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METABOLISM INSTITUTE

Resetting Type 2 Diabetes in the Duodenum: A Pathophysiological View

Lee M. Kaplan, MD, PhD

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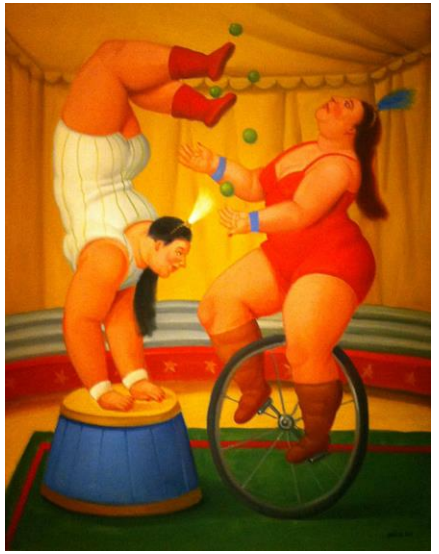
September 1, 2026



Fernando Botero, 1932-2023

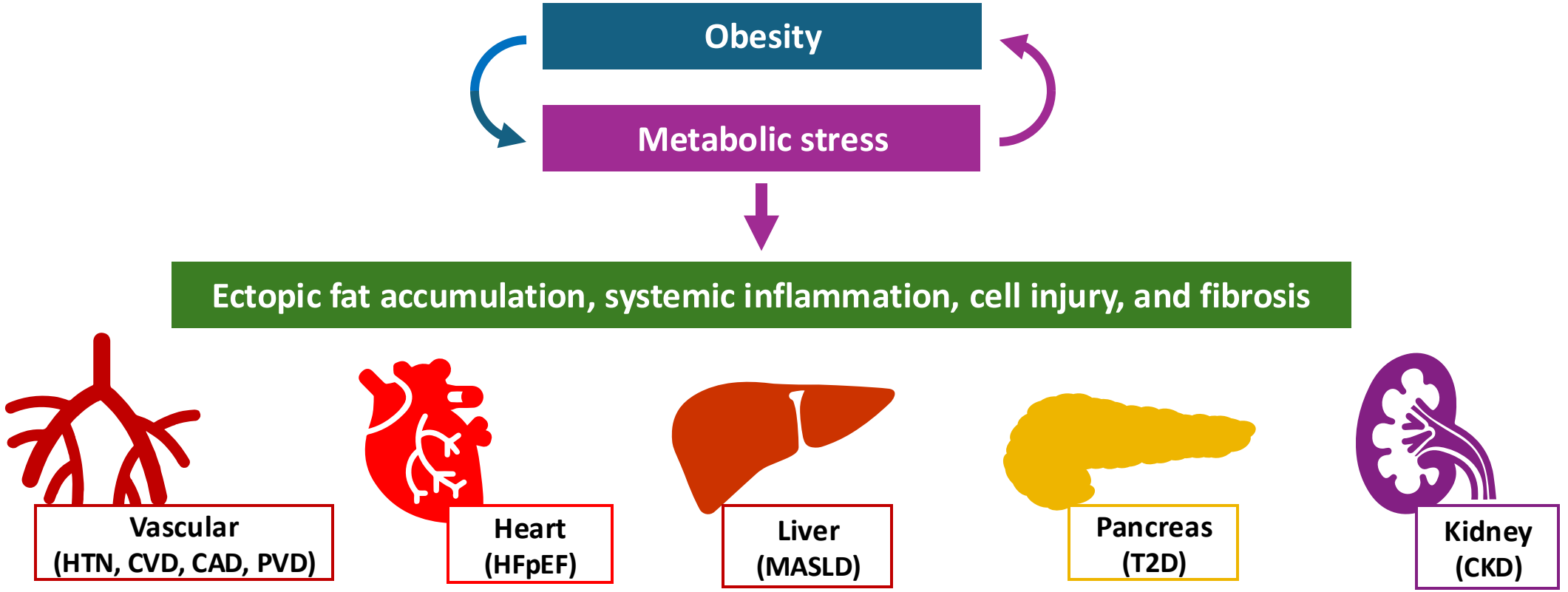
IFSO 2026 ● Metabolic Bariatric Endoscopy

Disclosures

I am currently or have recently been a consultant to the following companies and organizations:

