An Analysis of Proton Pump Inhibitor Therapy and Glycemic Control in Patients with Type 2 Diabetes Mellitus

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Disclosures

- There are no relevant financial relationships related to the content of this presentation to disclose

Learning Objective

By the end of this presentation, attendees should be able to:

- Analyze the role of PPI therapy in insulin-glucose homeostasis in patients with type 2 diabetes mellitus
- Describe the rationale for studying the association between gastrin-modulating therapies and glycemic response

T2DM = insulin resistance + impaired insulin secretion

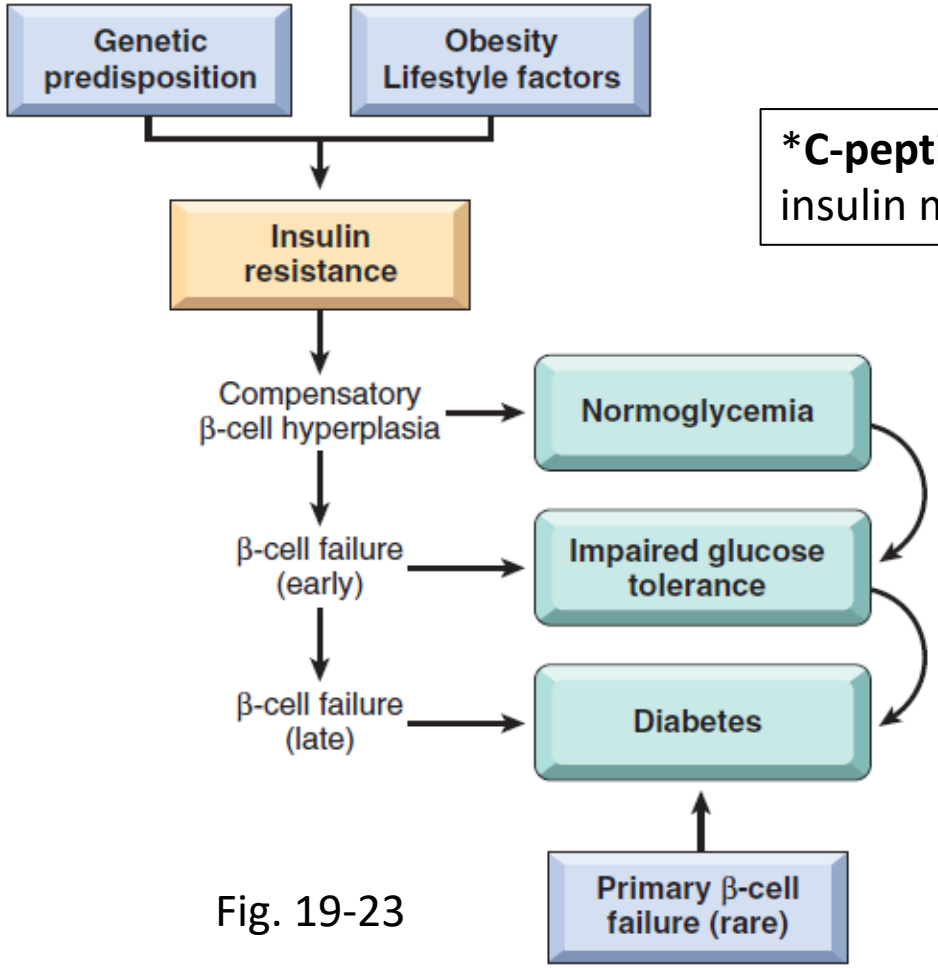


Fig. 19-23

***C-peptide:** endogenous insulin marker**

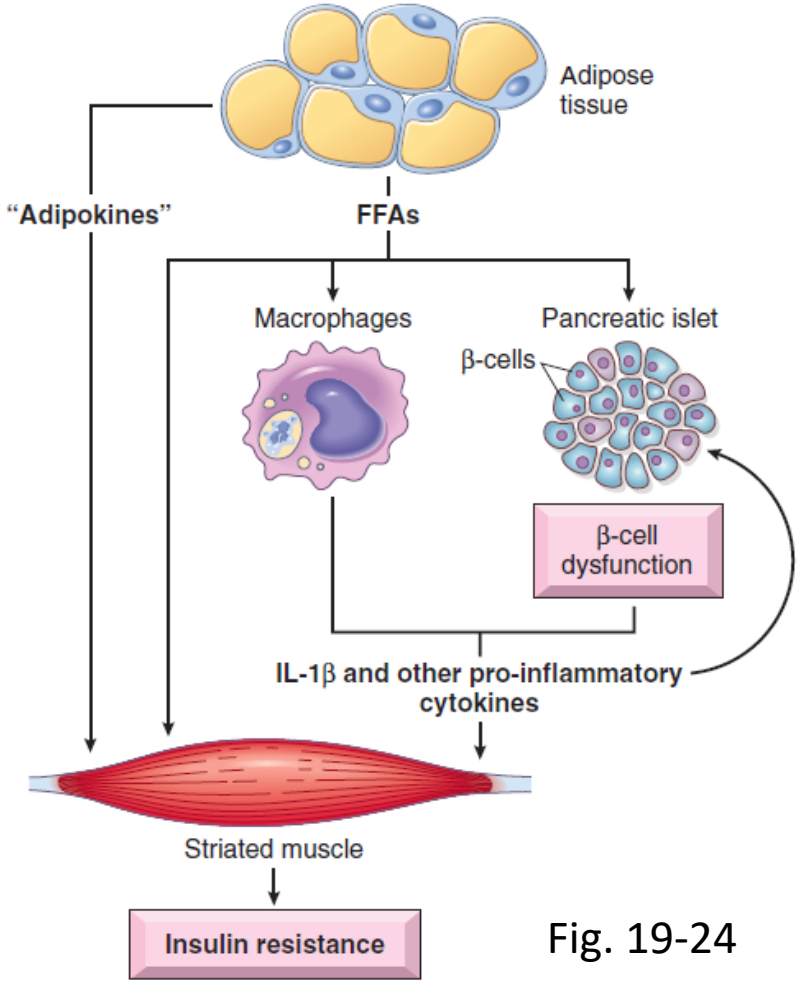
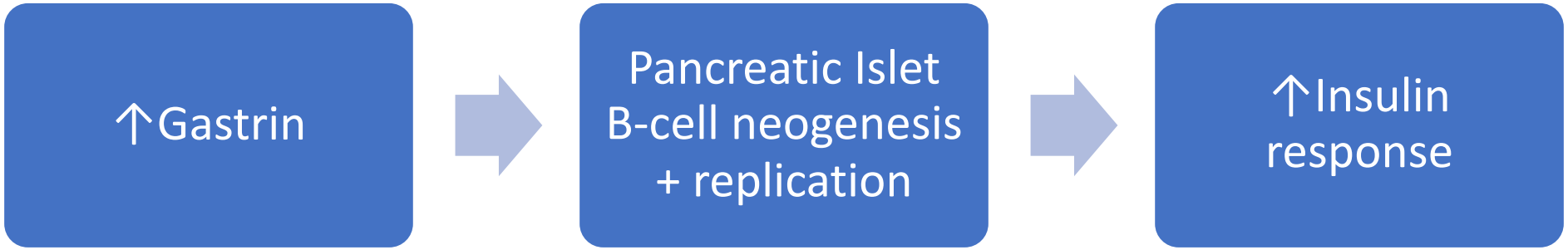


Fig. 19-24

Robbins Basic Pathology 9th edition [1]

