Obesity and Fat Metabolism in IBD: Clinical and Therapeutic Implications

Joëlle St-Pierre, MD PhD
Clinical Assistant Professor
University of Calgary

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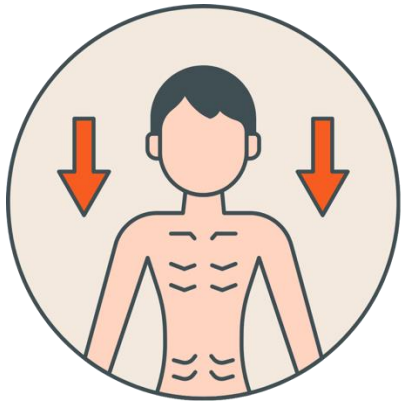
Disclosures

- Advisory board fees from Abbvie, Eli Lilly, Pfizer, Pendopharm
- Speaker fees from Takeda, Pfizer

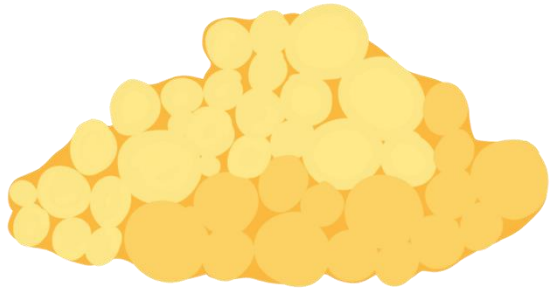
Objectives

1. Understand the immunometabolic role of fat and muscle in IBD
2. Recognize the therapeutic potential of GLP-1/GIP modulation
3. Integrate metabolic and nutritional strategies into IBD care

The changing face of body composition in IBD



IBD historically associated with an undernutrition and catabolic state



- Prevalence among patients with IBD (USA, France)[1-4]
  - **24-35%** overweight
  - **12-37.3%** obesity
- Canadian population data[5]
  - **35.8%** overweight
  - **29%** obesity

[1]Al Bacha R et al, Dig Liver Dis. 2023; [2]Flores A, et al, Dig Dis Sci. 2015; [3]Johnson AM, et al, JCC 2021; [4]Elangovan A et al, Crohns Colitis 360. 2023; [5]Statistics Canada 2023