- Altimmune
- Amgen
- AstraZeneca
- BaseCure Therapeutics
- Boehringer Ingelheim
- Dexcel Pharma
- Helicore
- Johnson & Johnson
- Kallyope
- Eli Lilly & Company
- MetaVia
- Neurogastrx
- Novo Nordisk
- Oxford Medical Products
- Perspectum
- Pfizer
- Protagonist Therapeutics
- Roche / Genentech
- Skye Bioscience
- SparkSeven Bio
- State 4 Therapeutics
- Structure Therapeutics
- The Last Food Fight
- Wave Life Sciences

Obesity stimulates a multi-system metabolic and inflammatory syndrome



The ideal therapy would be **safe** and **tolerable**, **improve cardio-metabolic, liver, kidney, and pancreatic outcomes**, and **reduce** the risk of **cancer**

Adapted from Sanyal AJ, 2024

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The magnitude of weight loss is important - but many benefits of obesity treatment are independent of weight loss

Obesity complication	Benefit increases with increasing weight loss	Primary benefit is largely independent of weight loss
Atherosclerotic cardiovascular disease	✓	Yes
Heart failure with preserved ejection fraction	✓	No
Type 2 diabetes	✓	Yes
Hypertension	✓	?
Dyslipidemia	✓	?
MASLD / MASH	✓	Yes
Sleep apnea	✓	No
Osteoarthritis	✓	?
Stress incontinence	✓	No
Gastroesophageal reflux	✓	No
Polycystic ovary syndrome	✓	?

Adapted from Cefalu WT *et al.*, *Diab Care* 2015

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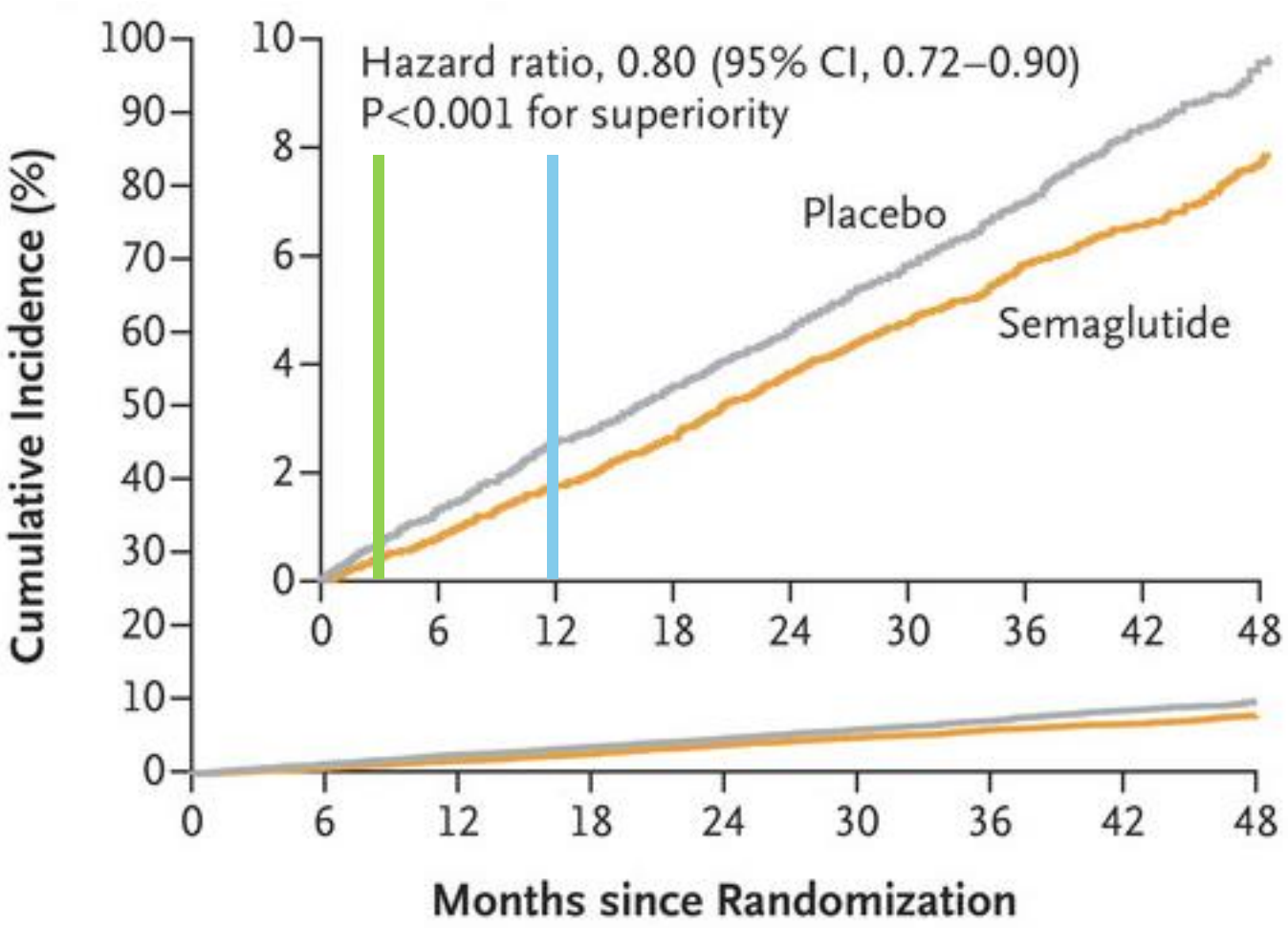
Semaglutide 2.4 mg reduces incidence of 3-point MACE by 20%*