Gastrin – a unique glycemic mediator



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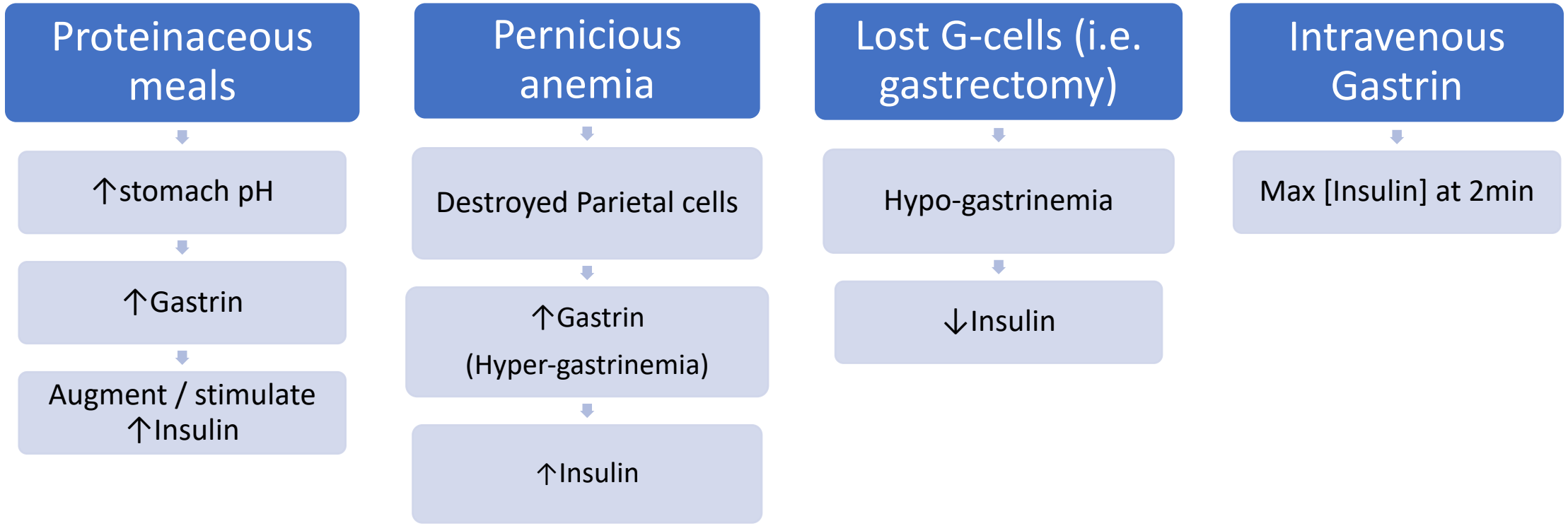
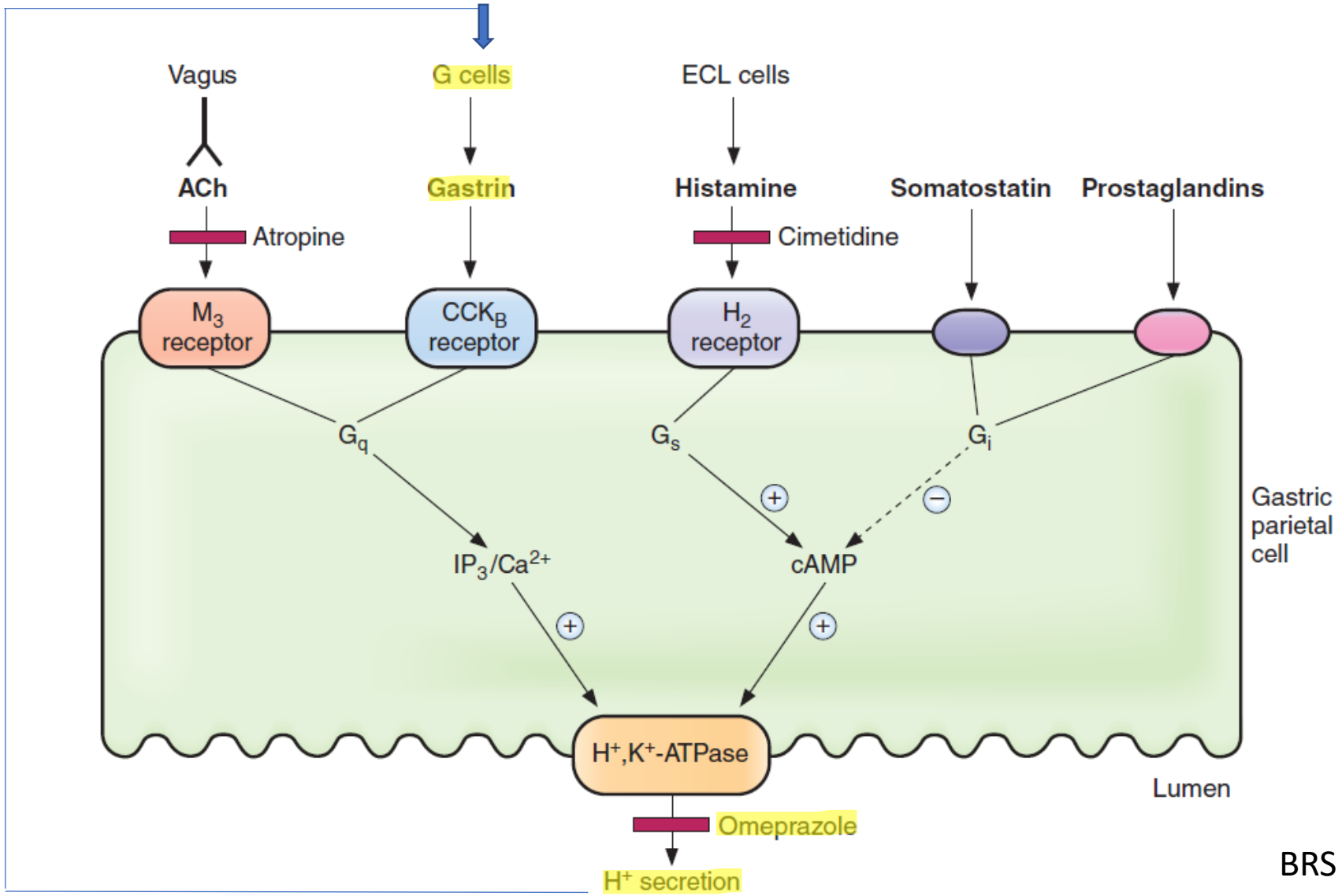