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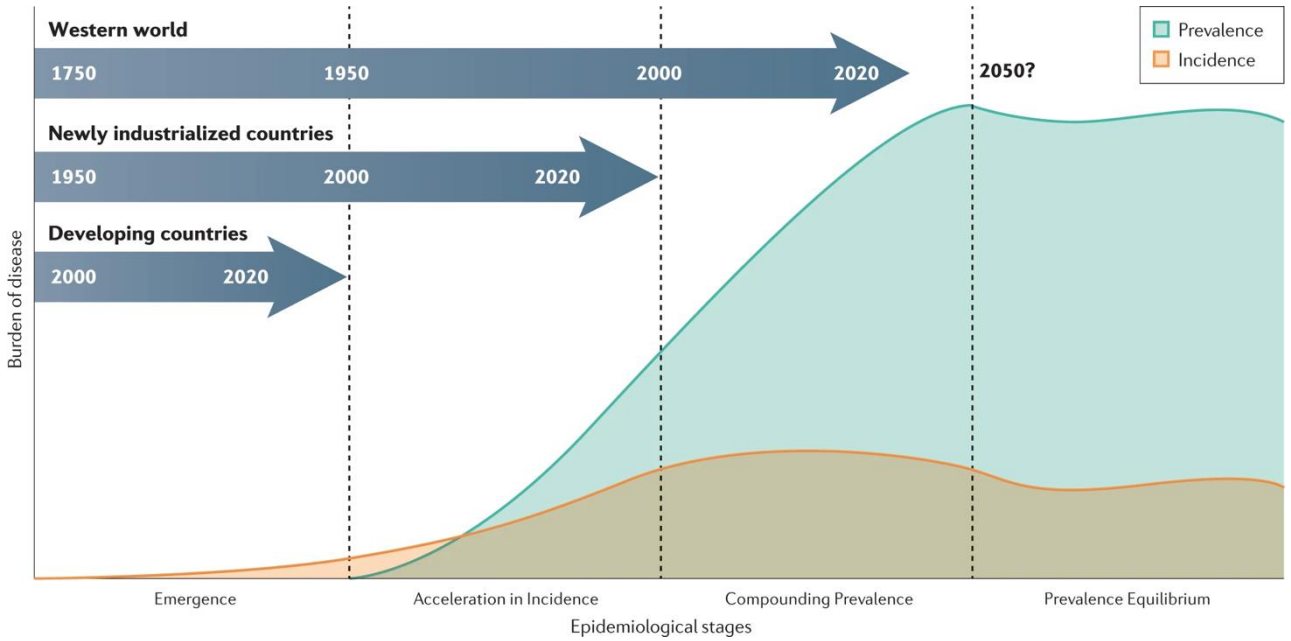
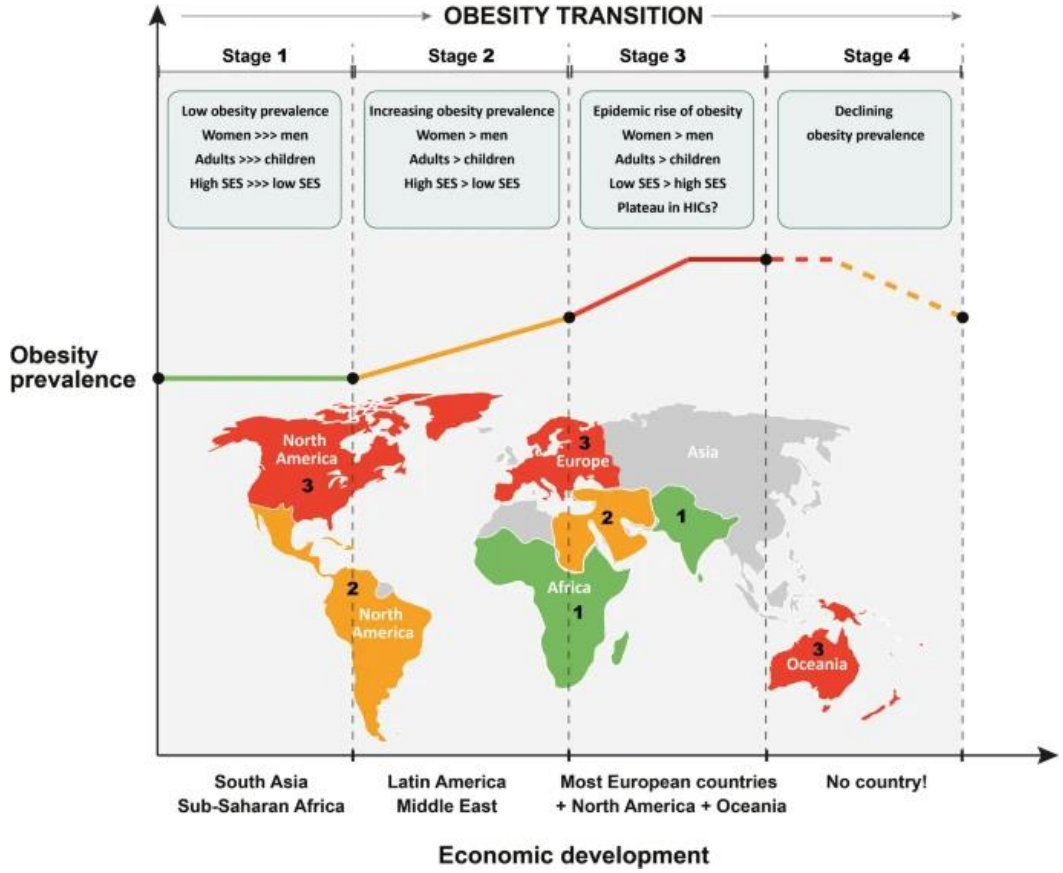
At a crossroads





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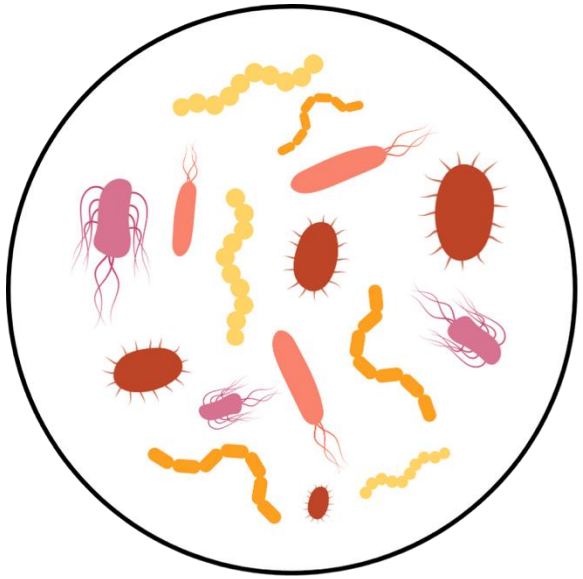
Kaplan G and Windsor J, Nat Rev Gastroenterol Hepatol. 2021; Koliaki C et al, Curr Obes Rep. 2023

Common factors between IBD and obesity



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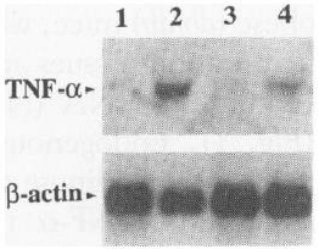
From fat storage to immune organ: >30 years of discovery

1993



TNF mRNA in adipose tissue of lean (1,3) and obese (2,4) mice.[1]

2000s

Macrophages are increased in adipose tissue during obesity and are the primary source of TNF

2007-2010

In obesity, switch in macrophage polarization from M2-like to pro-inflammatory M1-like