SELECT Trial Primary Endpoint



Lincoff AM et al., *N Engl J Med* 2023

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GLP-1 receptor agonist treatment of MASH is primarily weight loss-independent

press release

Novo Nordisk's Wegovy® (semaglutide 2.4 mg) was associated with liver health-related benefits not solely based on weight loss in adult patients with MASH with liver scarring, according to a new post hoc analysis

Steatohepatitis-related NITs improved in all groups receiving semaglutide 2.4 mg, with the greatest treatment effect observed for alanine aminotransaminase (ALT) in patients with weight loss of ≤7%.

For histological endpoints, semaglutide 2.4 mg, when compared to placebo, was associated with resolution in liver injury across a spectrum of weight loss thresholds, including low levels of weight loss (≤2%). In this subgroup, 48.4% of patients receiving semaglutide 2.4 mg showed

Source: Novo Nordisk

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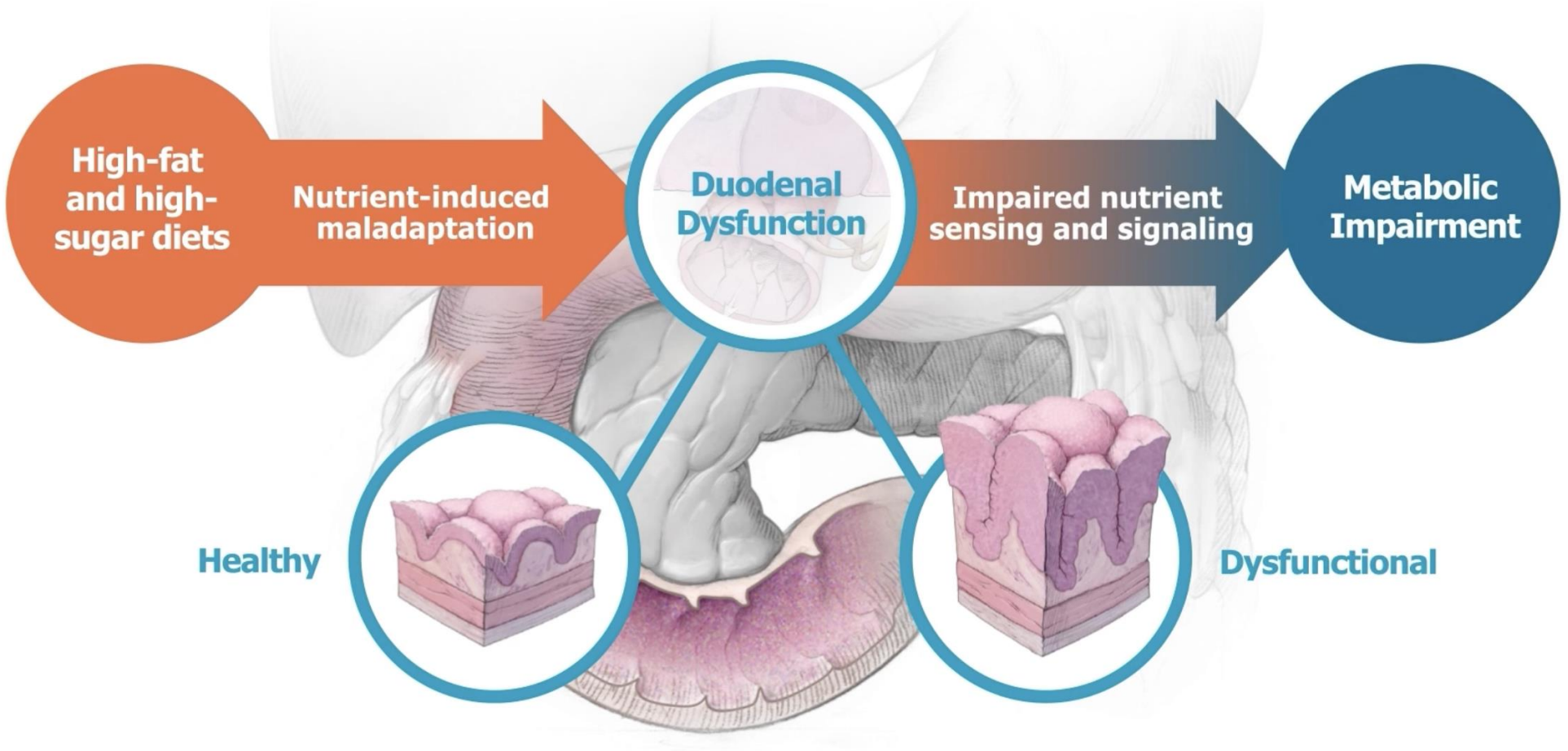
Model of duodenal dysregulation leading to metabolic dysfunction