PPI Therapy Indirectly Increases Gastrin Levels



BRS Physiology, 5th Ed. [7]

PPI Therapy Effect on Glycemic Control is Controversial

- <u>Supportive findings:</u>
  - Animal model studies have demonstrated improved glycemic control
  - Most clinical studies have reported significant improvement in glycemic control
  - Takebayashi and Inukai (2015):
    - **HbA1c**: 7.0% vs 7.6% (p = 0.002)
    - **Insulin** therapy (+) PPI: (-0.8%) reduction HbA1c (p = 0.02)
    - **2-yr** PPI therapy:
      - **HbA1c**: 7.1% ± 1.07% *vs* 7.4% ± 1.4% (p = 0.01)
      - **Fasting Plasma Glucose**: 127 ± 36.9 mg/dL *vs* 147.6 ± 49.6 mg/dL (p = 0.001)

- Other studies have shown no significant improvement of T2DM with PPI use…

AIM

- **Primary Question:**
  - Understand the effect of PPIs on glycemic control (HbA1c, C-peptide, and glucose) in patients with T2DM who are taking incretin hypoglycemic agents

- **Secondary**:
  - Study the association of PPI use with serum triglyceride level in patients with T2DM
  - Study the association of PPI use with coronary artery disease or cerebrovascular accidents in patients with T2DM

Study Design

Inclusion Criteria

- Diagnosis of type 2 diabetes (T2DM)
- Age >/= 18 year
- Received medical care at AnMed Health inpatient or outpatient facilities from 01/01/2018 to 12/31/2018

→

Slicer Dicer:

- T2DM → 18061 charts
- C-peptide → 271
- HbA1c → 215
- *PPI → 79

↓

PPI Group: 79 patients

Control group: 136 patients

→

Exclusion Criteria

- No C-peptide
- No HbA1c
- Type 1 diabetes
- Pregnant patients
- New onset T2DM (within 3 months)
- Recent hospitalization (within 3 months) for hyperglycemic decompensation
- Recent hospitalization (within 3 months) requiring critical care stay
- Recent use of (within 6 weeks) of oral or injectable steroids