2010s

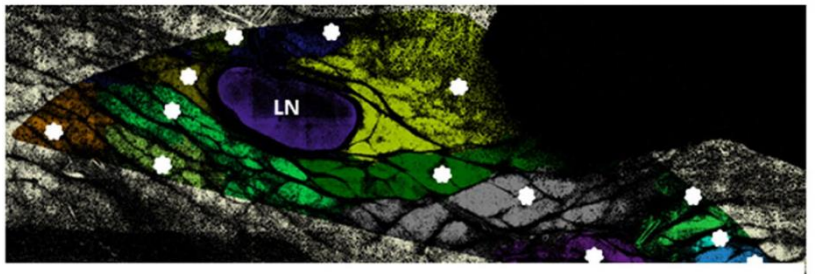
Changes in CD4, CD8 T-cells, T regs, B-cells and eosinophils in adipose tissue

Role of the innate immune system (e.g., NLRP3, TLRs) in adipose tissue inflammation

2020s

Spatial/omics mapping

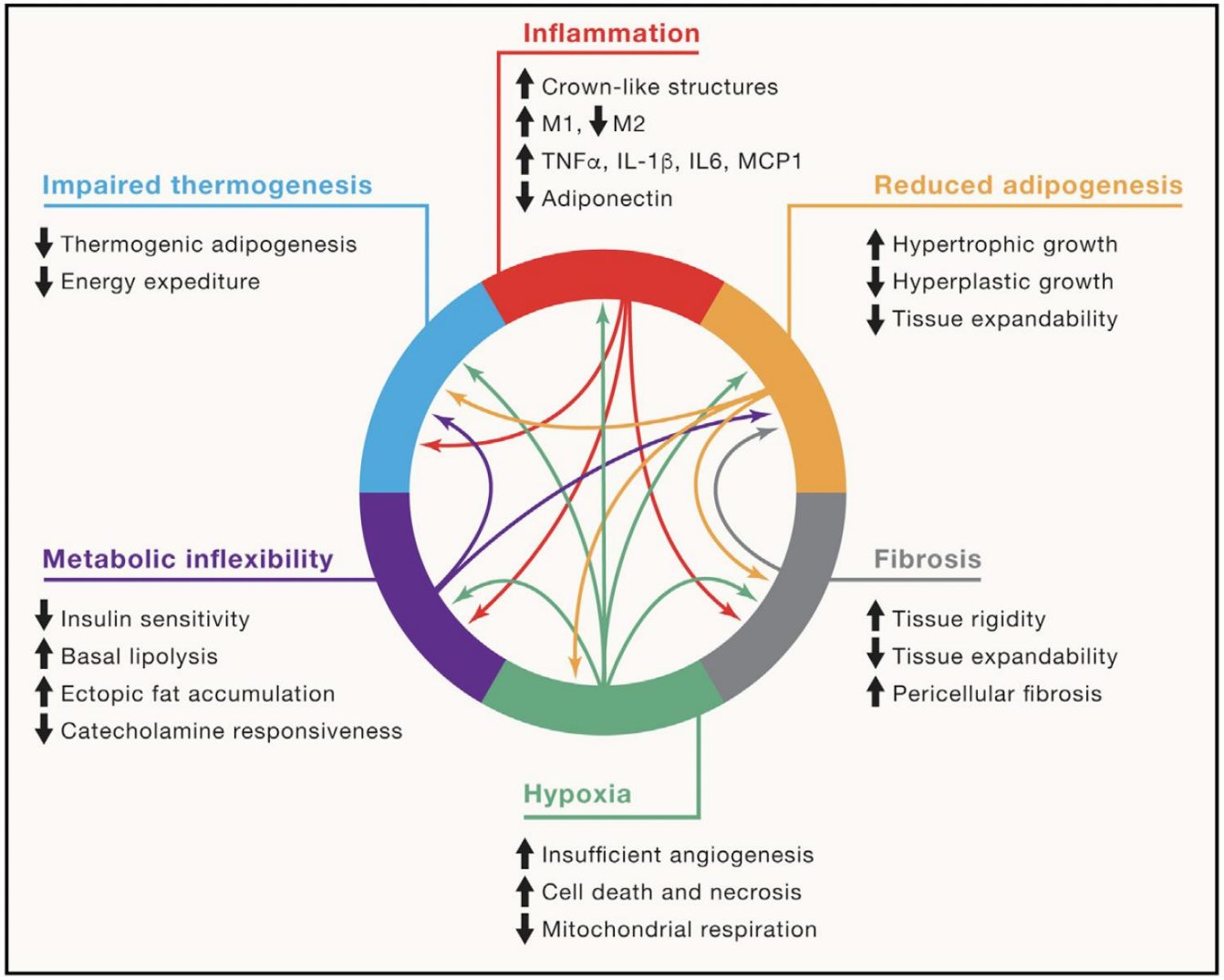
Emerging view of spatially distinct immune niches within adipose tissue



3D spatial imaging highlighting the existence of functionally and spatially distinct immune-metabolic niches within adipose tissue