Source: Fractyl Health

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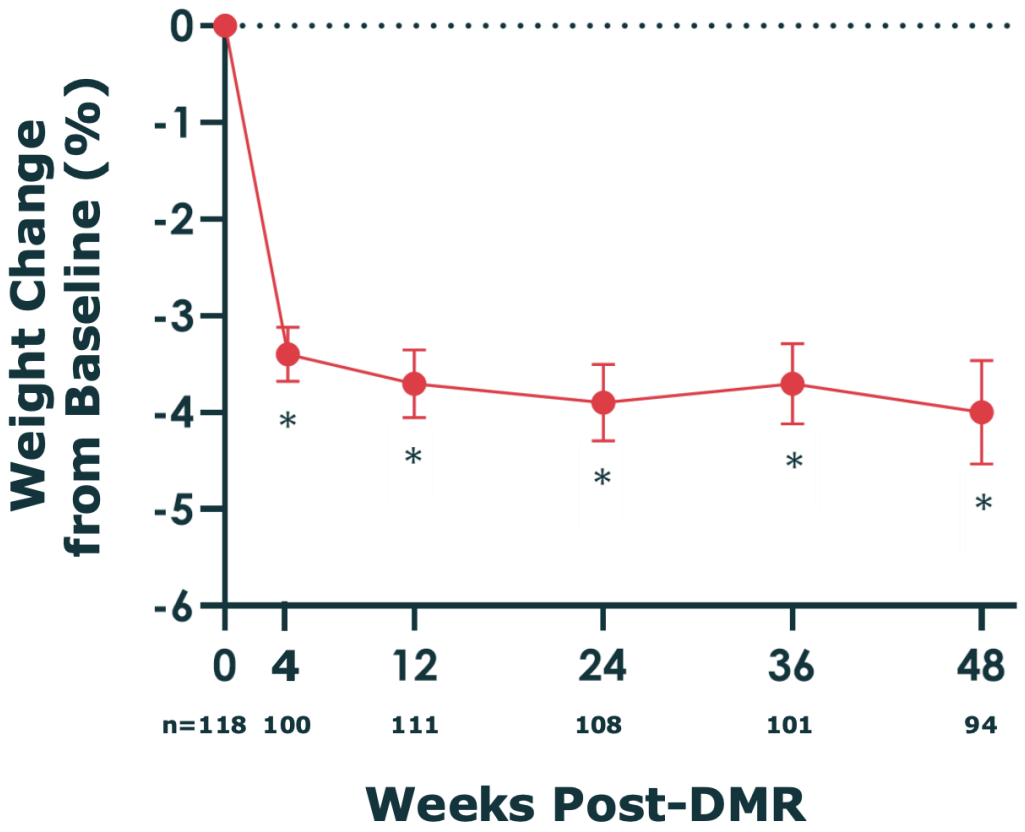
Duodenal mucosal resurfacing led to weight loss sustained through 48 weeks



