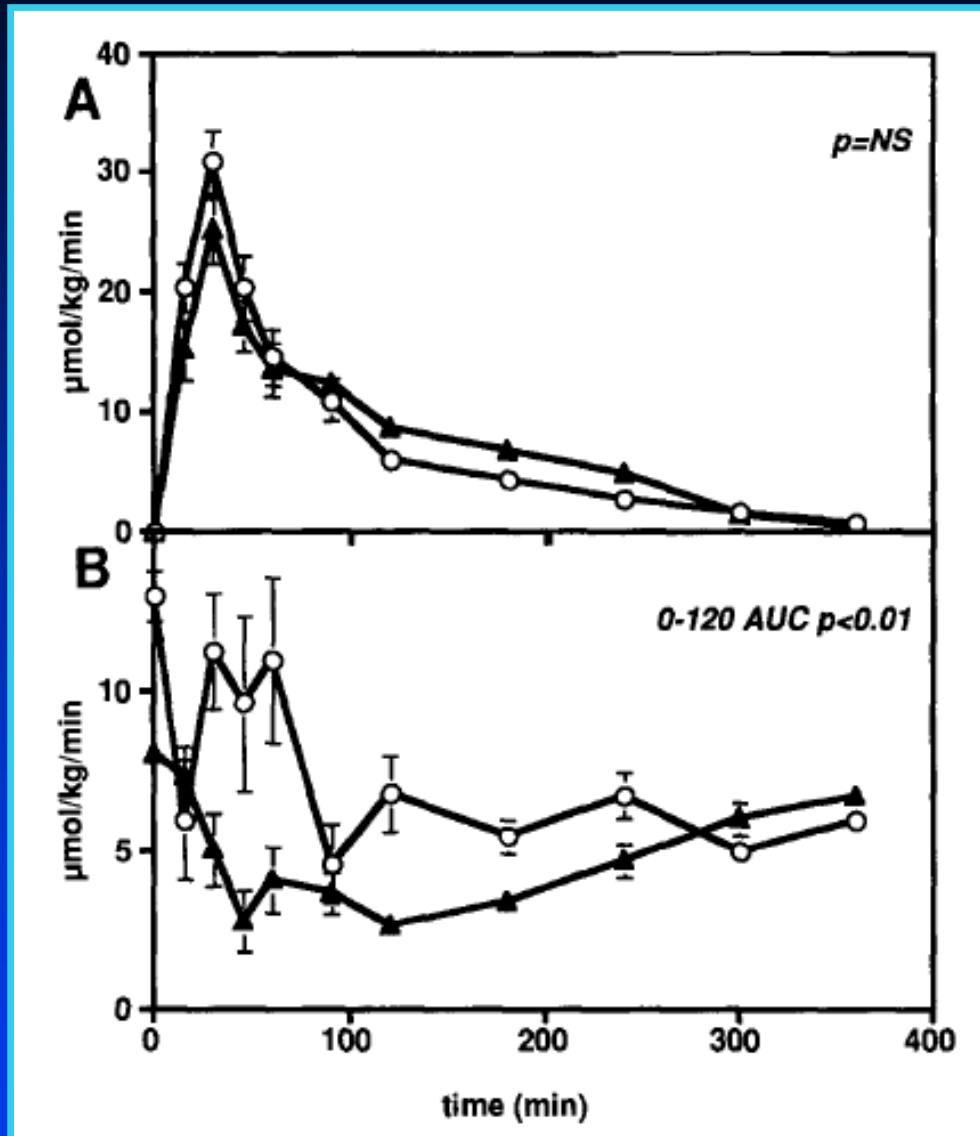


# Defects in Type 2 DM

- Despite elevated fasting insulin, insulin secretion is inappropriate for the degree of hyperglycemia
- Postprandial insulin responses are delayed and decreased in people with type 2 diabetes
- Suppression of postprandial glucagon secretion is also impaired in type 2 diabetes



# ...Other Factors in Diabetes



- The impaired suppression of endogenous glucose production is the major contributor to hyperglycemia in the postprandial period

# Effect of Bariatric Surgery on Diabetes

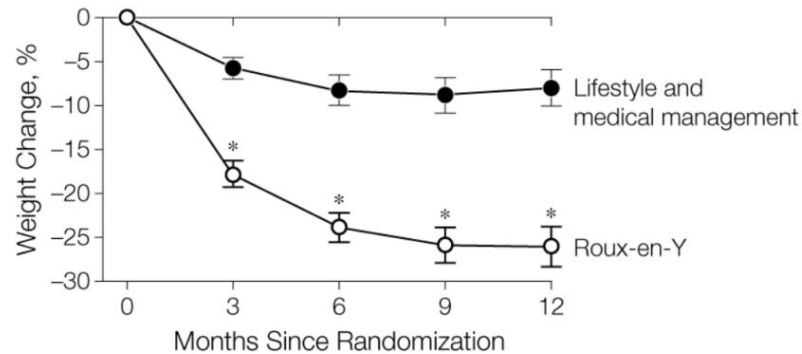
- A meta-analysis of 136 studies of bariatric surgery that included a total of 22,094 patients:
- 1417 of 1846 (76%) patients experienced complete resolution
- Diabetes resolved in 98.9% of patients undergoing DS
- 83.7% for RYGB and 47.9% for AGB





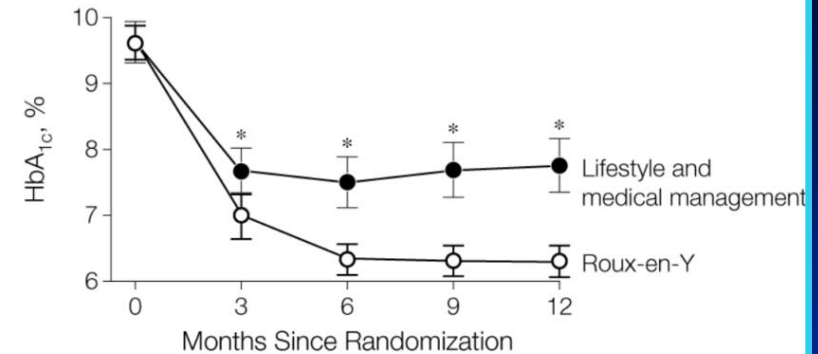
# Diabetes Surgery Study

A Percent weight change from baseline



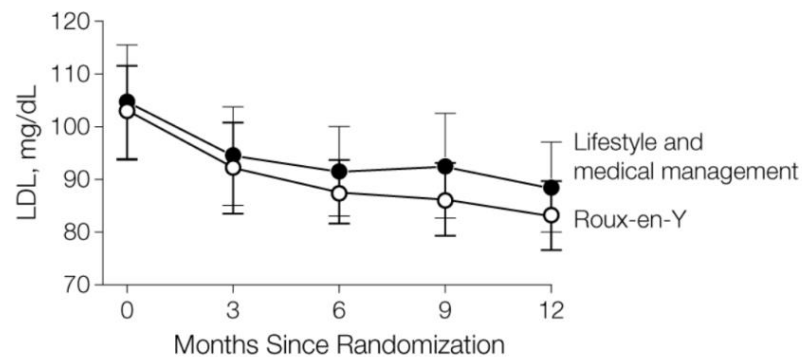
No. of participants					
Lifestyle and medical management	60	56	53	53	57
Roux-en-Y	60	54	57	55	57

B Hemoglobin A<sub>1c</sub>



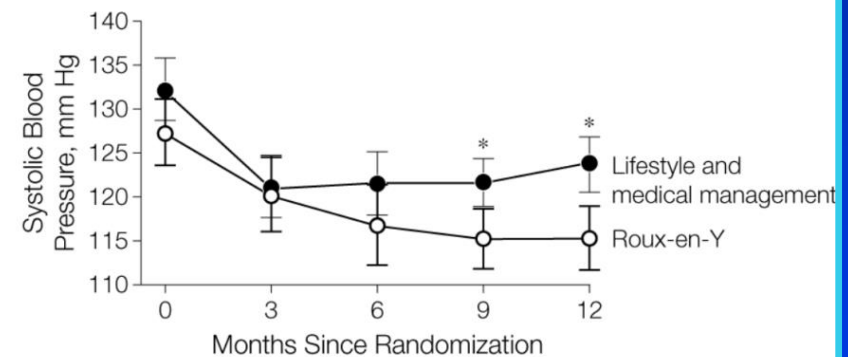
No. of participants					
Lifestyle and medical management	60	56	53	53	56
Roux-en-Y	60	54	57	55	57

C LDL cholesterol



No. of participants					
Lifestyle and medical management	60	56	53	53	54
Roux-en-Y	60	54	57	55	57

B Systolic blood pressure

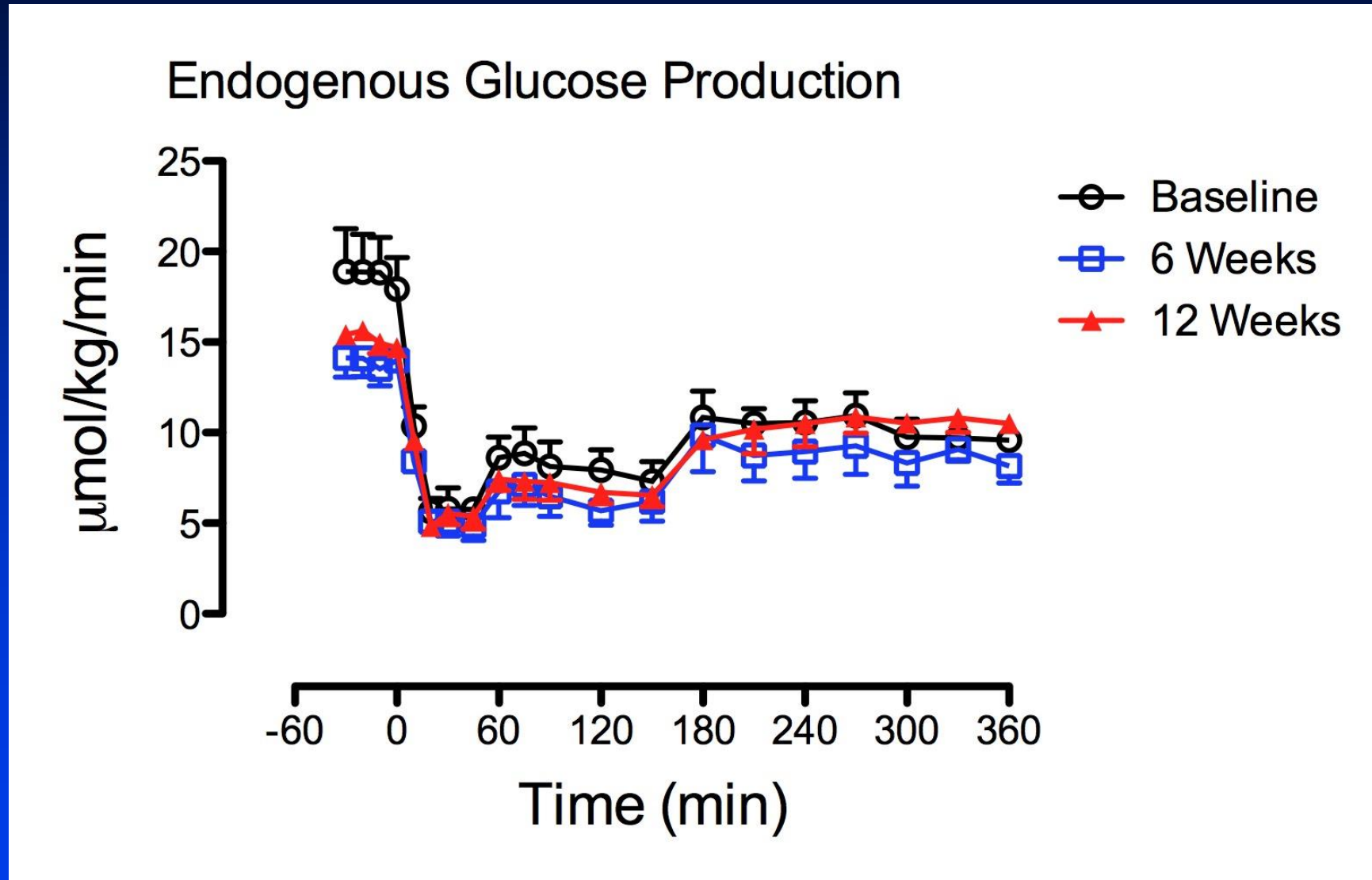


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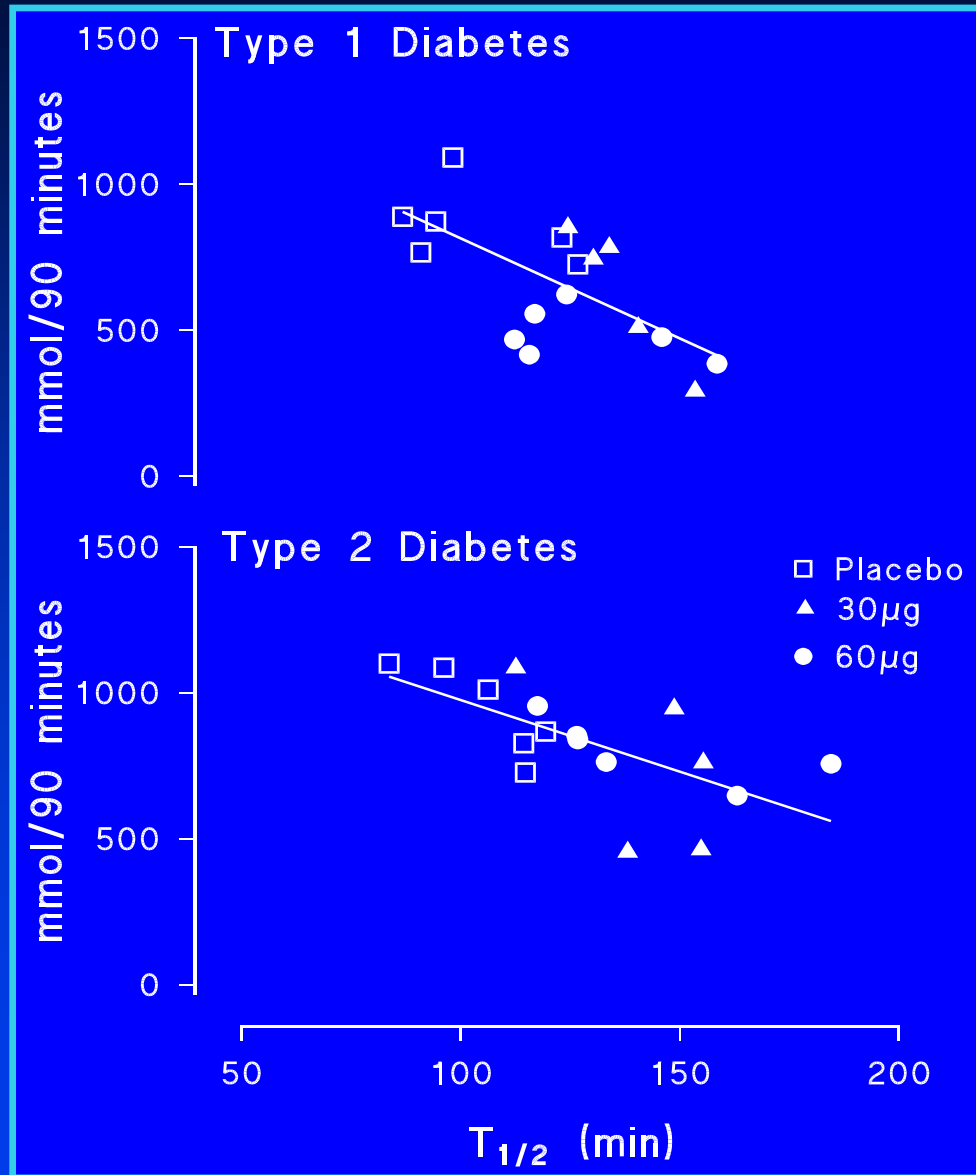
# How Does Bariatric Surgery Help Diabetes?