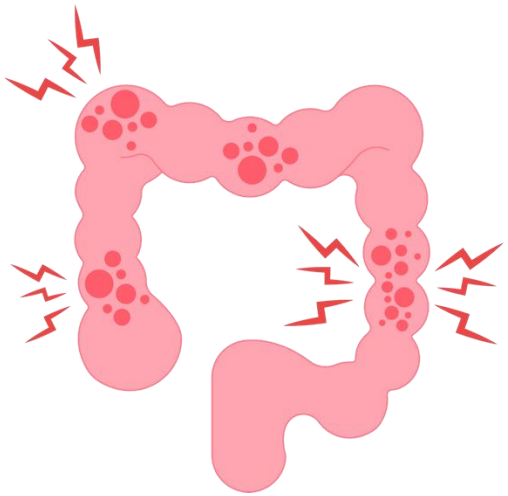
[1]Hotamisligil et al, Science, 1993; [2]Dichamp et al, Sci Rep, 2019

Adipose tissue dysfunction has many consequences

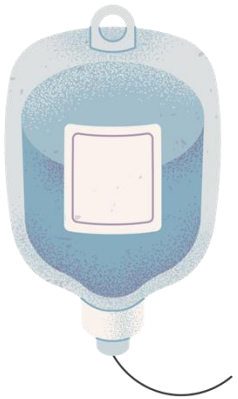


Sakers et al, Cell, 2022

VAT as a clinical modifier in IBD



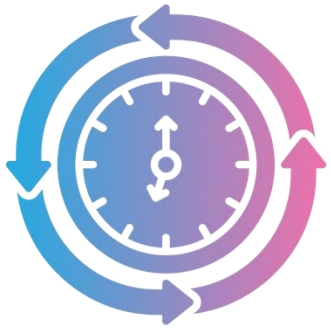
Associated with complex Crohn's phenotypes (fibrostenotic, penetrating)[1]



Reduced response to anti-TNF[2]

Increased risk of requiring surgery[3,4]

Increased risk of post-op complications[5,6]



Increased risk of endoscopic recurrence[7]

[1]Reviewed in Bauer-Rowe et al, Cell, 2025; [2]Shen et al, Dis of Colon and Rectum, 2018; [3]Gu et al, IBD, 2022; [4]Van Der Sloot et al, IBD, 2017; [5]Stidham et al, IBD, 2015; [6]Ding et al, Colorectal Dis, 2015; [7]Holt et al, APT, 2017

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The Constellation study: VAT and biologic response

Gastroenterology 2023;165:963–975

Higher Intra-Abdominal Visceral Adipose Tissue Mass Is Associated With Lower Rates of Clinical and Endoscopic Remission in Patients With Inflammatory Bowel Diseases Initiating Biologic Therapy: Results of the Constellation Study

Andres J. Yarur,[1,2] Alexandra Bruss,[2] Andrea Moosreiner,[2] Poonam Beniwal-Patel,[2] Lizbeth Nunez,[2] Brandon Berens,[2] Jean F. Colombel,[3] Stephan R. Targan,[1] Caroline Fox,[2] Gil Y. Melmed,[1] Maria T. Abreu,[4] and Parakkal Deepak[5]

[1]Division of Gastroenterology and Hepatology, Inflammatory Bowel Disease Institute, Cedars Sinai Medical Center, Los Angeles, California; [2]Division of Gastroenterology and Hepatology, Medical College of Wisconsin, Medical College of Wisconsin, Milwaukee, Wisconsin; [3]Mount Sinai School of Medicine, New York, New York; [4]Center for Inflammatory Bowel Diseases, Division of Gastroenterology and Hepatology, University of Miami, Miller School of Medicine, Miami, Florida; and [5]Division of Gastroenterology and Hepatology, Washington University in St Louis School of Medicine, St Louis, Missouri