Source: Fractyl Health

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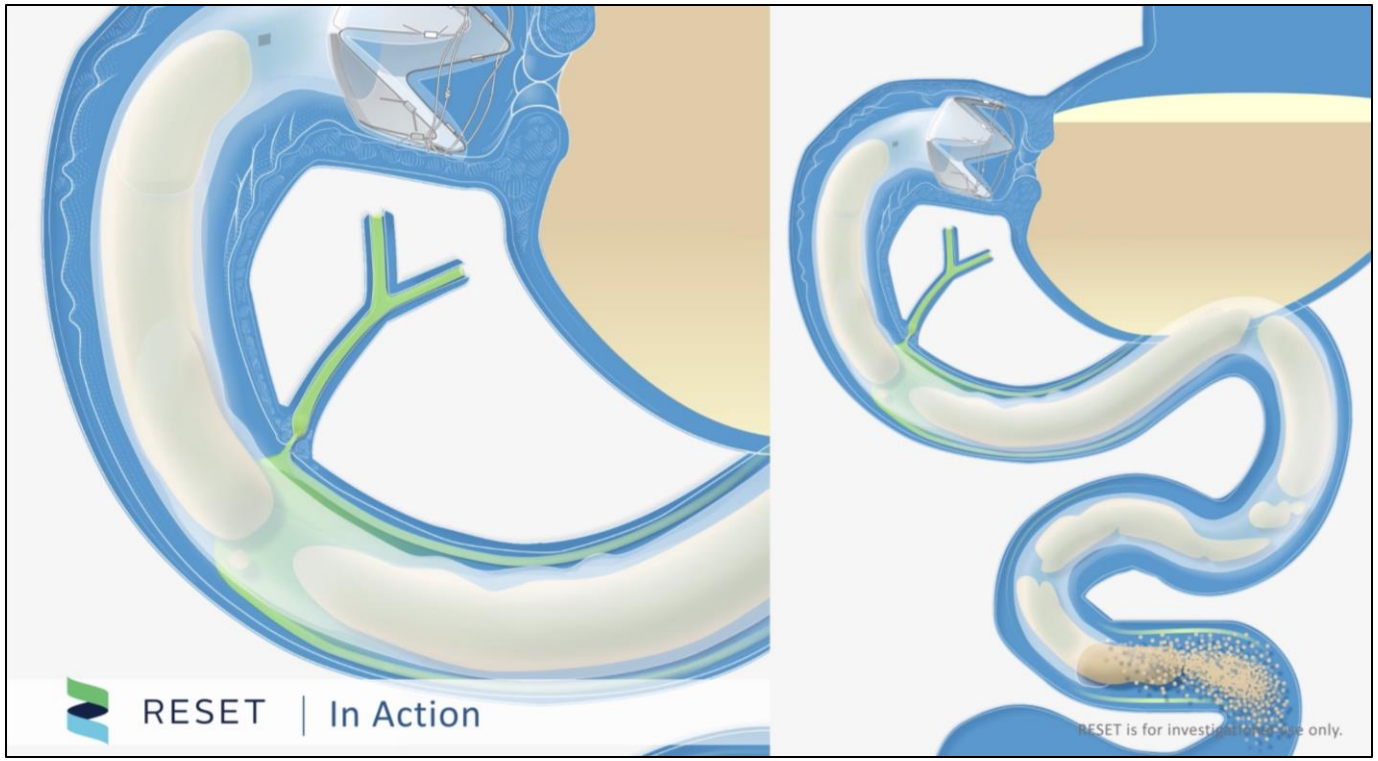
Duodenal liner blocks interaction between ingested nutrients and intestinal mucosa