- **Restricted food intake?**
- **Rate of nutrient delivery/absorption?**
- **Gut hormones?**

# Effects of Caloric Restriction Comparable to Post-bariatric Surgery on Glucose



# Pramlintide and Postprandial Glucose AUC



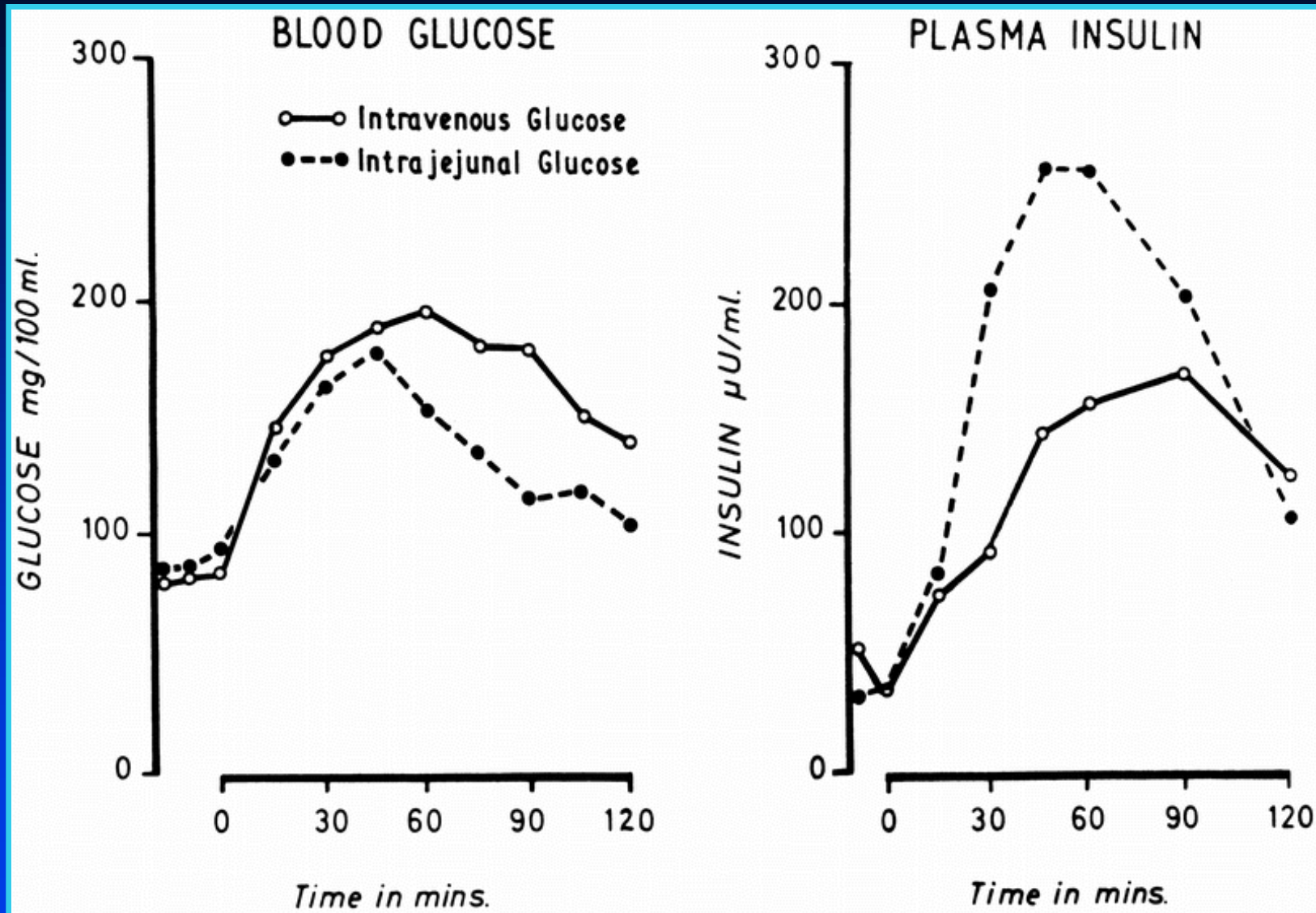
**Gastric emptying  
may influence  
blood glucose**

Vella. Neurogastroenterol Motil. 2002;14:123-131.





# The Incretin Effect



# GLP-1 Receptor



GLP-1 (7,36)  $\longrightarrow$  GLP-1 (9,36)  
**ACTIVE HORMONE** **INACTIVE HORMONE**

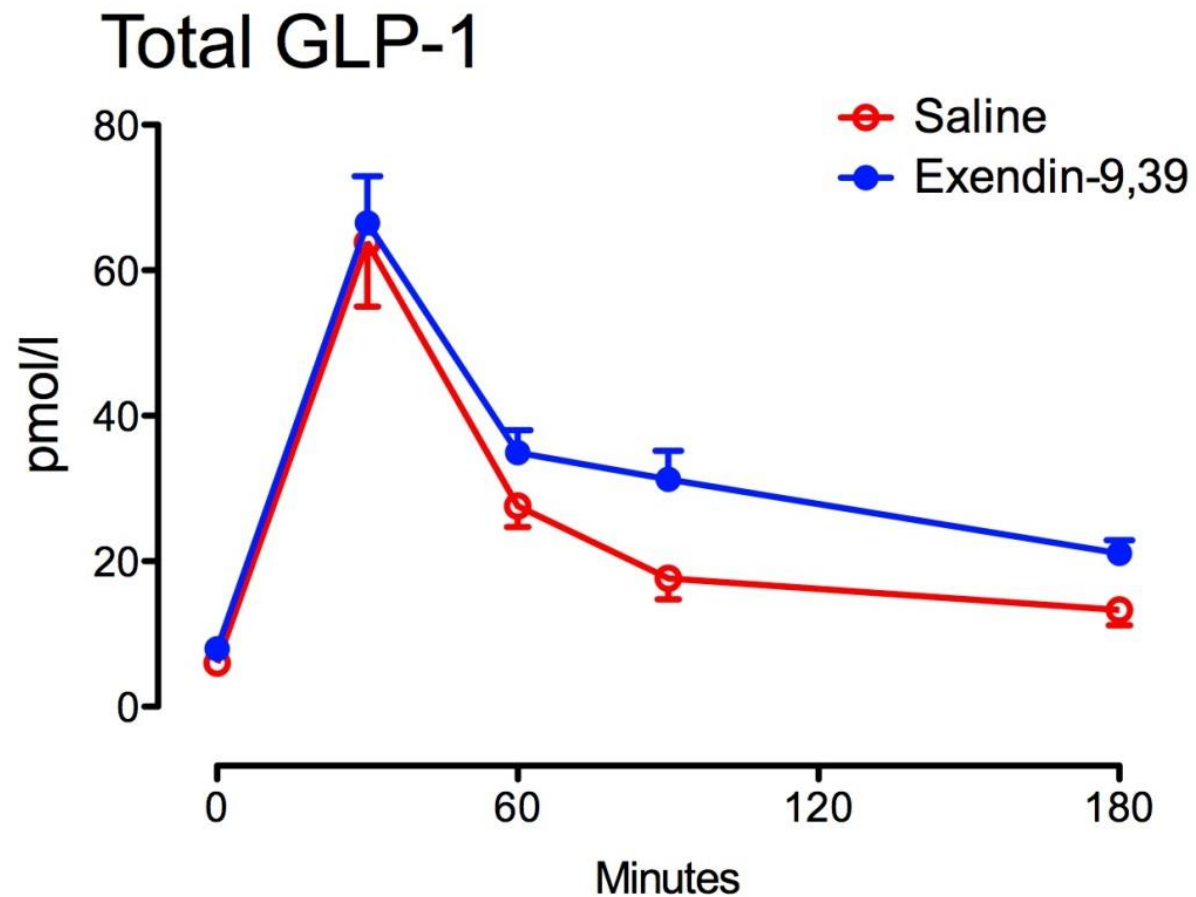
**Agonist**

**Antagonist**

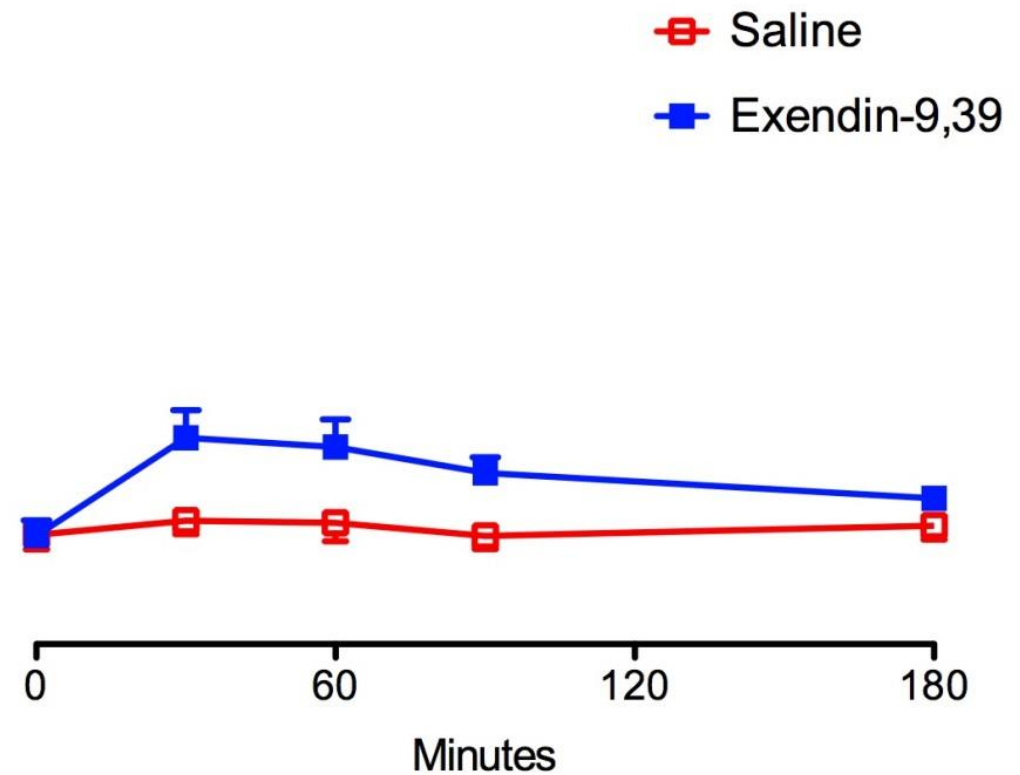
Exendin-4 (7,39) - - - -  $\longrightarrow$  Exendin-4 (9,39)

**Differences in function during antagonist administration  
can be attributed to the actions of GLP-1**

# Post-RYGB



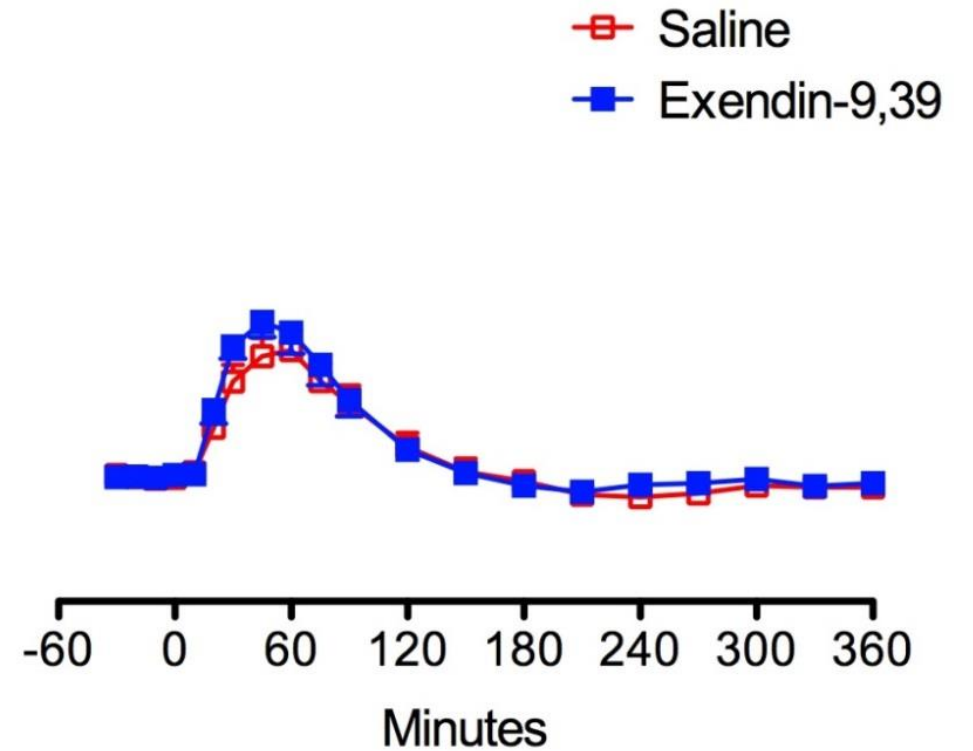
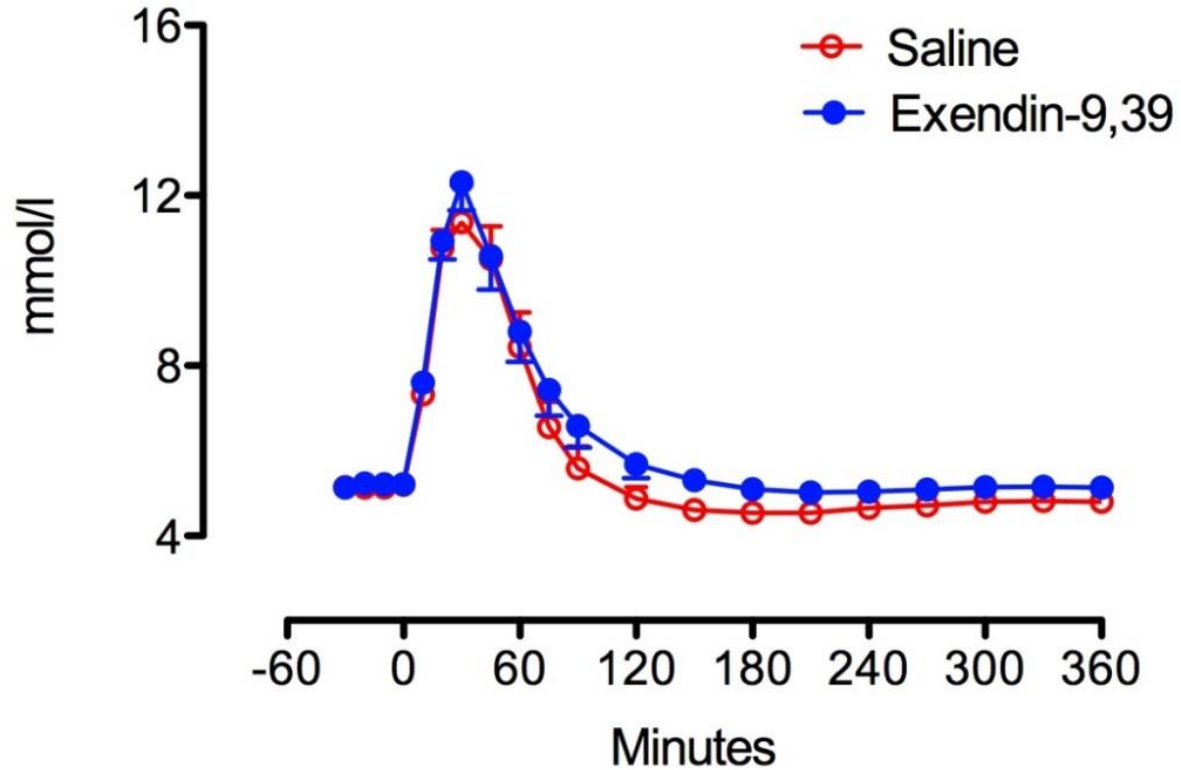
# Controls