↓

17,846 patients excluded

* PPI = Pantoprazole + Omeprazole + Esomeprazole + Dexlansoprazole

Patient Baseline Characteristics

Variable		PPI (N=79)	⊘ (N=136)	P value
Sex	Male	33 [41.7%]	51 [37.5%]	0.53
	Female	46 [58.3%]	85 [62.5%]	
Race	AA	27 [34.2%]	29 [21.3%]	0.10
	CC	47 [59.5%]	102 [75.0%]	
	Other	5 [6.3%]	5 [3.7%]	

Variable	PPI	⊘	P value
Age (years)	56.46 ± 13.2	50.68 ± 16.8	0.09
BMI	33.53 ± 8.5	32.5 ± 8.1	0.40

Variable	PPI (N=79)	⊘ (N=136)	P value
Insulin	58 [73.4%]	107 [78.7%]	0.40
Aspirin	41 [51.9%]	56 [41.2%]	0.15
Statin	57 [72.1%]	90 [66.2%]	0.35
HTN	67 [84.8%]	100 [73.5%]	0.06
CAD	48 [60.8%]	23 [16.9%]	0.01
TIA / Stroke	10 [12.6%]	5 [3.7%]	0.50

⊘ = No PPI

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⊘ = No PPI

Results: Comparison of glycemic markers and metabolic profile

Variable	PPI (N=79)	⊘ (N=136)	P value
HbA1c	8.6 ± 2.1	8.3 ± 2.0	0.37
C-peptide	3.1 ± 2.4	2.4 ± 2.3	0.037
LDL	79.6 ± 34.0	89.73 ± 32.9	0.046
Triglyceride	206.7 ± 162	205.1 ± 3.44	0.97
Vitamin D	28.7 ± 13.54	27.2 ± 14.7	0.51

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Conclusions / Clinical Implications

- *No causal relationships – only **associations** between groups*

Findings:

- Greater C-peptide levels in PPI group
- No statistically significant change in HbA1c
- Higher prevalence of CAD in the PPI group
- Lower LDL levels in the PPI group

Limitations

- Small sample size → limited statistical power
- Variety of type and severity of comorbid conditions
- Retrospective study
- No accurate way to confirm patients were actively taking all medications (including PPI) – “recall bias”

Future Research Directions

- Additional studies are needed on this topic
  - Larger sample size → greater statistical power → stronger associations
  - Research to understand causal relationships (i.e. PPI with CAD, LDL, and HTN)
  - Randomized Controlled Trials

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References

1. Kumar V, Abbas A, Aster J. Chapter 19 – Endocrine System: Endocrine Pancreas. *Robbins Basic Pathology 9th edition*. Elsevier, 2018, pg 742-743.
2. Rooman I, Lardon J, Bouwens L. Gastrin stimulates beta-cell neogenesis and increases islet mass from transdifferentiated but not from normal exocrine pancreas tissue. *Diabetes*. 2002;51:686–690.
3. Téllez N, Joanny G, Escoriza J, Vilaseca M, Montanya E. Gastrin treatment stimulates β-cell regeneration and improves glucose tolerance in 95% pancreatectomized rats. *Endocrinology*. 2011;152:2580–2588.
4. Creutzfeldt W. Gastrointestinal Hormones and Insulin Secretion. *N Engl J Med.* 1973; 288:1238-1239. DOI: 10.1056/NEJM197306072882312
5. Rehfeld JF, Stadil F, Baden H, Fischerman K. The enteral insulin-stimulation after Whipple's operation. *Diabetologia*. 1975 Jun;11(3):207-10.
6. Rehfeld JF, Stadil F. The effect of gastrin on basal- and glucose-stimulated insulin secretion in man. *J Clin Invest*. 1973 Jun;52(6):1415-26.
7. Costanzo L. Chapter 6, part IV: GI Secretion. BRS Physiology, 5th ed. *Wolters Kluwer Health*, 2018, Pg 204-205.
8. Takebayashi K, Inukai T. Effect of proton pump inhibitors on glycemic control in patients with diabetes. *World J Diabetes*. 2015 Aug 25; 6(10): 1122–1131.

Questions?