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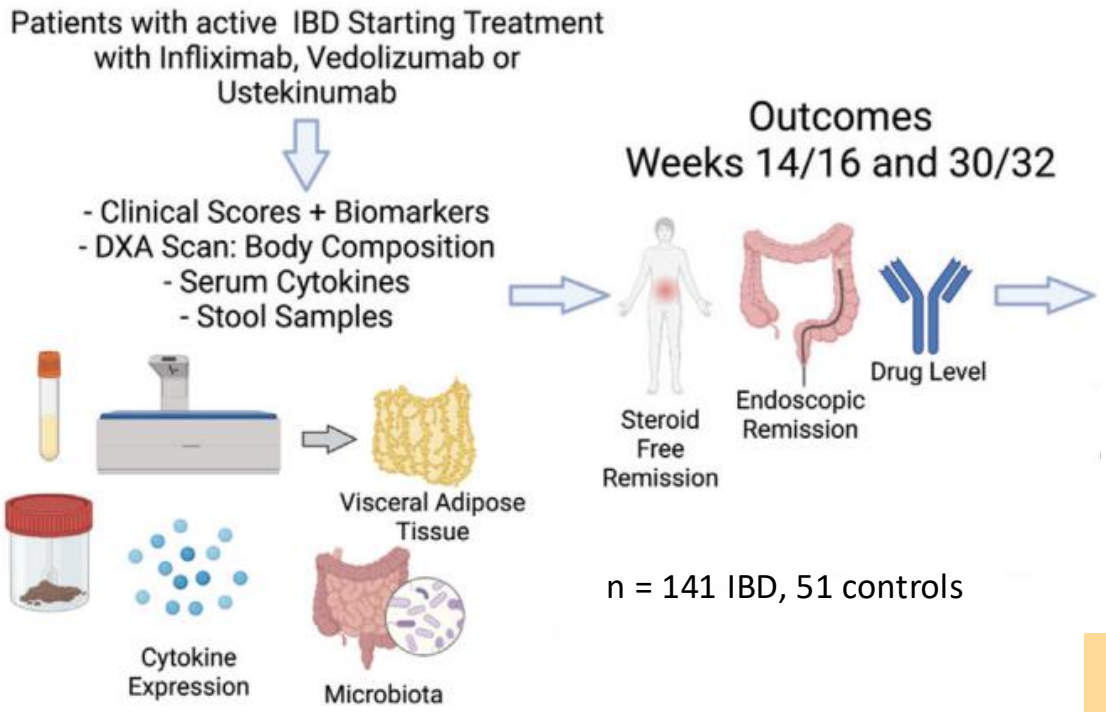
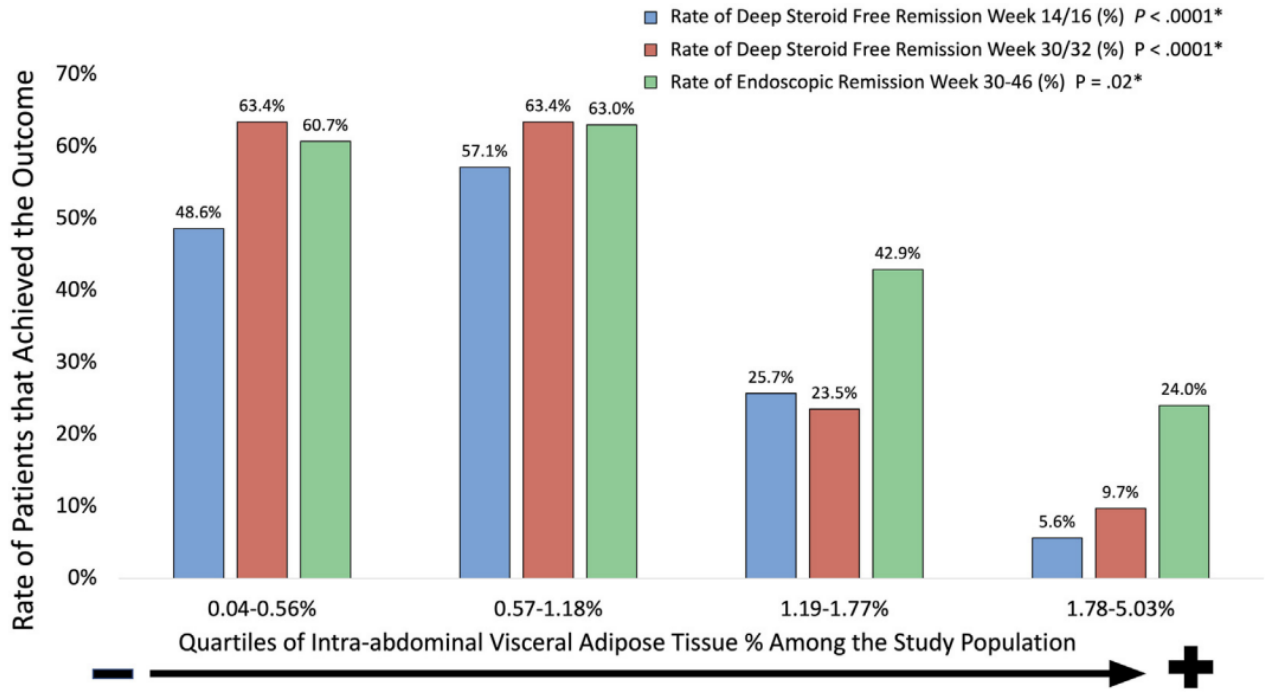
The Constellation study: VAT and biologic response