# Post-RYGB

# Controls

## Glucose

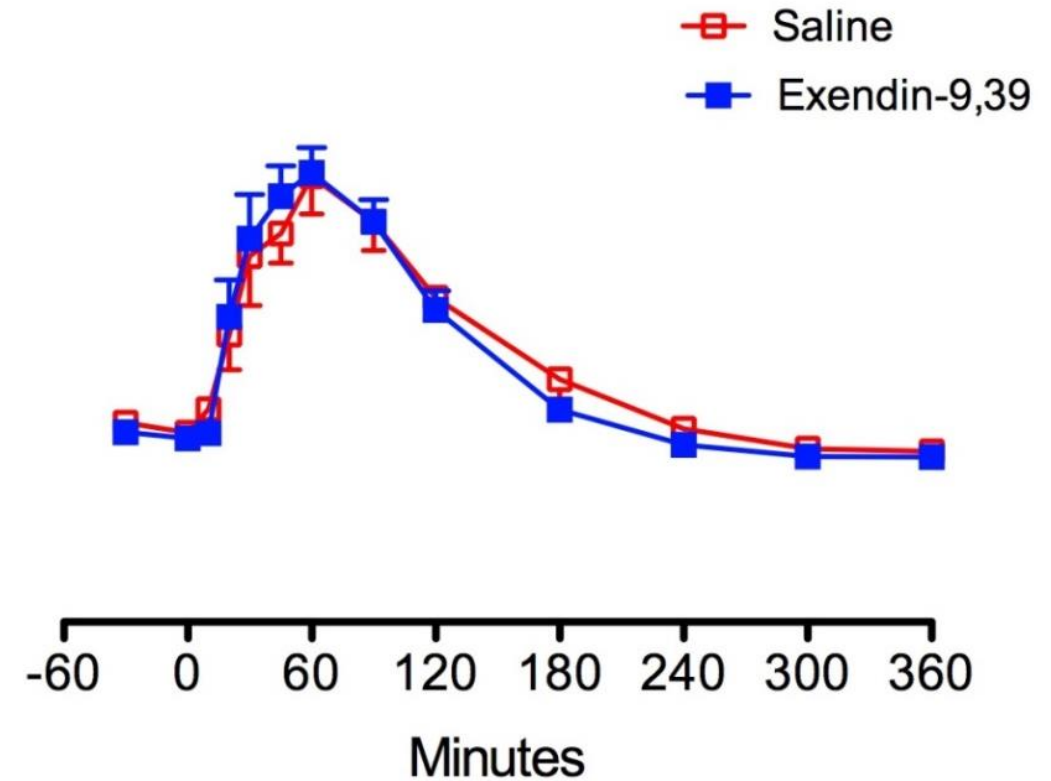
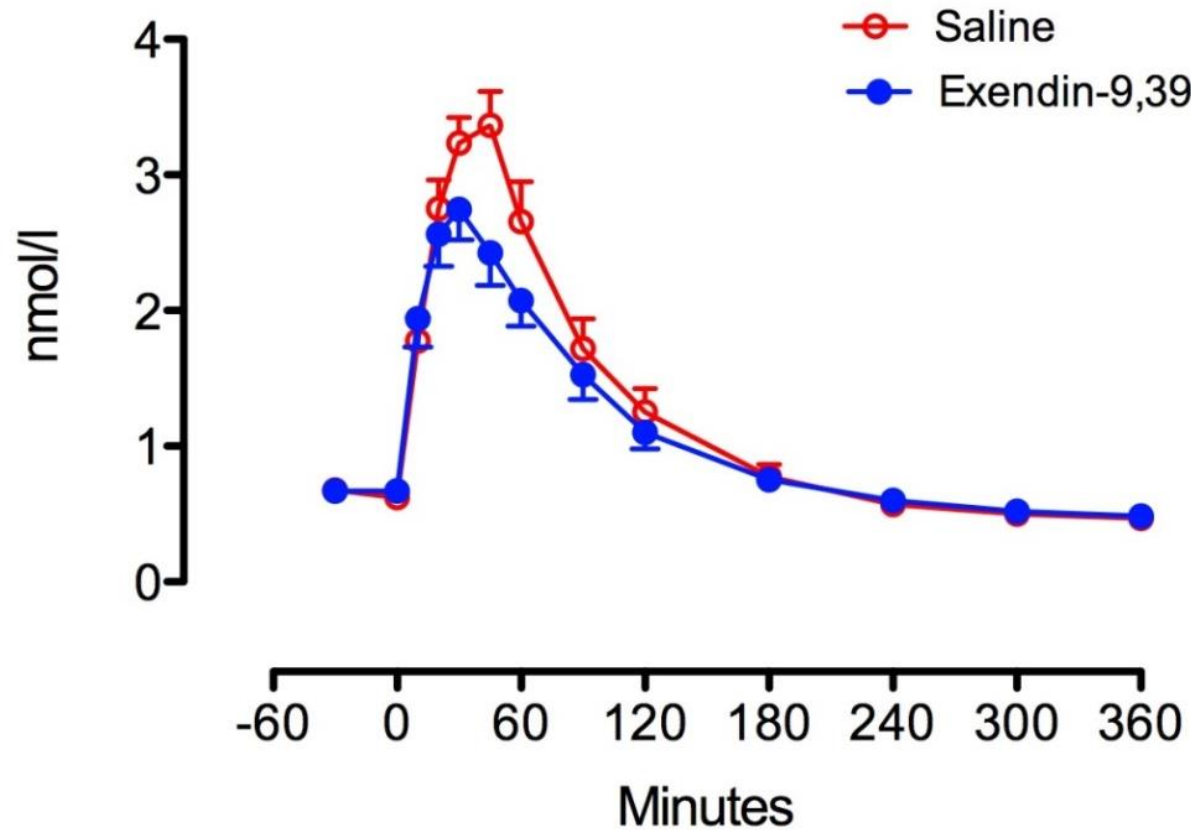