Source: Morphic Medical

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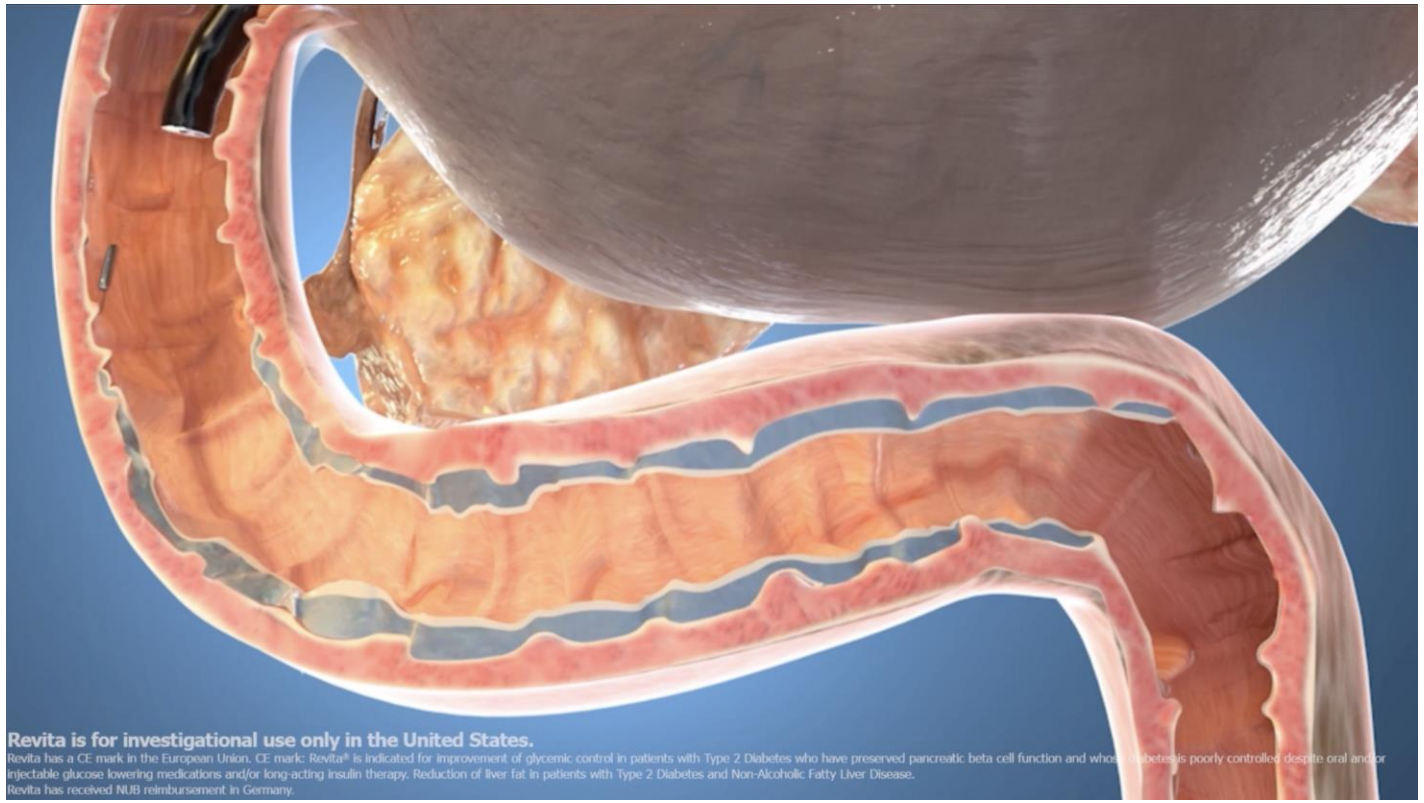
Duodenal mucosal resurfacing blocks interaction between ingested nutrients and intestinal mucosa