n = 141 IBD, 51 controls

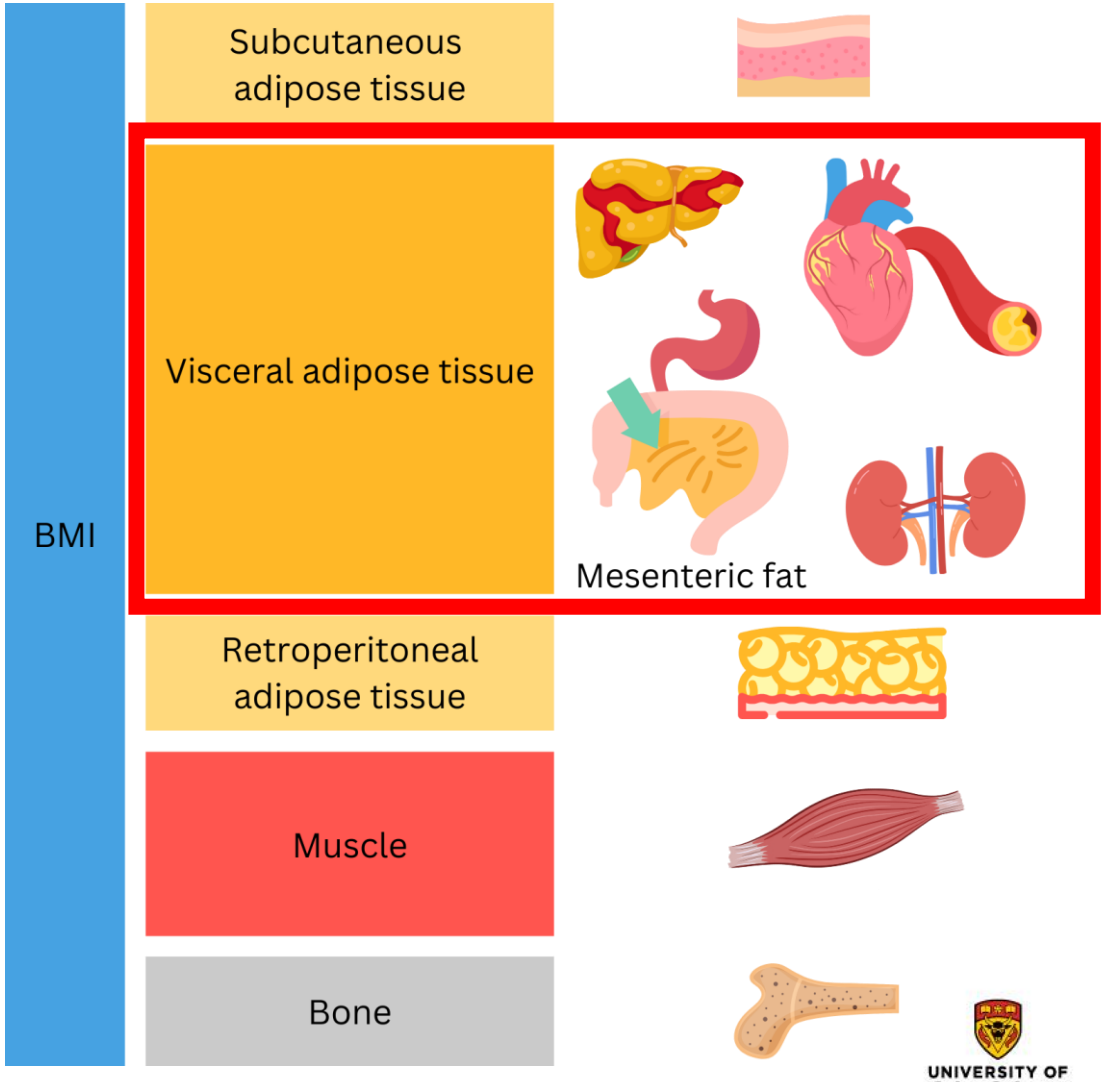


- High VAT → ↓ remission (34 % overall)
- Odds of achieving deep remission ↓ 60 % for each 1 % VAT mass increase
- Association held for CD and UC
- Consistent across all three biologics.