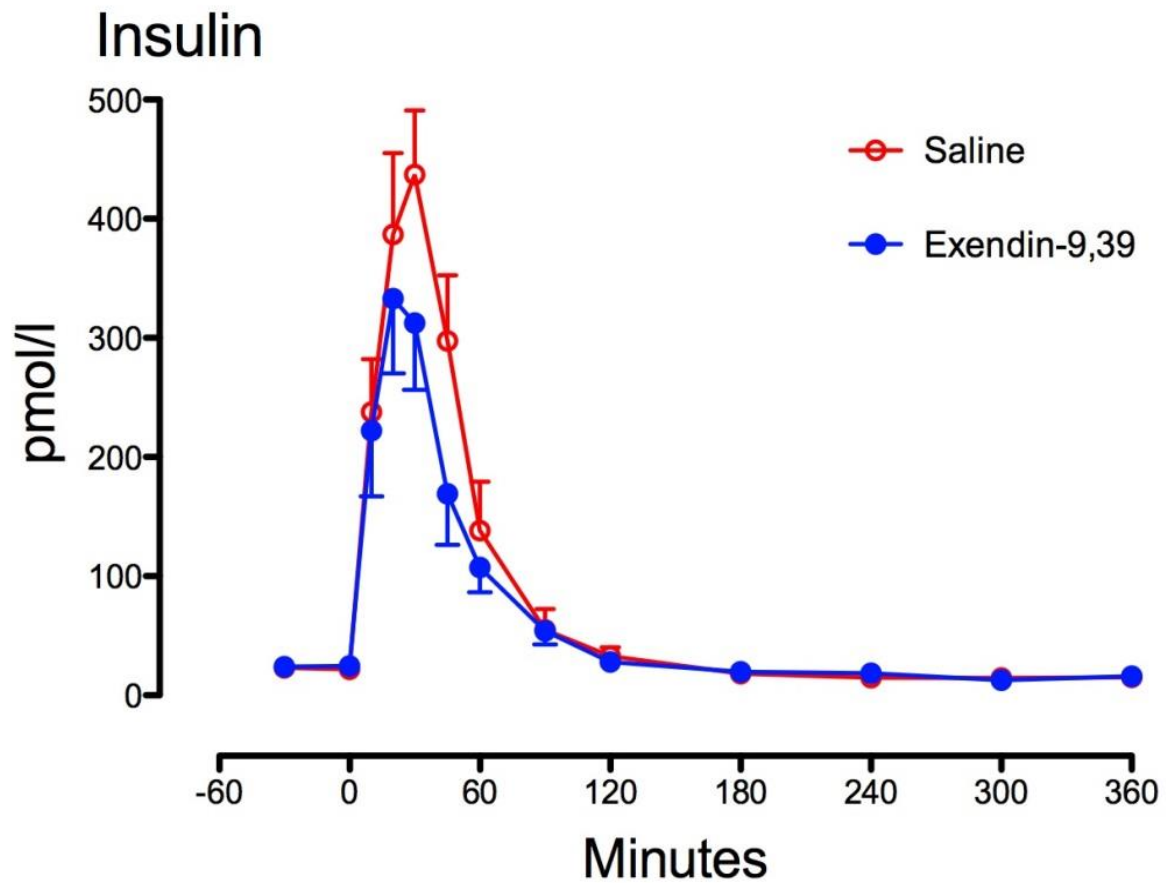
# Post-RYGB

# Controls

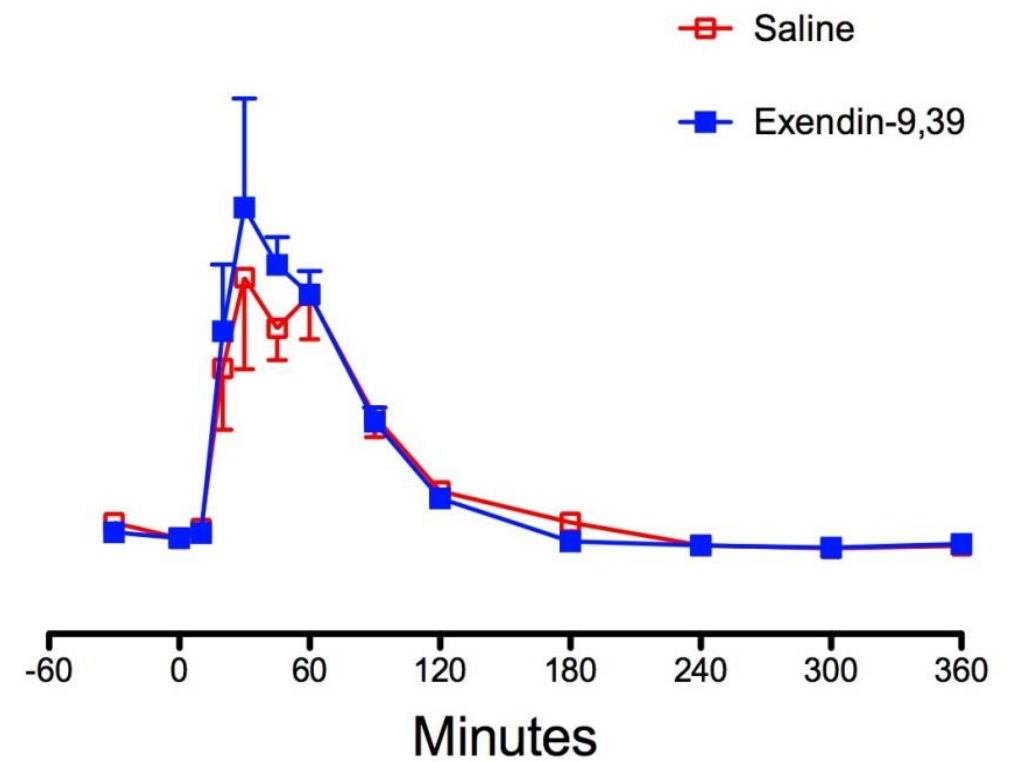
## C-Peptide



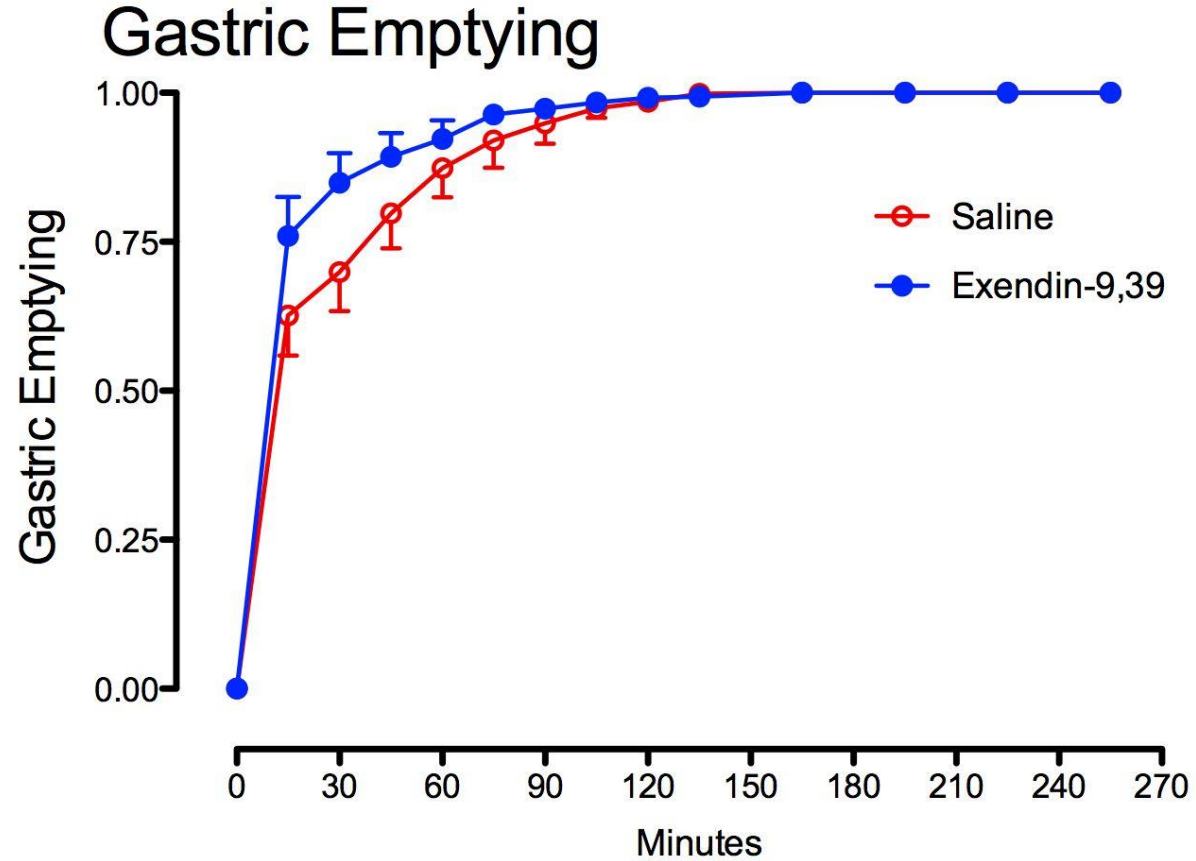
# Post-RYGB



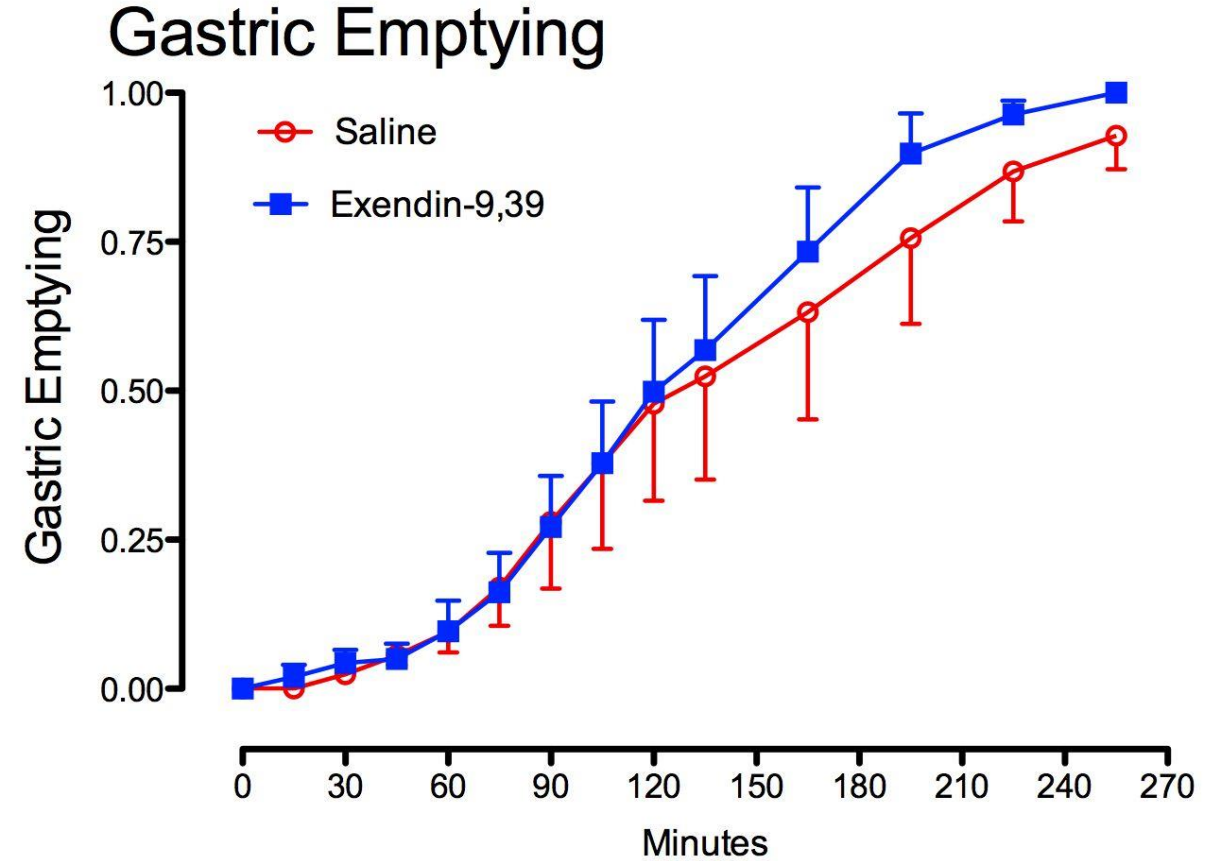
# Controls



# Post-RYGB



# Controls

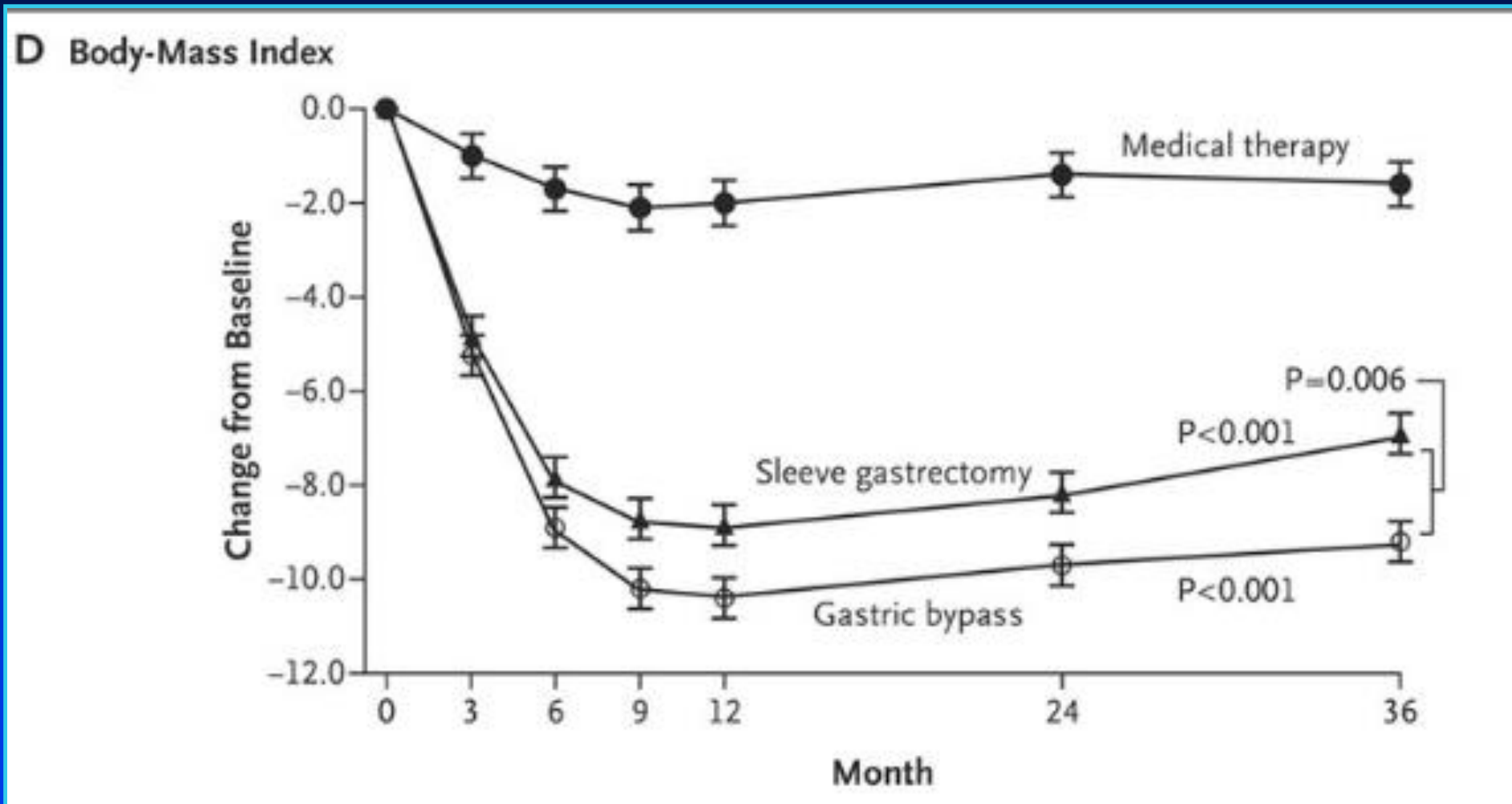


# GLP-1 Effects After Roux-en-y Gastric Bypass

- Slight improvement in insulin secretion
- Slight reduction in rates of gastric emptying
- Slight improvement in post-meal glucose tolerance
- Some reduction in food intake (unpublished data – A. Vella)



# Bariatric Surgery versus Intensive Medical Therapy for Diabetes — 3-Year Outcomes



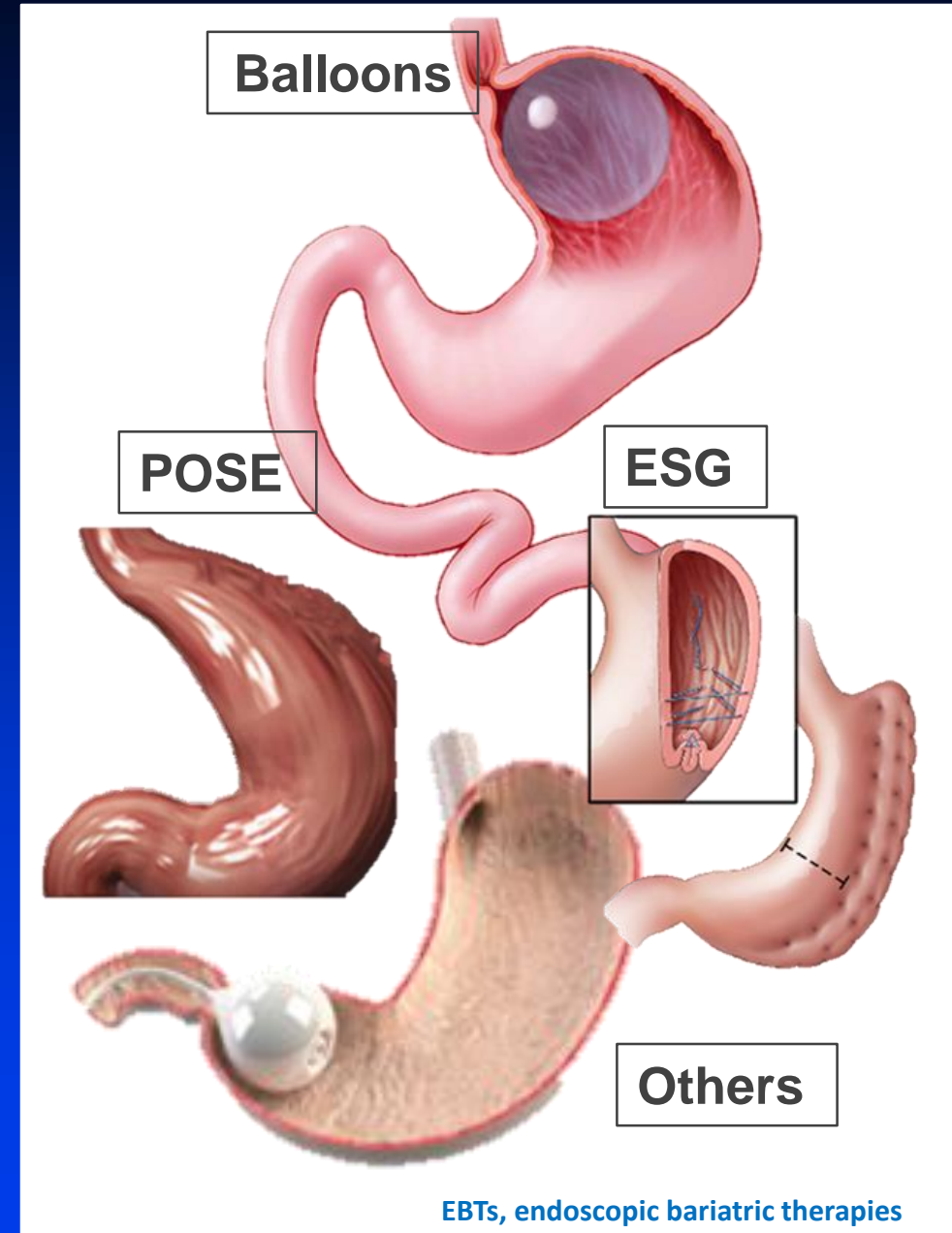
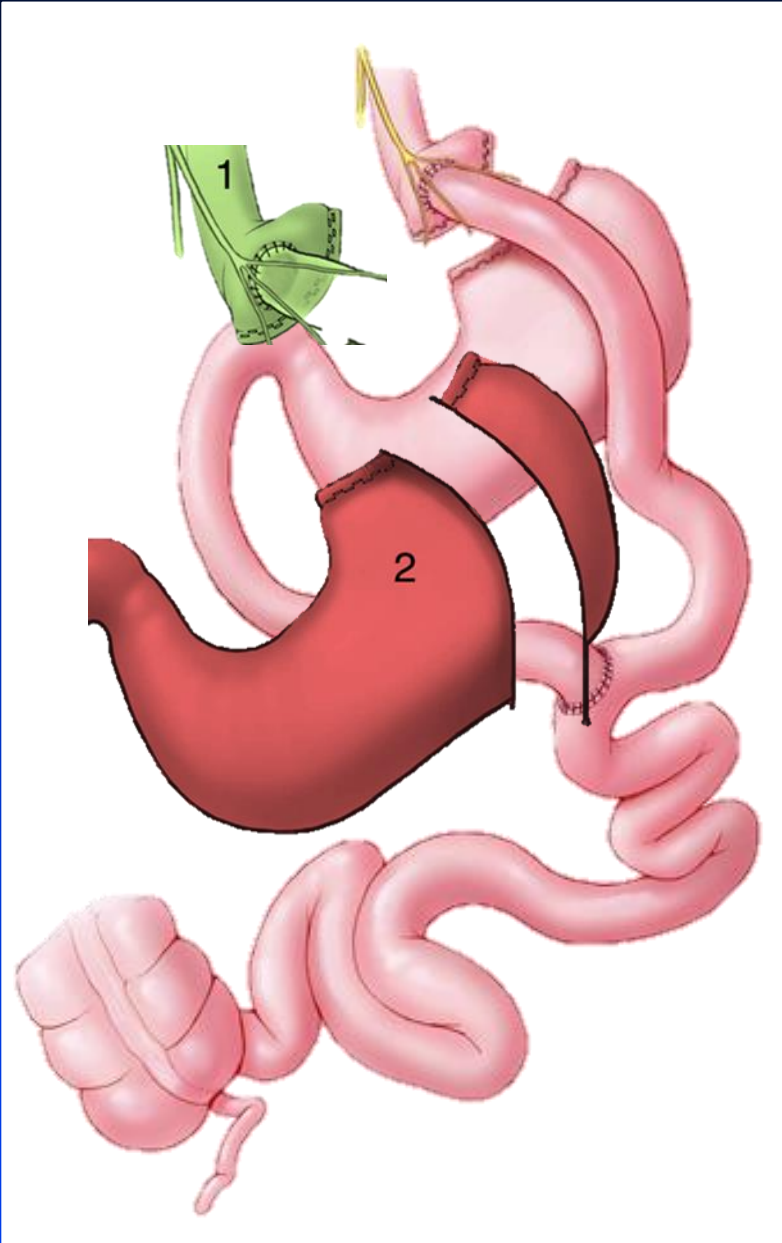
Schauer. NEJM. 2014;370:2002-2013.



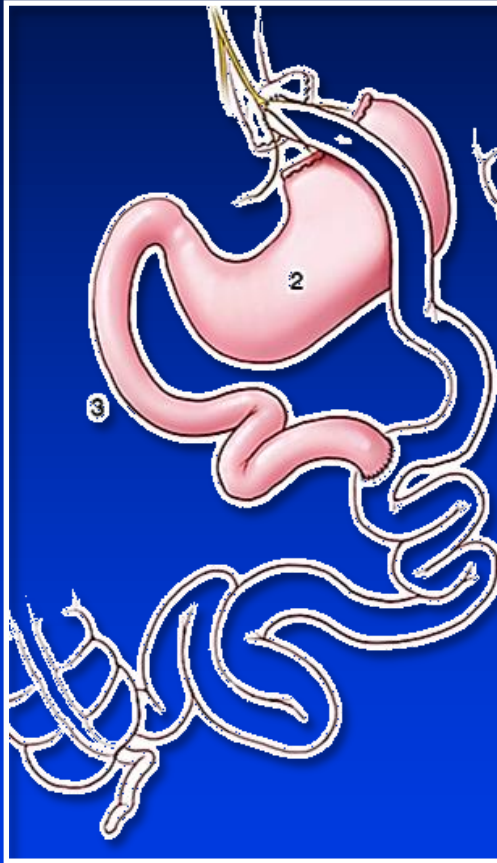
# Are Endoscopic Procedures the Next “Bariatric Surgery”?