Source: Morphic Medical

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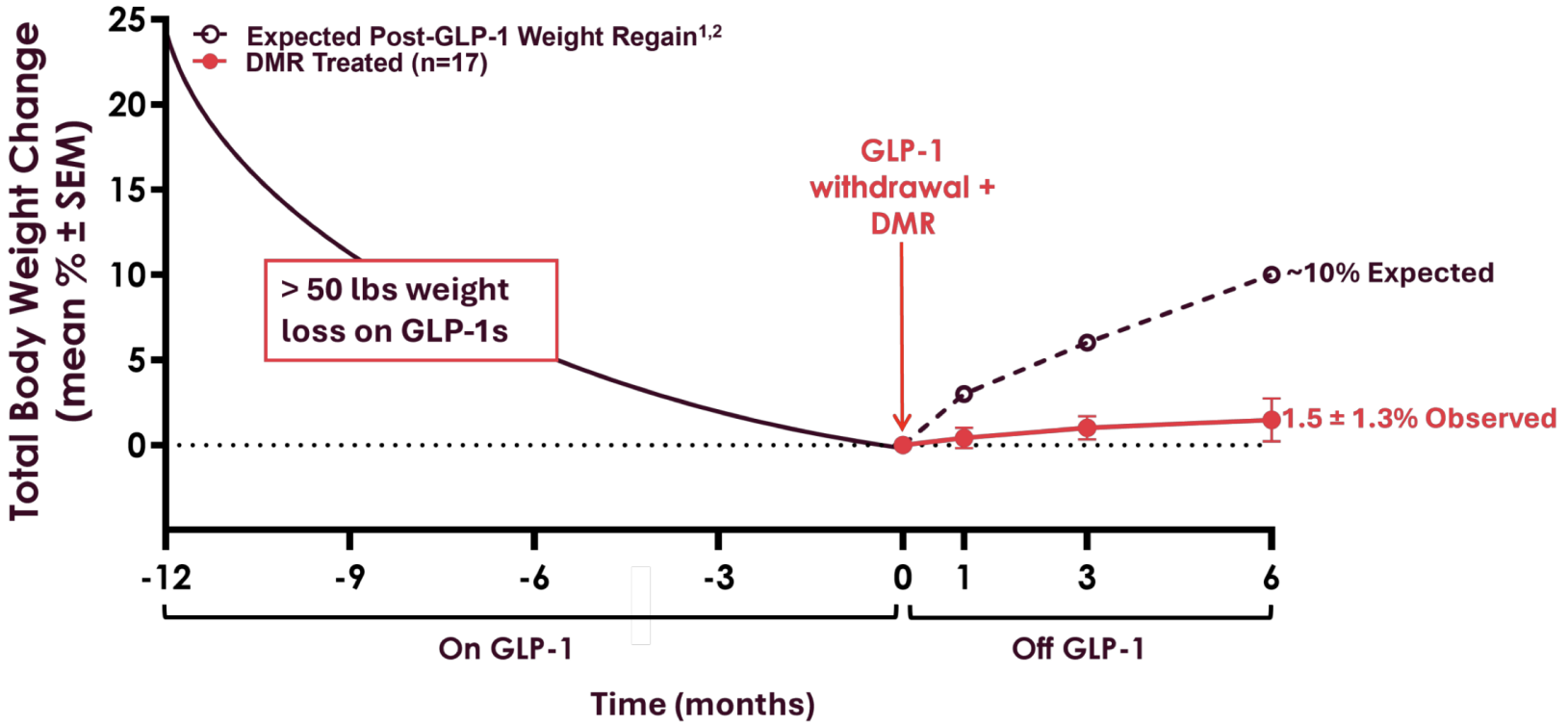
DMR helps maintain weight loss induced by GLP-1 receptor agonist treatment



Source: Fractyl Health

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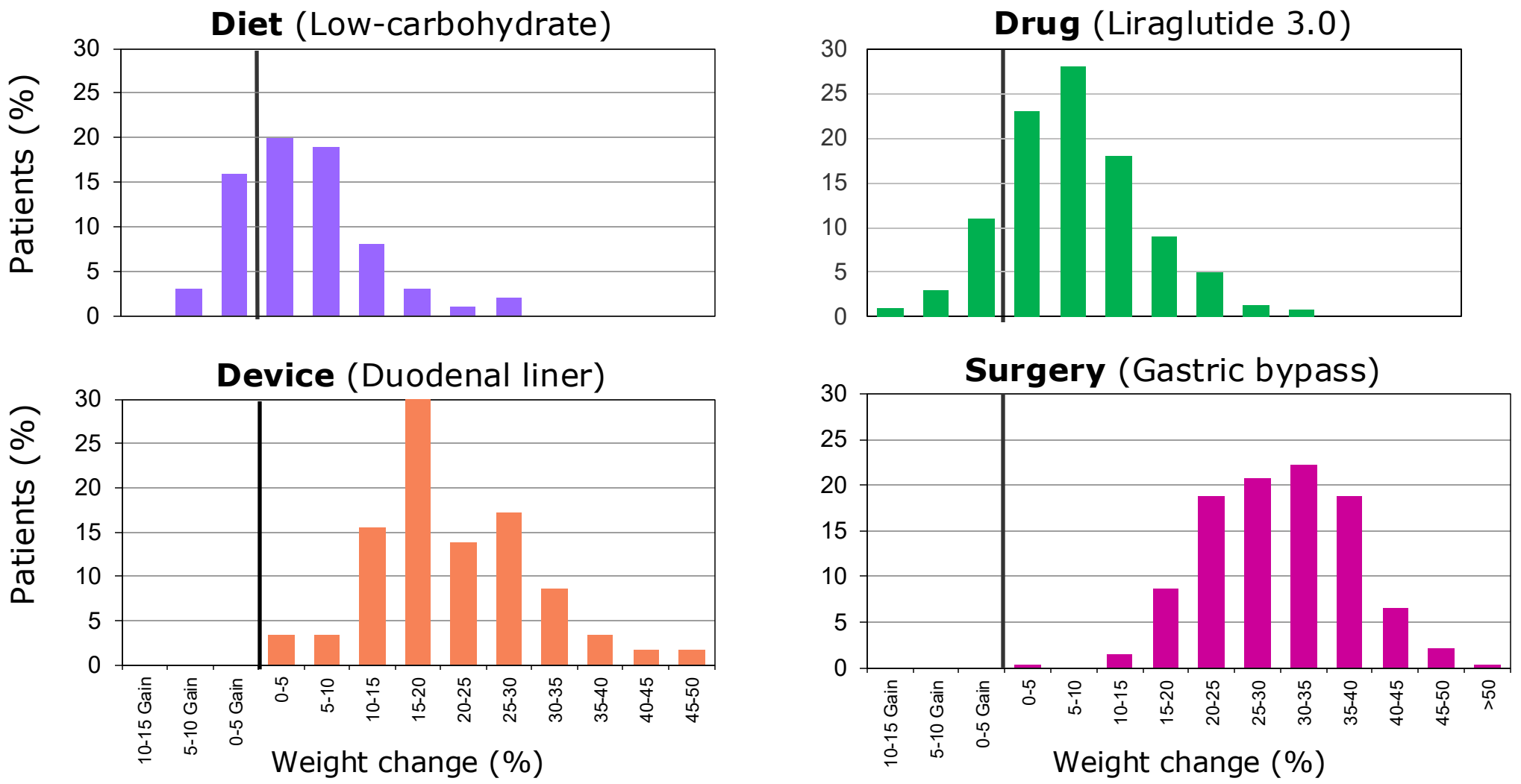
All obesity therapies exhibit wide patient-to-patient variability