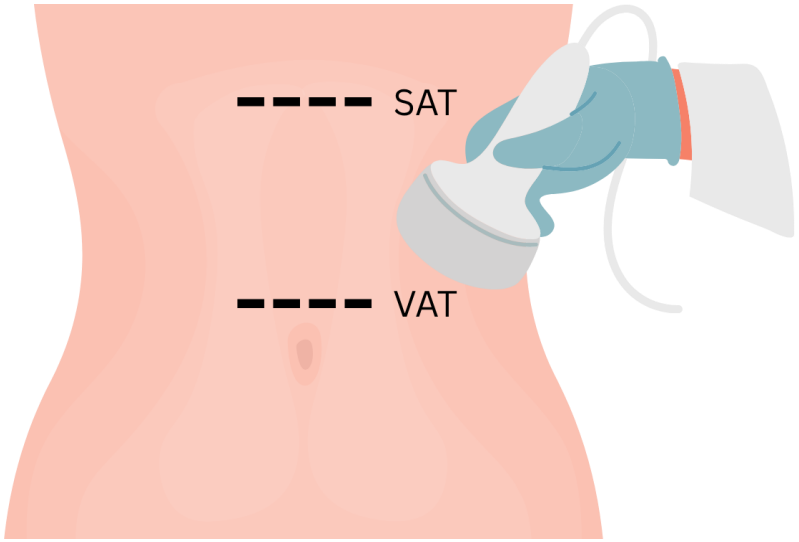
Yarur et al, Gastroenterology, 2023

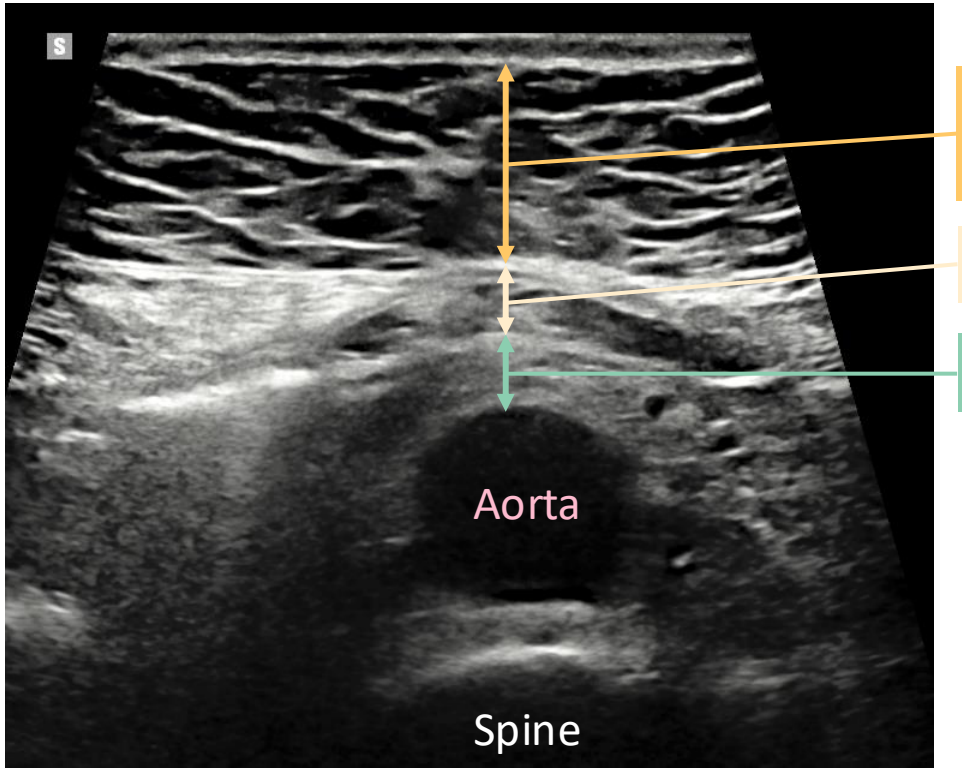
Challenges in quantifying and studying adiposity in IBD

- Measuring adiposity is challenging
  - BMI as an imperfect marker
  - DXA (Gold standard)
  - CT, MRI, US
- Definitions and adipose component vary
  - VAT has stronger associated with MetS and is the most associated with “metabolic inflammation”
- Ethnicity and gender not well captured in current literature
- Steroid exposure and inflammatory burden are not well captured



Ultrasound as a point-of-care test to assess VAT





Subcutaneous adipose tissue (SAT)

Pre-peritoneal fat pad (PPF)

Visceral adipose tissue (VAT)

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From VAT to creeping fat: The mesenteric continuum

- Shared origin, distinct behavior
  - Both arise from visceral mesenteric depots, but creeping fat represents a localized expansion around diseased bowel loops.
  - Adipocytes in creeping fat exhibit enhanced immune cell infiltration, ECM remodeling, and proximity-driven signaling with inflamed mucosa.

- From systemic to local immunometabolism
  - VAT acts as an endocrine organ, influencing systemic inflammation and metabolic tone.
  - Creeping fat acts as a paracrine organ, amplifying or containing intestinal inflammation through direct crosstalk.

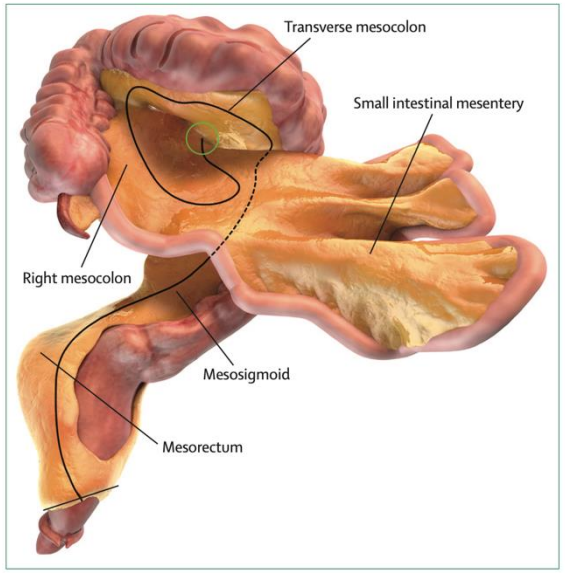
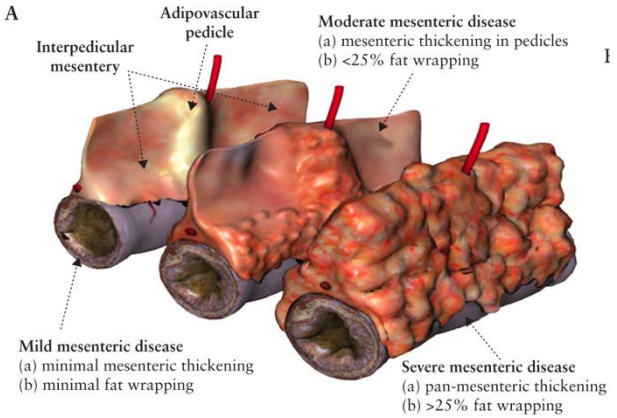