- **Gastric balloons – resurfacing of 1990s approaches**
- **Barrier approaches to mimic nutrients bypassing duodenum**
- **Endoscopic suturing of stomach to mimic gastric sleeve**
- **Aspirate contents from stomach**

# Gastric EBTs



# Small Bowel EBTs



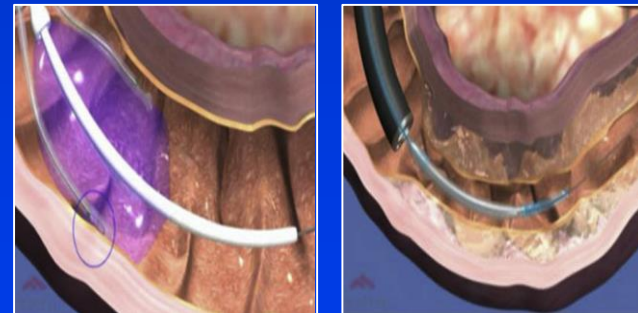
## Duodenal Sleeves



## Gastroduodenojejunal Sleeves

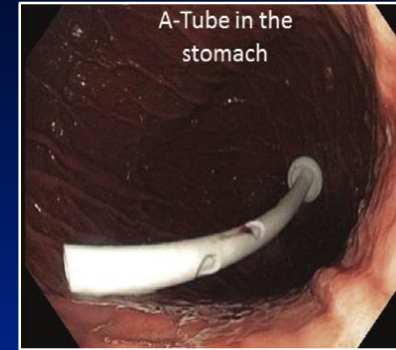
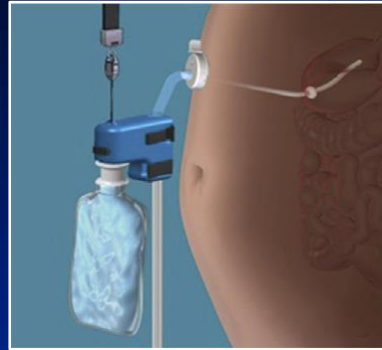


## Duodenal Mucosal Resurfacing



# Other EBTs

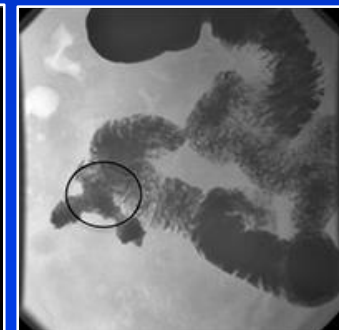
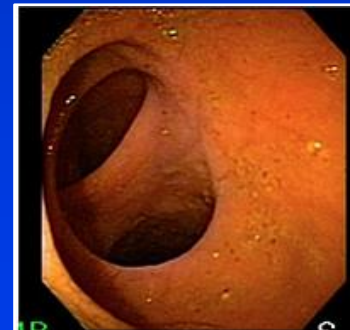
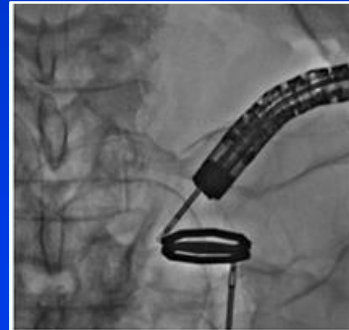
## Aspiration Therapy



## Full Sense Device

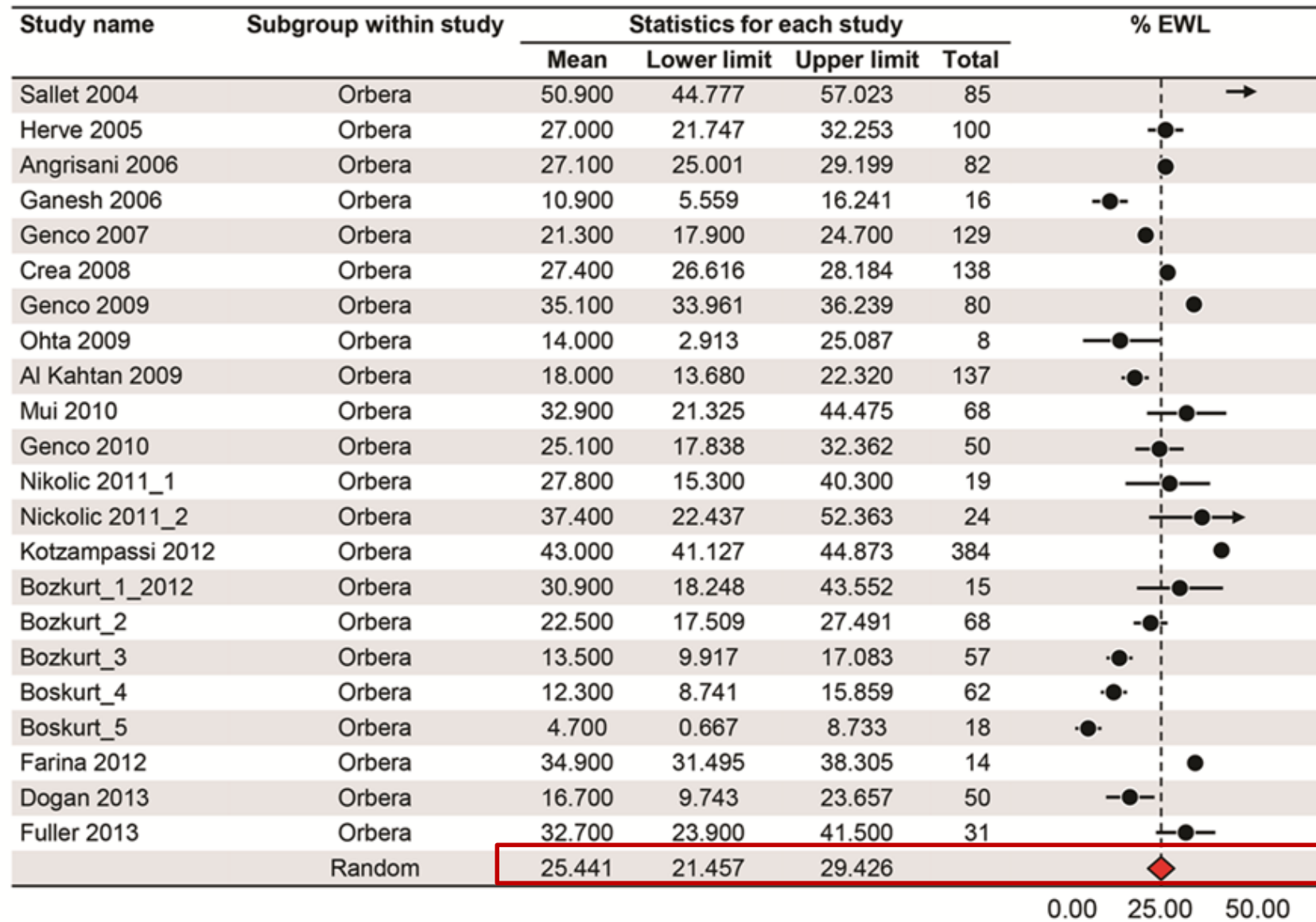


## Self-assembling Magnets for Endoscopy



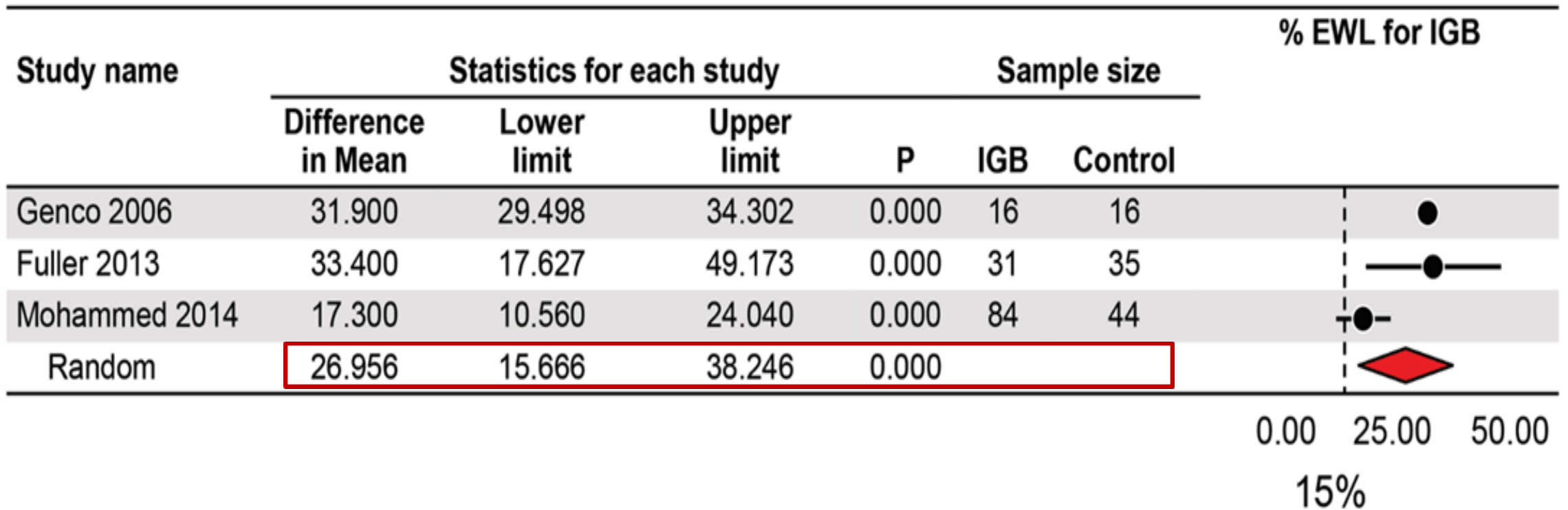


## % EWL

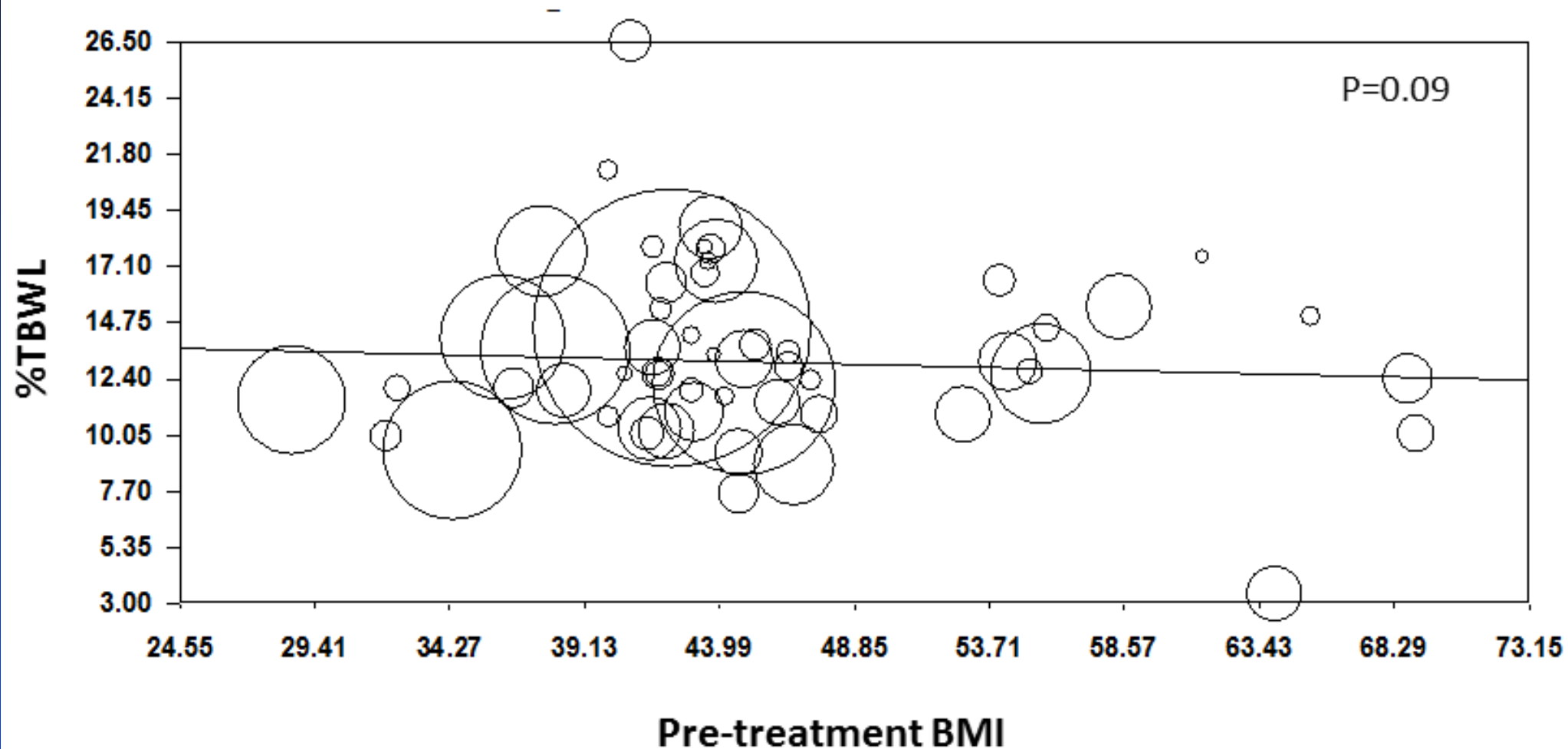
 at 12 months with Orbera IGB




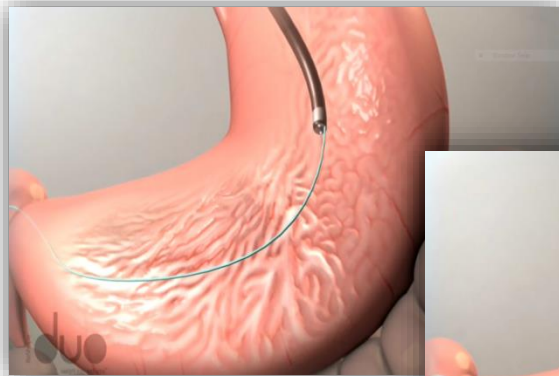
## Mean difference in % EWL between Orbera IGB and control groups in RCTs



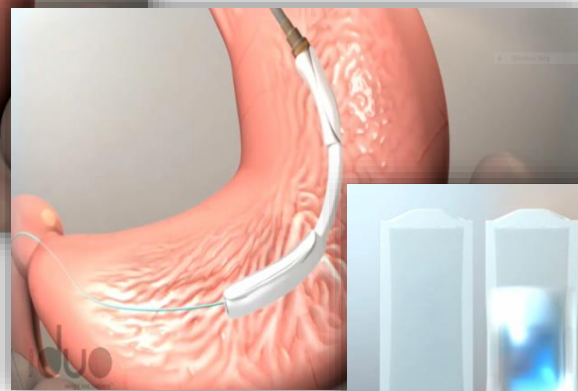
**%EWL with Orbera IGB at a range of base-line BMI**