Kaplan LM, 2016

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Weight loss from duodenal mucosal resurfacing showed similar variability

Individual patient weight loss at 48 weeks

Source: Fractyl Health

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There is a growing list of diseases that have now been demonstrated to benefit from effective treatment of the underlying obesity

- Type 2 diabetes (T2D) – 2007
- Atherosclerotic cardiovascular disease (ASCVD) – 2023
- Heart failure with preserved ejection fraction (HFpEF) – 2023
- Atrial fibrillation – 2025
- Chronic kidney disease (CKD) – 2024
- Metabolic dysfunction-associated steatotic liver disease (MASLD/MASH) – 2021
- Obstructive sleep apnea (OSA) – 2024
- Obesity-associated cancers – as a group – 2022
  – endometrial, meningioma, ovarian – 2025
- Osteoarthritis – 2024
- Polycystic ovary syndrome (PCOS) – a major cause of infertility in women – 2024
- Opiate addiction and other drug dependency states – 2025
- Vertebral fractures – 2026
- Psoriasis and psoriatic arthritis – 2026
- Alcohol use disorder - 2026

Kaplan LM, 2026

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Conclusions

- Intestinal mucosa plays a central role in metabolic regulation and is a key component of gastric bypass and similar surgical interventions
- Mucosal dysfunction can cause or exacerbate metabolic dysfunction leading to injury in multiple organs
- Ingested nutrients may promote mucosal signaling dysfunction
- Disruption of interaction between ingested nutrients and intestinal mucosa can lead to restitution of metabolic function
- The duodenum, as an accessible region of the small bowel, is an attractive target for manipulation of intestinal mucosal signaling
- The beneficial effect on metabolic function of manipulating the intestinal mucosa on metabolic function may be largely independent of weight loss
- The cellular and molecular mechanisms by which these effects occur remain unknown but may include intestinal peptides, bile acids, vagal afferents and ingested nutrients themselves

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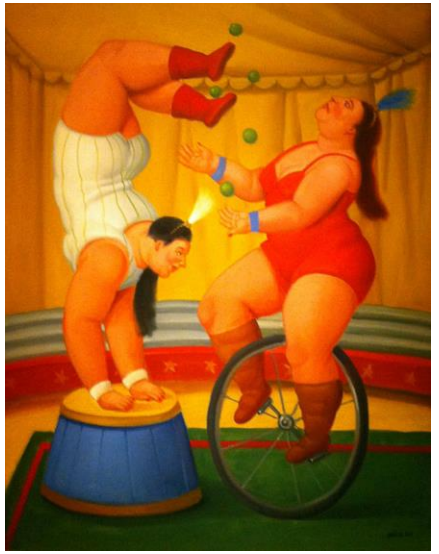

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