Appetite, Glycemia and Entero-Insular Hormone Responses Differ Between Oral, Gastric-Remnant and Duodenal Administration of a Mixed Meal Test After Roux-en-Y Gastric Bypass

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How a surgical complication provided an experimental model....

Baseline
37 years old male patient, non-diabetic
RYGB for severe obesity (BMI 43 kg/m\(^2\)) in a peripheral hospital

4 months
Reoperation for internal hernia, complicated by intestinal perforation
Postoperative septic shock -> transfer our tertiary bariatric referral center
Upon arrival at USZ:
Laparotomy to repair intestinal perforations
Insertion of a double-lumen percutaneous gastrostomy to the remnant stomach
  - gastric decompression
  - post-pyloric enteral nutrition (tip of line: D3)

6 months -> weight stabilized (BMI = 35 kg/m\(^2\)), good general condition
Bariatric surgery’s effect on Type 2 diabetes mellitus

Metabolic Surgery in the Treatment Algorithm for Type 2 Diabetes: A Joint Statement by International Diabetes Organizations

Diabetes Care 2016;39:861–877 | DOI: 10.2337/dc16-0236

The Long-Term Effects of Bariatric Surgery on Type 2 Diabetes Remission, Microvascular and Macrovascular Complications, and Mortality: a Systematic Review and Meta-Analysis

Binwu Sheng¹ · Khoa Truong² · Hugh Spitler² · Lu Zhang² · Xuetao Tong³ · Liwei Chen⁰
Bariatric surgery’s effect on Type 2 diabetes mellitus

1. Weight-loss independent improvement of T2DM
2. Different effect of different surgical procedures
3. Gut-hormones play a key role
GLP-1 effects in humans

GLP-1 secreted upon the ingestion of food
*Half-life* = 2-3 min

1. β-cell: Enhances glucose-dependent insulin secretion in the pancreas = INCRETIN

2. α-cell: Suppresses postprandial glucagon secretion

3. Liver: reduces hepatic glucose output

4. Stomach: slows the rate of gastric emptying

5. Brain: Promotes satiety and reduces appetite

Glycemic control after RYGB: Mechanism?

GLP-1 and other hormones (PYY, GIP)

Improved insulin response and action

Normalization of plasma insulin and glucose

Anti-incretin factor

FOREGUT

HINDGUT

Post-bariatric gut hormone response in humans
Switching on/off the RYGB

ClinicalTrials.gov Identifier: NCT01025999

Pournaras D, Bueter M, Surg Obes Rel Dis. 2012
Dirksen C, Diab Care. 2010
Systemic bias in study design

Speed of food arrival into the intestines might matter

Nutrients delivered into the duodenum lead to

a. comparable changes in Gut hormones, Glucose metabolism & Appetite as orally

b. but different to the gastrostomy
New concept

**Design**
Resource 200 ml test meal in 4min
Baseline to 120 min blood tests
2x each route

**Gastric emptying assessment**
Gastrografin with X-ray 30min later

**Ethical approval**
Cantonal Ethics Committee of Zürich
BASEC-Nr. Req-2017-0616
Gut hormone response

Hypothesis: Correct! Duodenal = Oral
Gut hormone response

**GIP**

- Oral (AUC = 43214)
- Duodenal (AUC = 32518)
- Gastric (AUC = 25675)

- **Time (minute)**

- **GIP (pg/ml)**

```
0 0 30 60 90 120
0 200 400 600 800
```
Other factors may play a role...

Glucose metabolism

Glucose

Insulin

Oral (AUC = 723)

Duodenal (AUC = 652)

Gastric (AUC = 597)

Oral (AUC = 65254)

Duodenal (AUC = 17304)

Gastric (AUC = 4806)
Appetite (Visual analogue scale)

**Hunger**

- Oral (AUC = 217)
- Duodenal (AUC = 712)
- Gastric (AUC = 1166)

**Fullness**

- Oral (AUC = 982)
- Duodenal (AUC = 487)
- Gastric (AUC = 0)
Gastric emptying at 20 minutes
Main limitation

$n = 1$ (ethical obstacles to reproduce the model)
Discussion
1. Adaptation of Roux-limb «Enteroplasticity»

**GLP1-cell (L) hyperplasia after RYGB**

![Image showing GLP1-cell hyperplasia](image1.png)

**GLUT1 upregulation**

![Image showing GLUT1 upregulation](image2.png)

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Hansen, Bueter. Plos One. 2013
2. Fast gastric-pouch emptying

Gastric pouch emptying rate of glucose drink extremely rapid -> $T_{1/2}$ of 3 min
(Scintigraphic measurement)

Supraphysiologic intestinal nutrient delivery of 107 kcal/min = x 25 increase
Post-RYGB physiology seems to be more complex than initially thought

Forgut/hindgut theory needs to be challenged in future trials

For example, by testing the role of
- intestinal food arrival velocity
- Roux-limb adaptation
Marco Bueter, MD, PhD  Rolf Graf, PhD
Robert E. Steinert, PhD  Felix Beuschlein, MD, PhD
Hanna Hosa, MD  Pierre-Alain Clavien, MD, PhD

Thomas Lutz, Dr. med. vet. (physiology of eating)

David E. Cummings, MD, PhD (diabetologist)

Pelagia Kakka (line art figure)