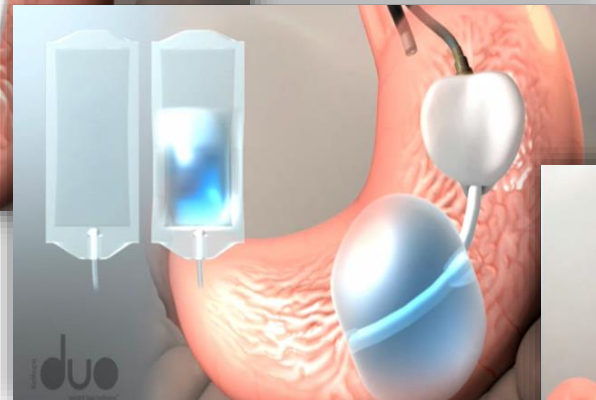
# ReShape Duo Intragastric Balloon



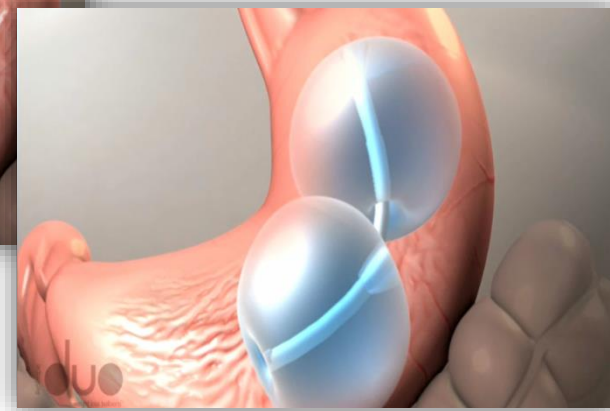
**Place Guidewire**



**Place Uninflated  
Balloons**



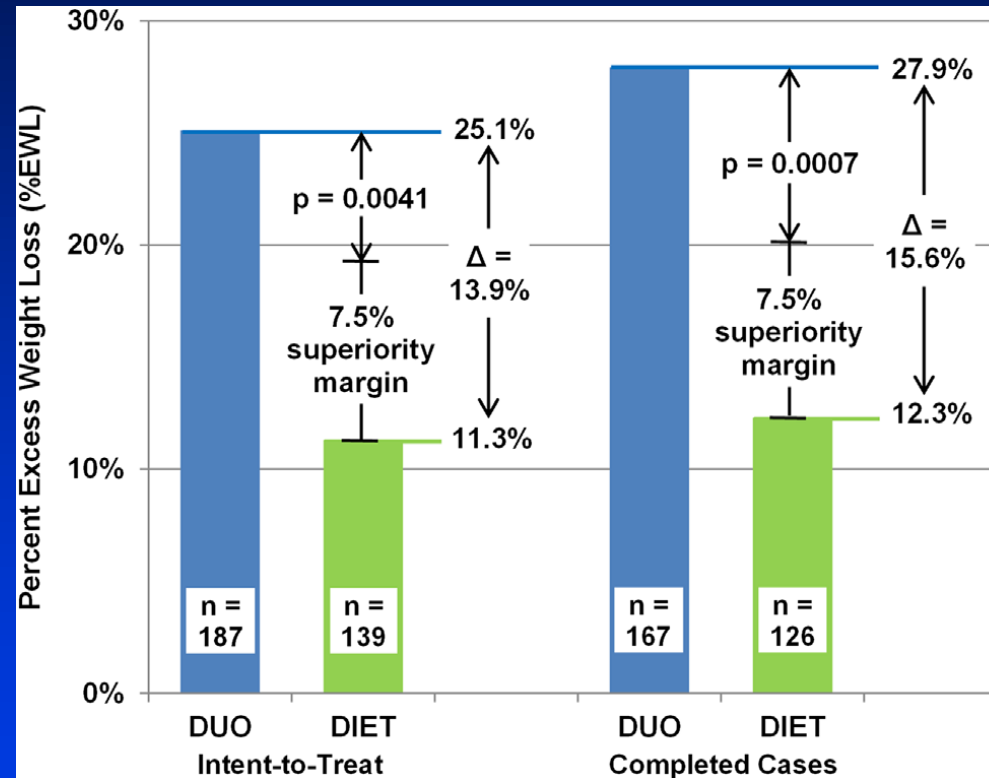
**Inflate Balloons**



**Remove Placement  
Catheter**

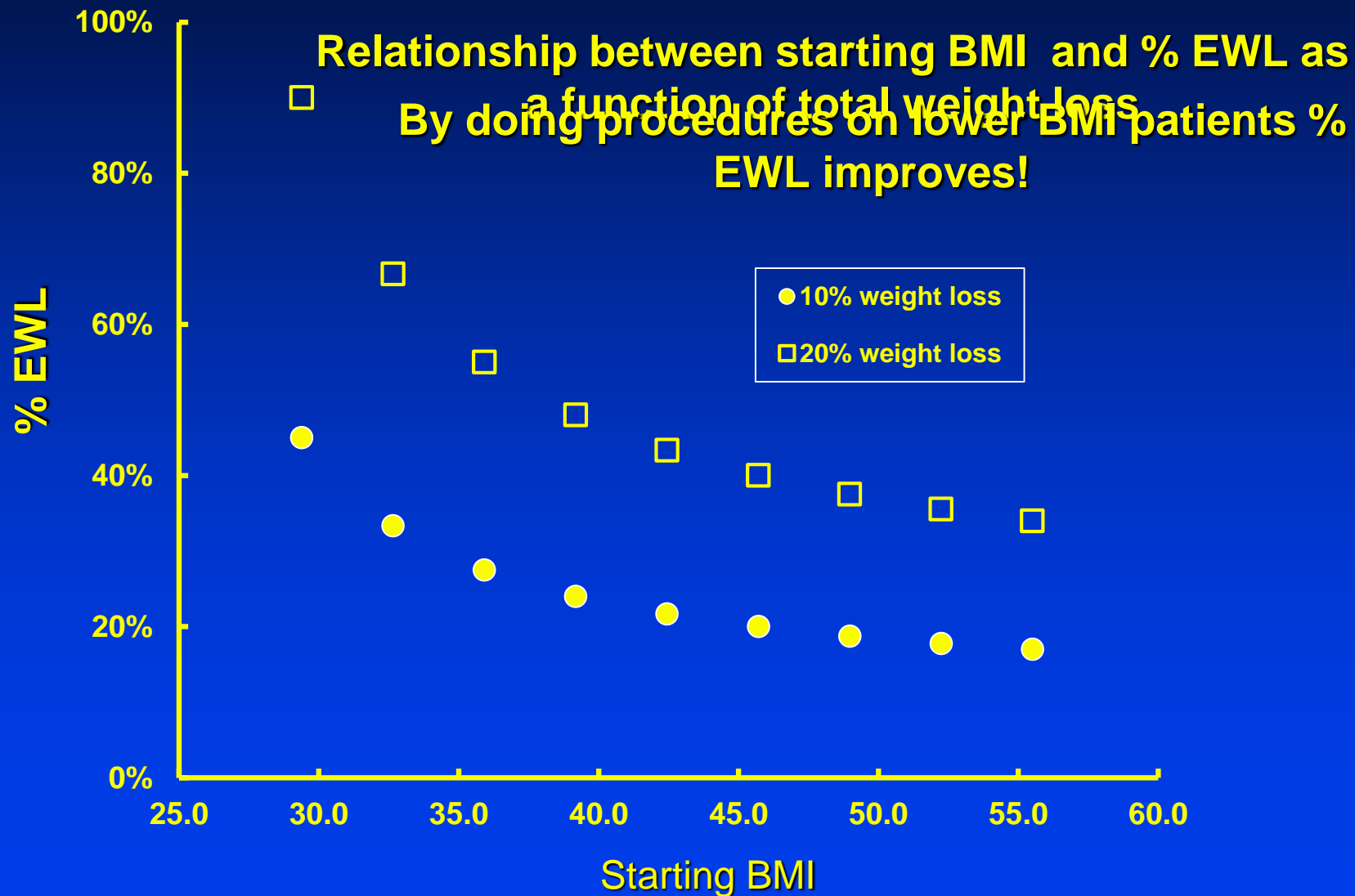
# ReShape Duo IGB Pivotal US RCT: REDUCE Trial

**%EWL at 24 weeks (balloon removal)**

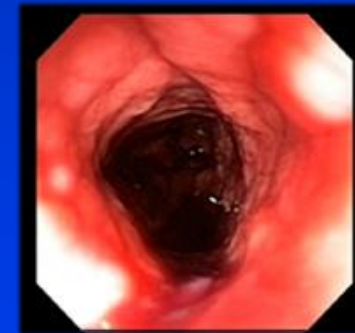
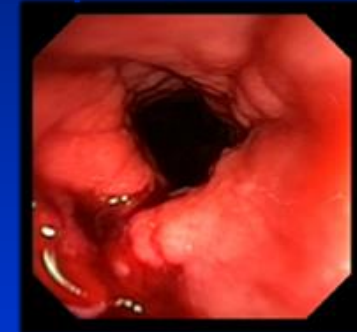
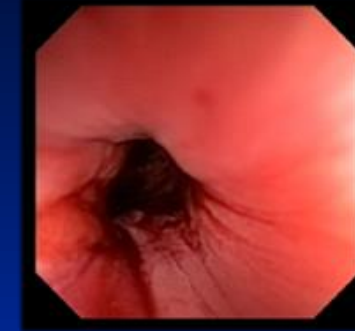
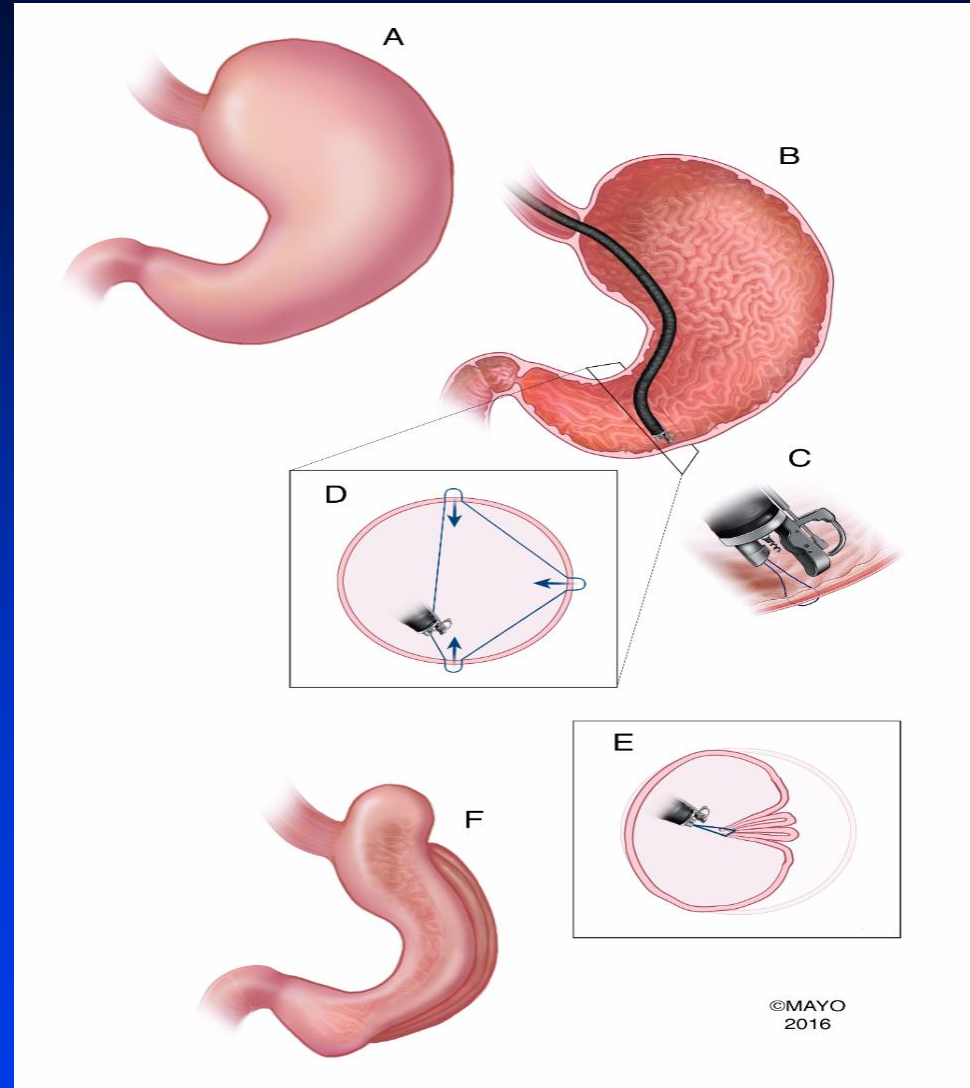
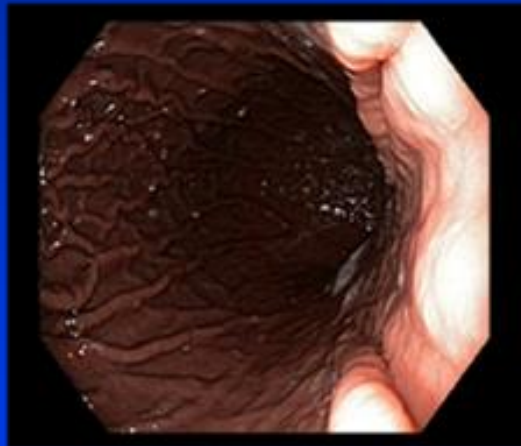
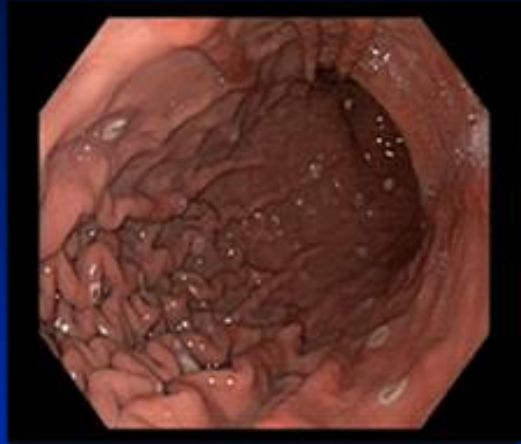


**%EWL at 48 weeks (24 weeks after IGB removal) 18.8%**

# How to Achieve Better Weight Loss Results with Procedures

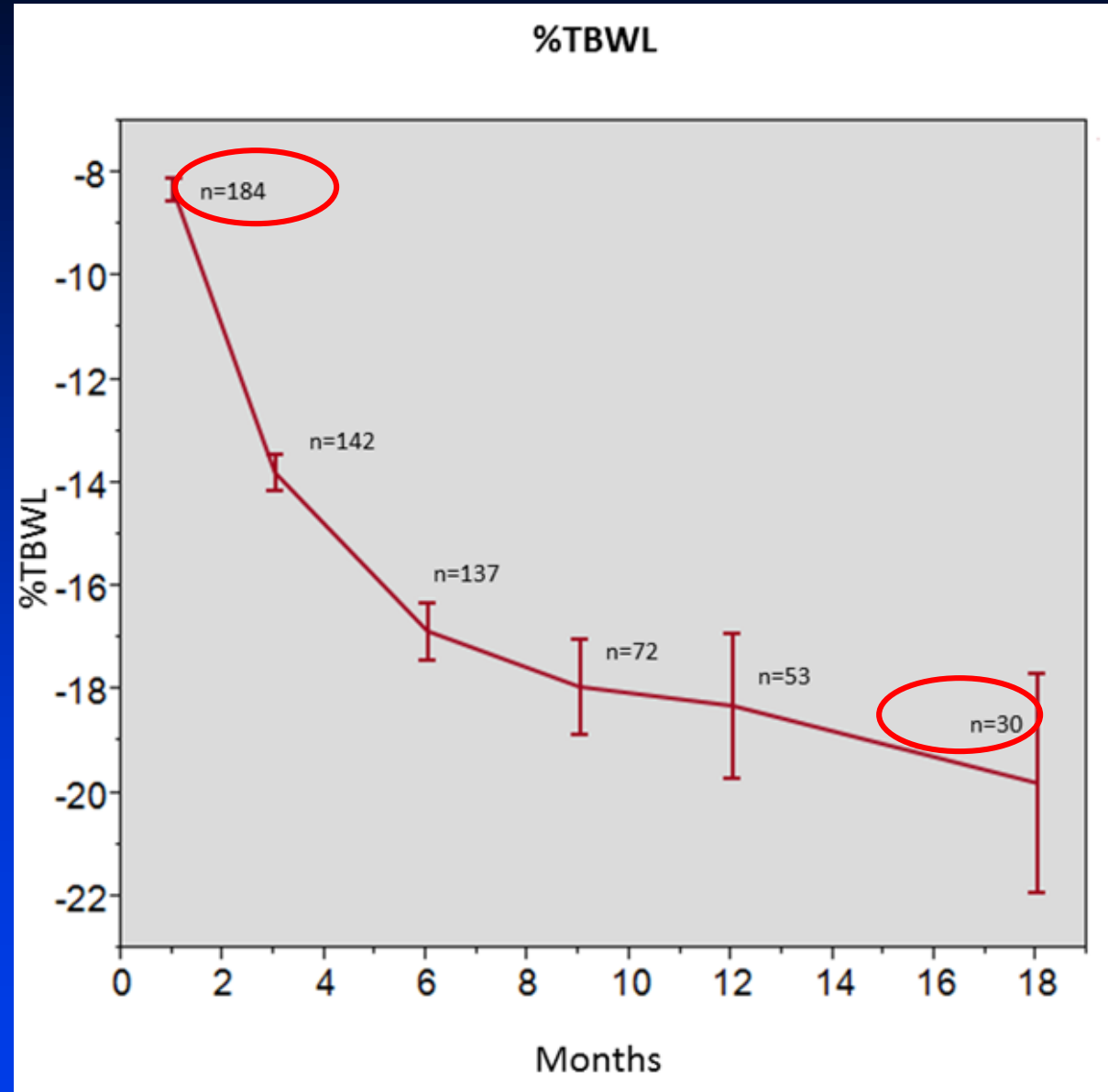


# Endoscopic Sleeve Gastroplasty - Evolution





# ESG Multi-Center Study: 242 Patients



■Lopez-Nava, et al. Gastroenterology.2015;

■DOI: [http://dx.doi.org/10.1016/S0016-5085\(15\)30037-8](http://dx.doi.org/10.1016/S0016-5085(15)30037-8)



# **US Pivotal Randomized Study PATHWAY Study**

**173 Subject / randomized open-label  
10 center study. Study completed**

**Data being evaluated by FDA**

**Expect approval early next year**

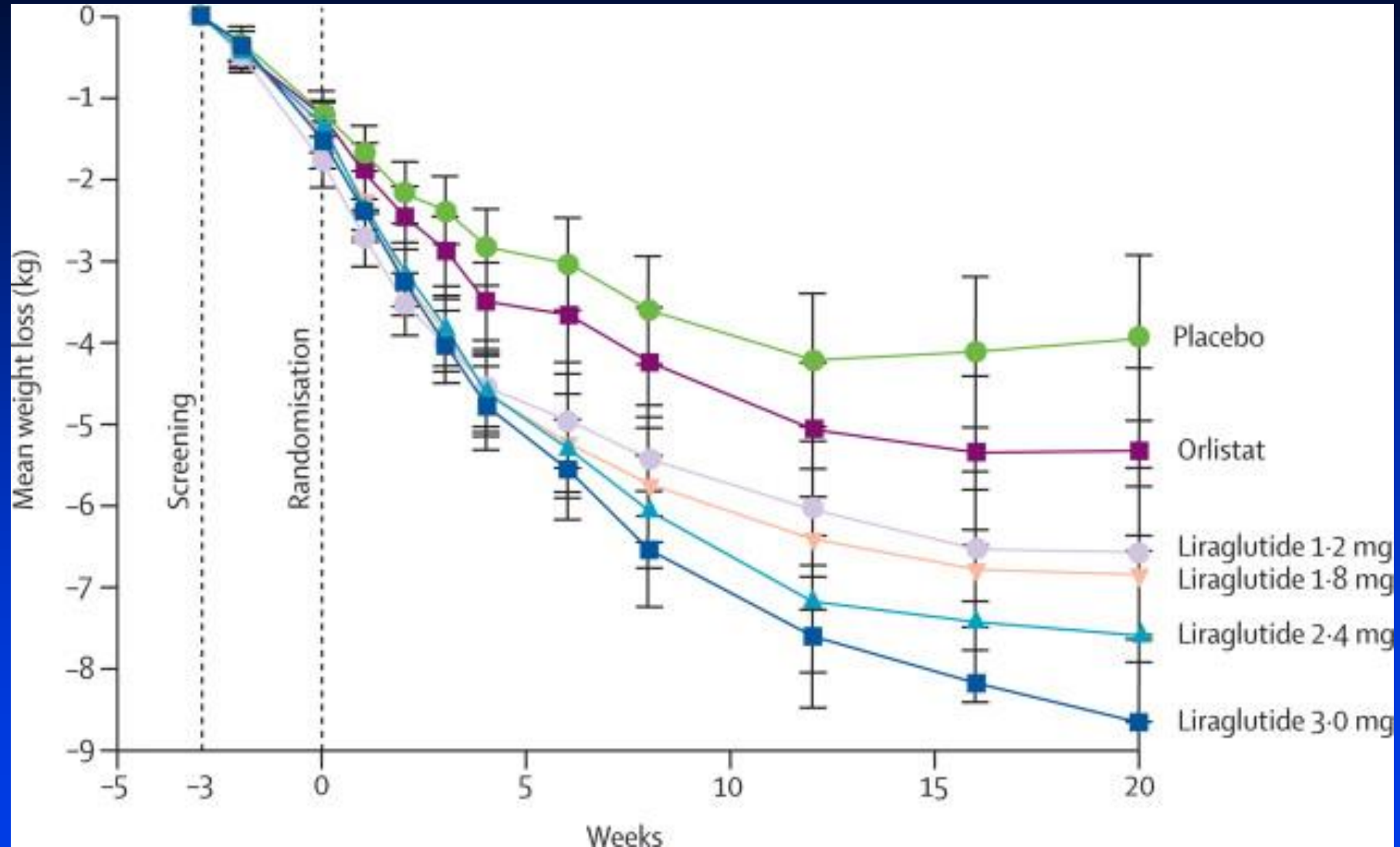


# Gut and Adipose Hormone

## Approaches for Appetite Regulation

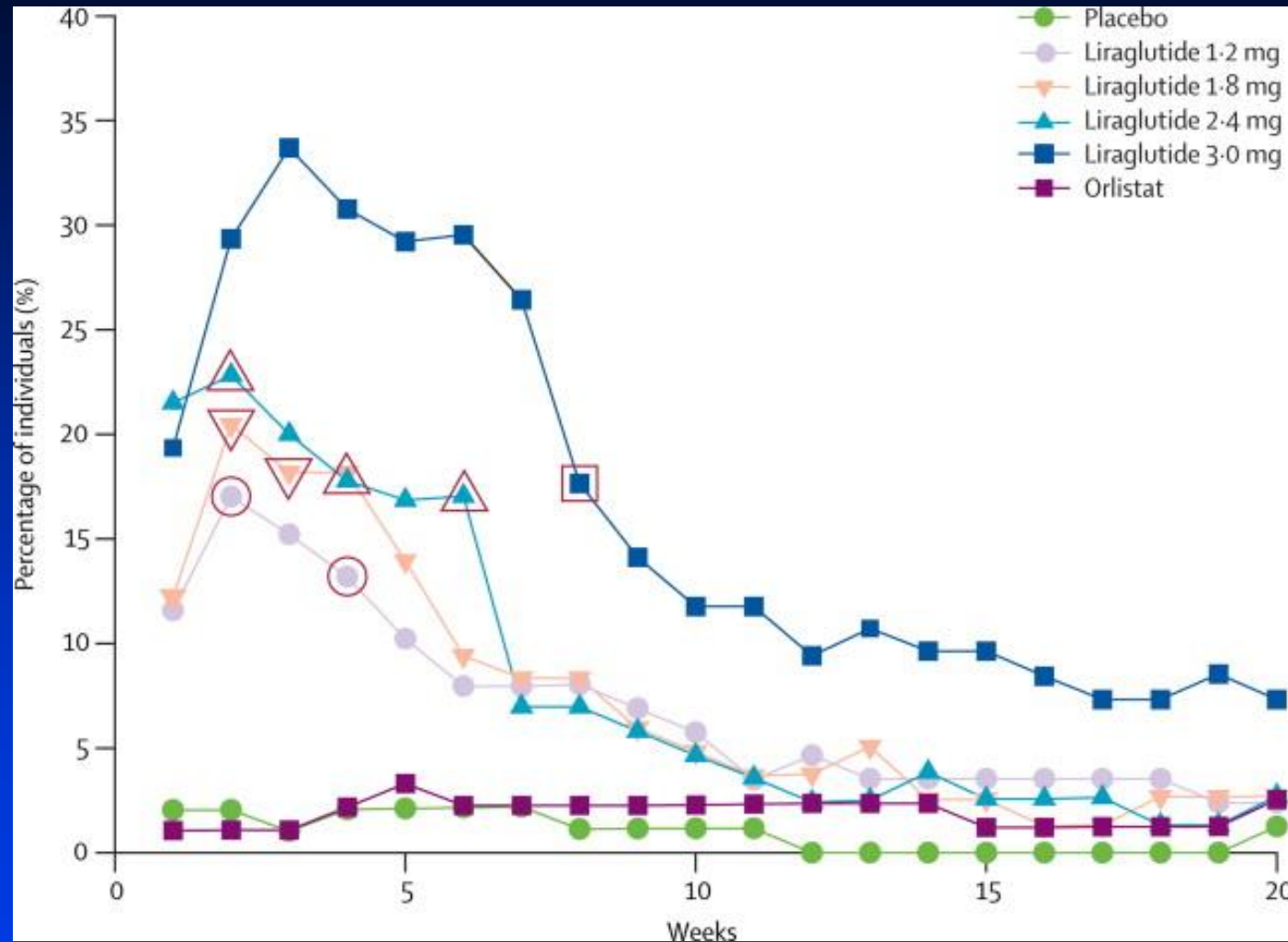
- CCK agonists
- GLP-1 agonists
- PYY<sub>3-36</sub>
- Oxyntomodulin
- Ghrelin
- Leptin

# Liraglutide Weight Loss Results



Astrup et al. Lancet. 2009;374:1606 – 1616.

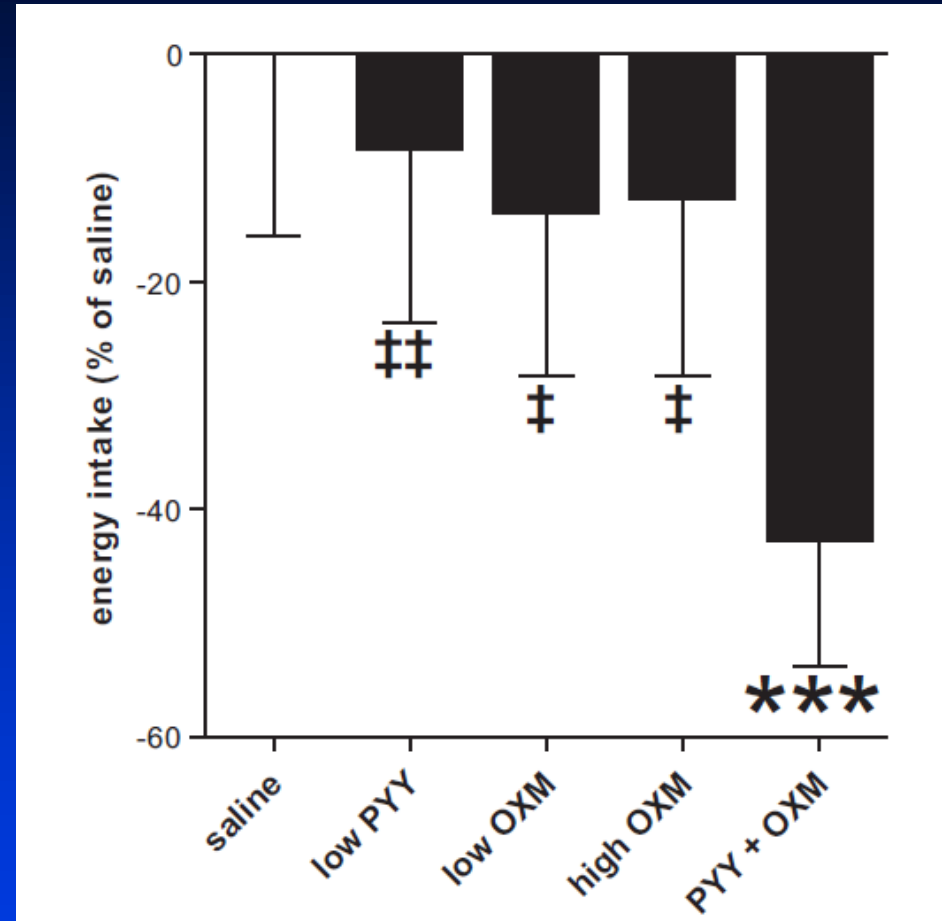
# Liraglutide Side Effects



Percentage of individuals with nausea; each individual who withdrew because of nausea is shown by a red symbol.

# PYY<sub>3-36</sub> and Oxyntomodulin

- Oxyntomodulin is a GLP-1 receptor agonist
- These hormones are co-secreted by intestinal L cells in response to meals
- Co-infusion results in substantial reductions in food intake



\*\*\* P<0.001 vs saline

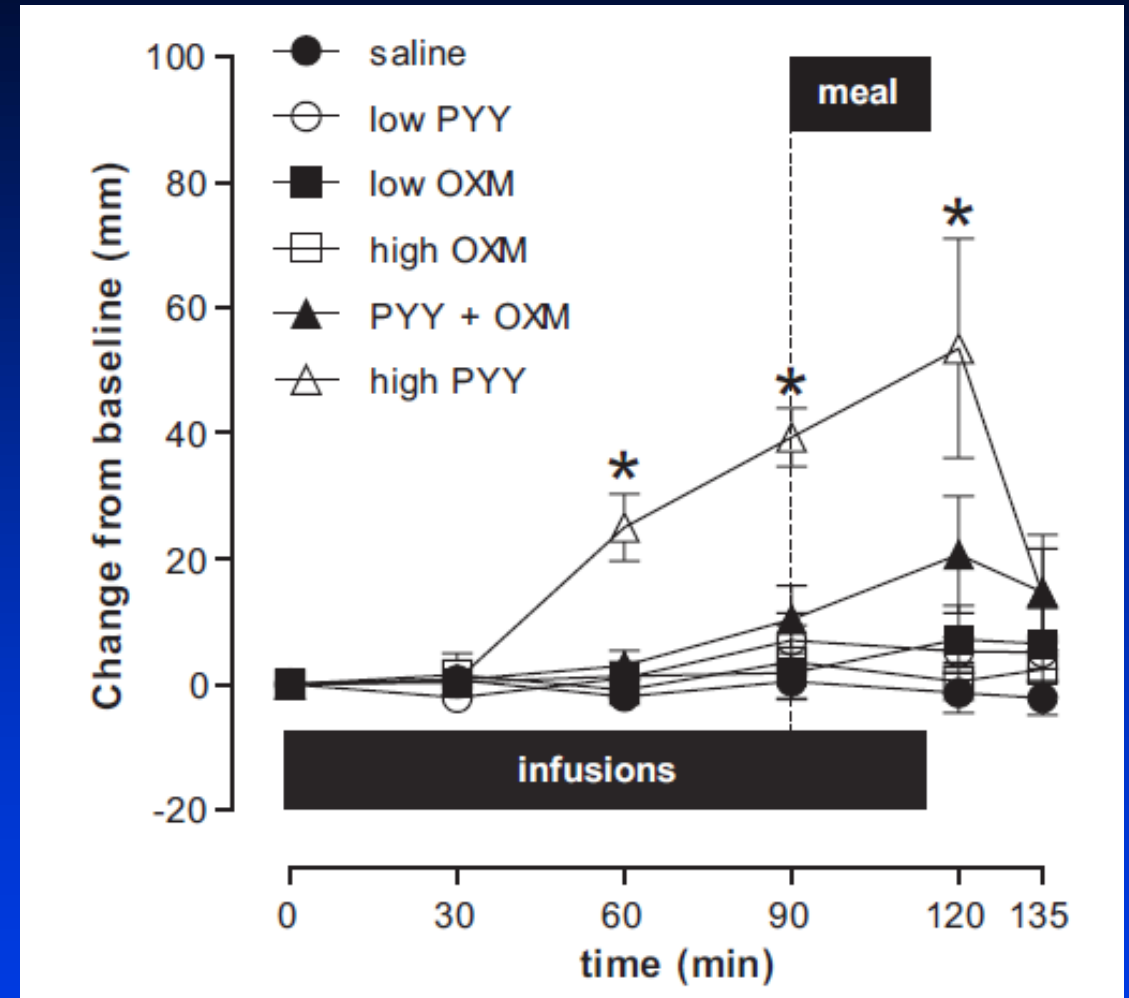
‡ P<0.05 vs PYY<sub>3-36</sub> + OXM

‡‡ P<0.01 vs PYY<sub>3-36</sub> + OXM



# PYY<sub>3-36</sub> and Oxyntomodulin

- Higher doses of PYY<sub>3-36</sub> needed to best reduce food intake
- Also associated with greater ratings of nausea
- When those without nausea excluded the reduction in food intake from combined Rx was ~ 1/3

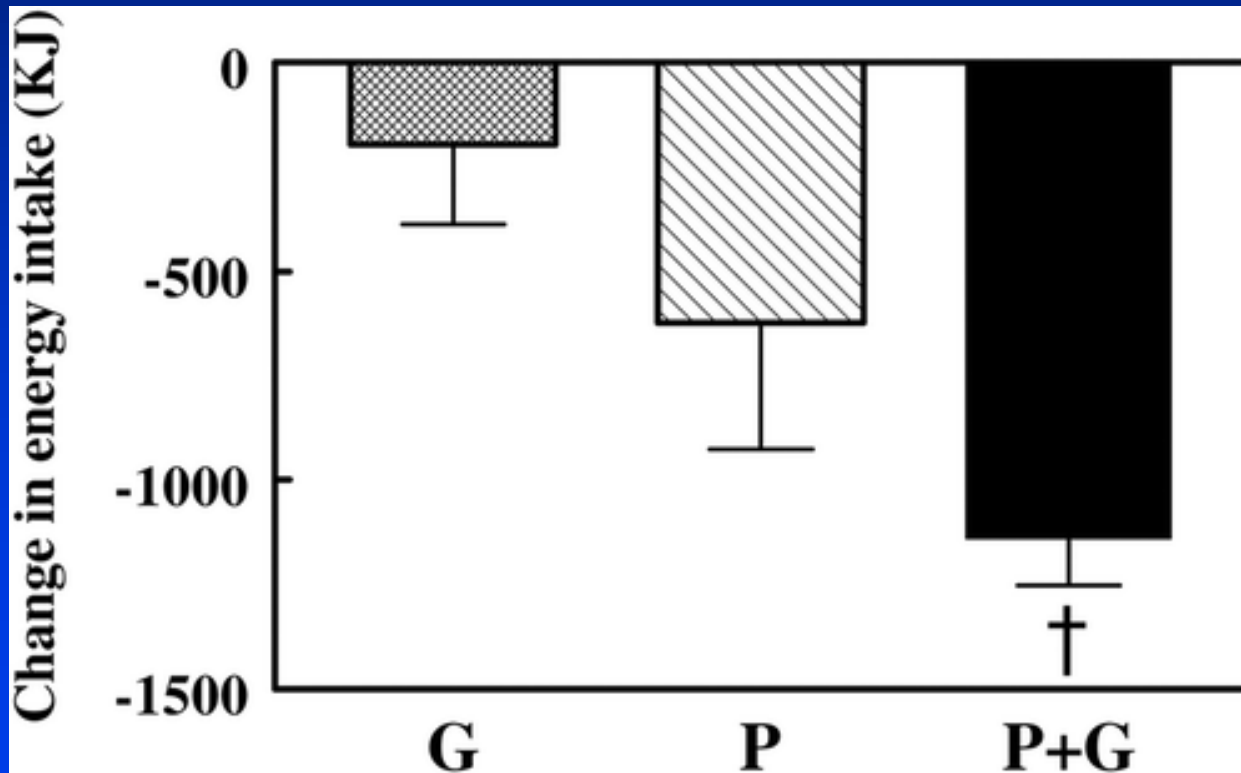


\* P<0.05 vs saline



# PYY<sub>3-36</sub> and GLP-1

- Similar to finding with PYY<sub>3-36</sub> and oxyntomodulin, co-infusion of PYY<sub>3-36</sub> and GLP-1 results in greater reductions in food intake than single infusions of either.

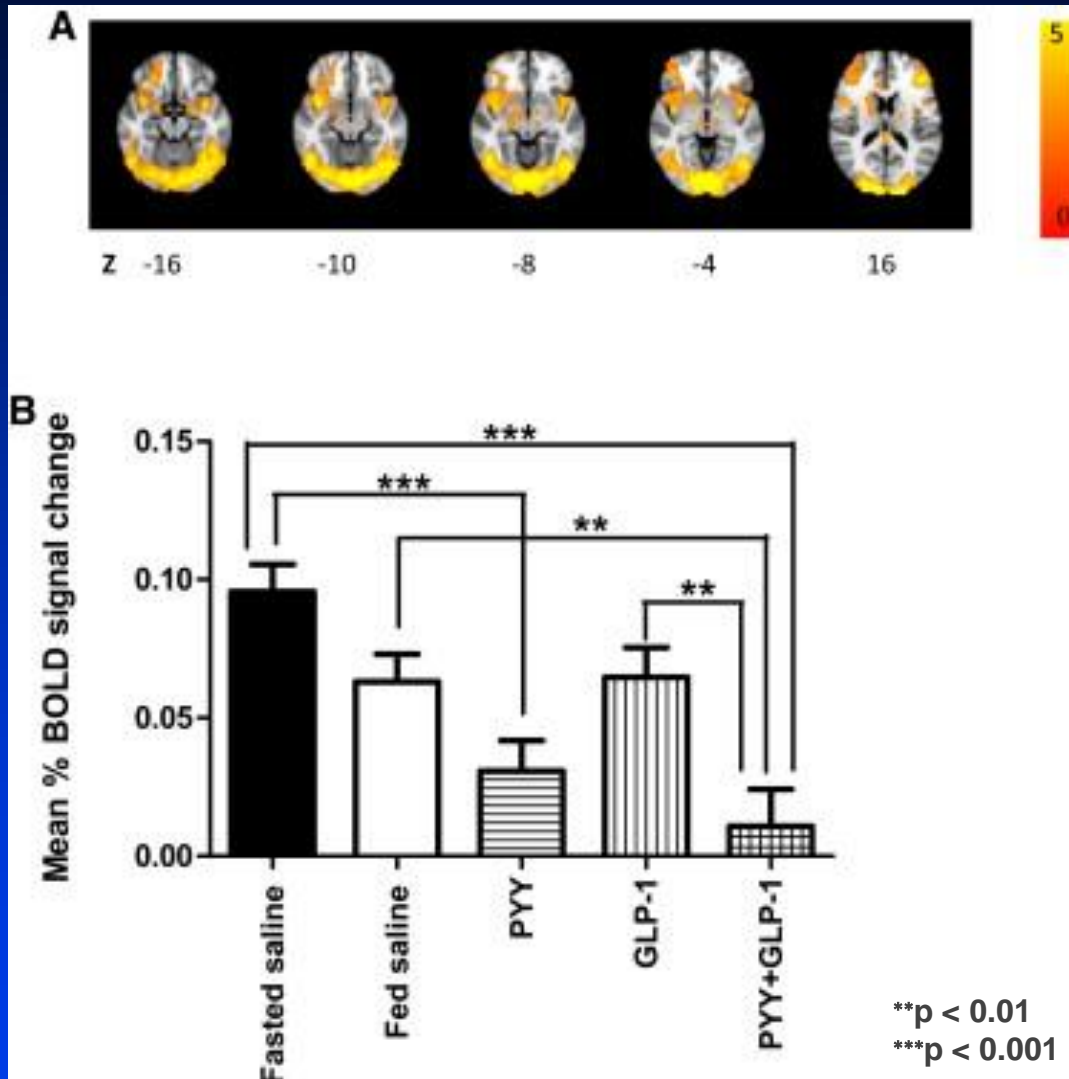


†,  $P < 0.05$ , compared with all other groups

Neary et al. Endocrinology 2005;146: 5120–5127.

# PYY<sub>3-36</sub> and GLP-1

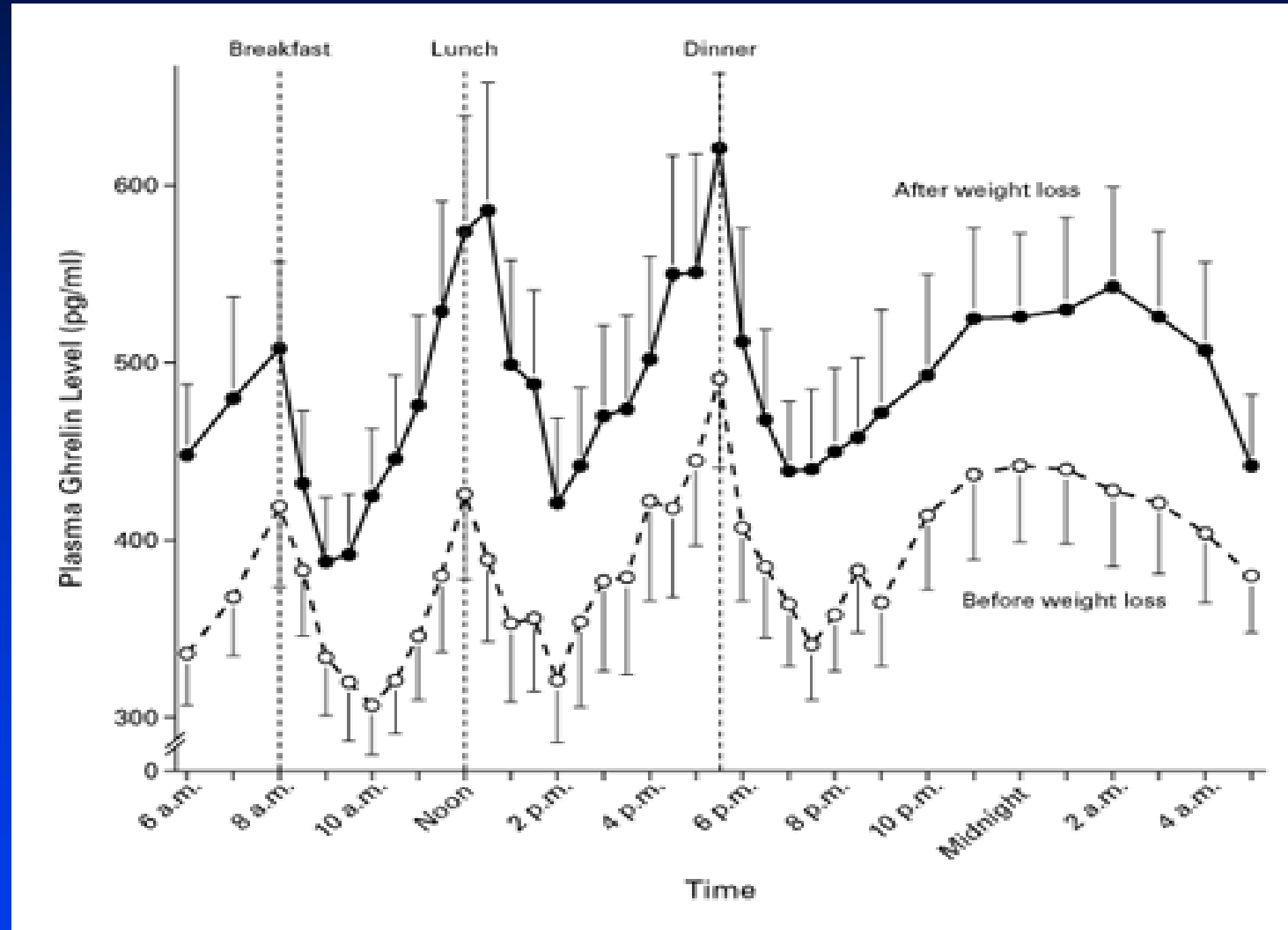
Co-infusion of PYY<sub>3-36</sub> and GLP-1 results in similar changes in regional brain appetite center metabolism as meal ingestion.



# Ghrelin

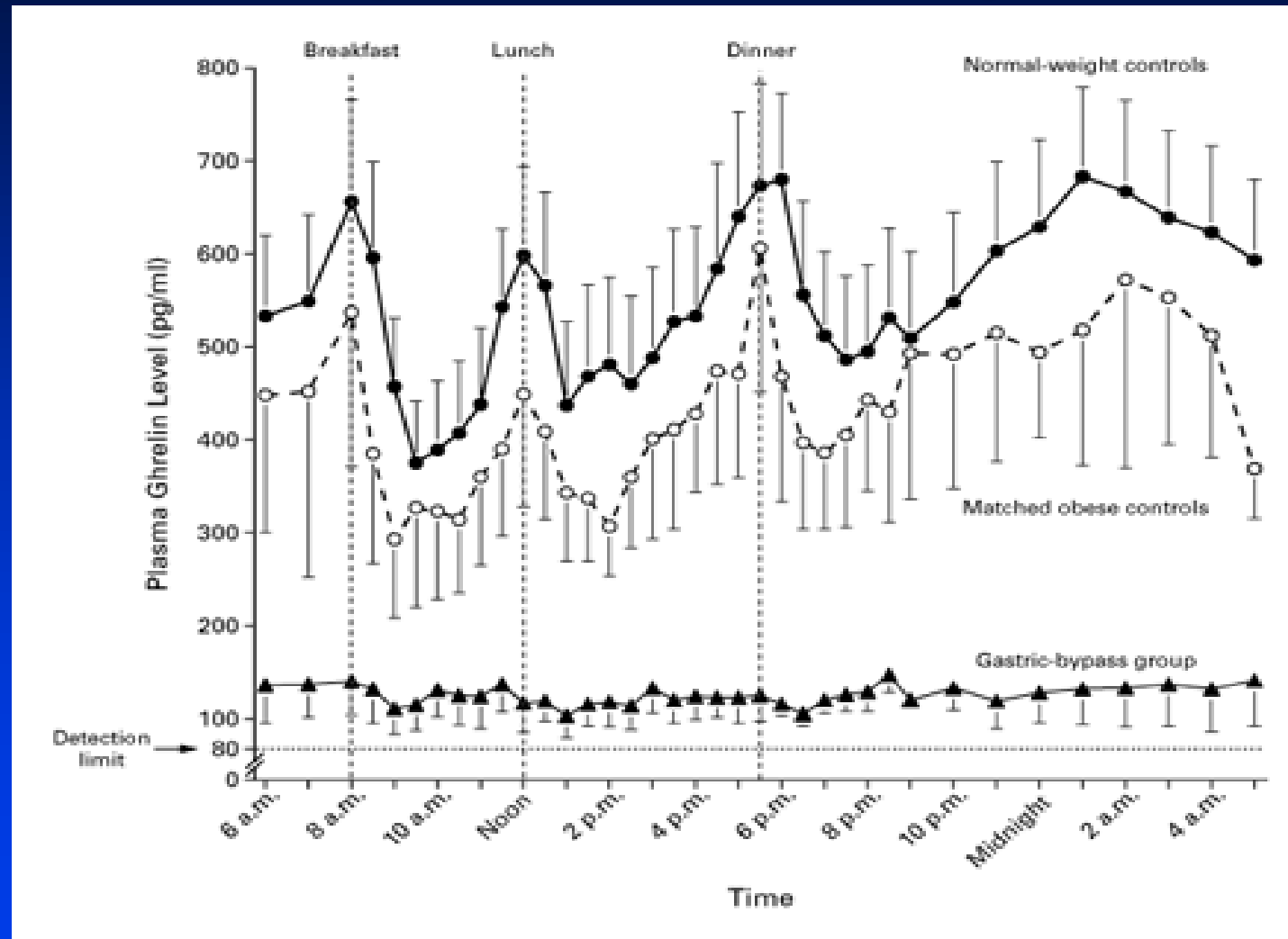
- Originally described as a peptide produced primarily by the stomach that stimulates GH secretion
- Found to be an orexigenic molecule
- Ghrelin levels increase between meals and fall after meals
- Therapeutic value of ghrelin antagonists unproven

# Serum Ghrelin Before and After Weight Loss



Cummings et al. NEJM. 2002;346:1623-1630.

# Serum Ghrelin After Gastric Bypass Surgery



# Summary

- **Several GI hormones clearly regulate appetite**
- **Although they require injection, there seem to be fewer “off target” effects than with other approaches**
- **Whether endoscopic procedure, gut hormone administration or some combination will replace bariatric surgery is unknown**





# CMHC WEST

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