***Figure 1*: Digital representation of the small and large intestines and associated mesentery**



Coffey JC, O'Leary DP, Lancet Gastroenterol Hepatol. 2016; Coffey et al, JCC 2018; Culligan et al, Ann Surg 201; Tsounis et al, IBD, 2023

What is the link between creeping fat, microbiota and inflammation?

CellPress

Cell

Article

Translocation of Viable Gut Microbiota to Mesenteric Adipose Drives Formation of Creeping Fat in Humans

Connie W.Y. Ha,[1] Anthony Martin,[1] Gregory D. Sepich-Poore,[3] Baochen Shi,[4] Yizhou Wang,[5] Kenneth Gouin,[2,5] Gregory Humphrey,[6] Karenina Sanders,[6] Yasiru Ratnayake,[7] Kelvin S.L. Chan,[7] Gustaf Hendrick,[1] J.R. Caldera,[2] Christian Arias,[1] Jacob E. Moskowitz,[1] Shannan J. Ho Sui,[8] Shaohong Yang,[1] David Underhill,[1,2] Matthew J. Brady,[9] Simon Knott,[2,5] Kelly Kaihara,[10] Michael J. Steinbaugh,[8] Huiying Li,[4] Dermot P.B. McGovern,[1] Rob Knight,[6,11] Phillip Fleshner,[1,12] and Suzanne Devkota[1,2,13,*]

Ha et al, Cell, 2020

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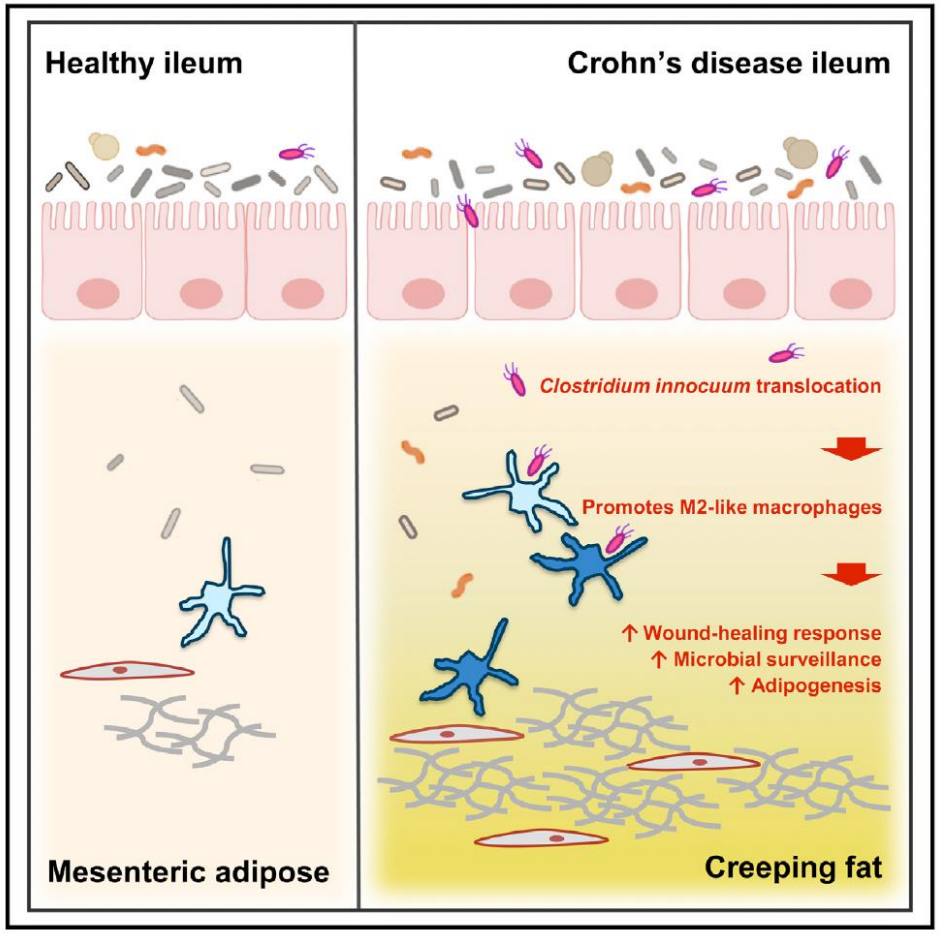
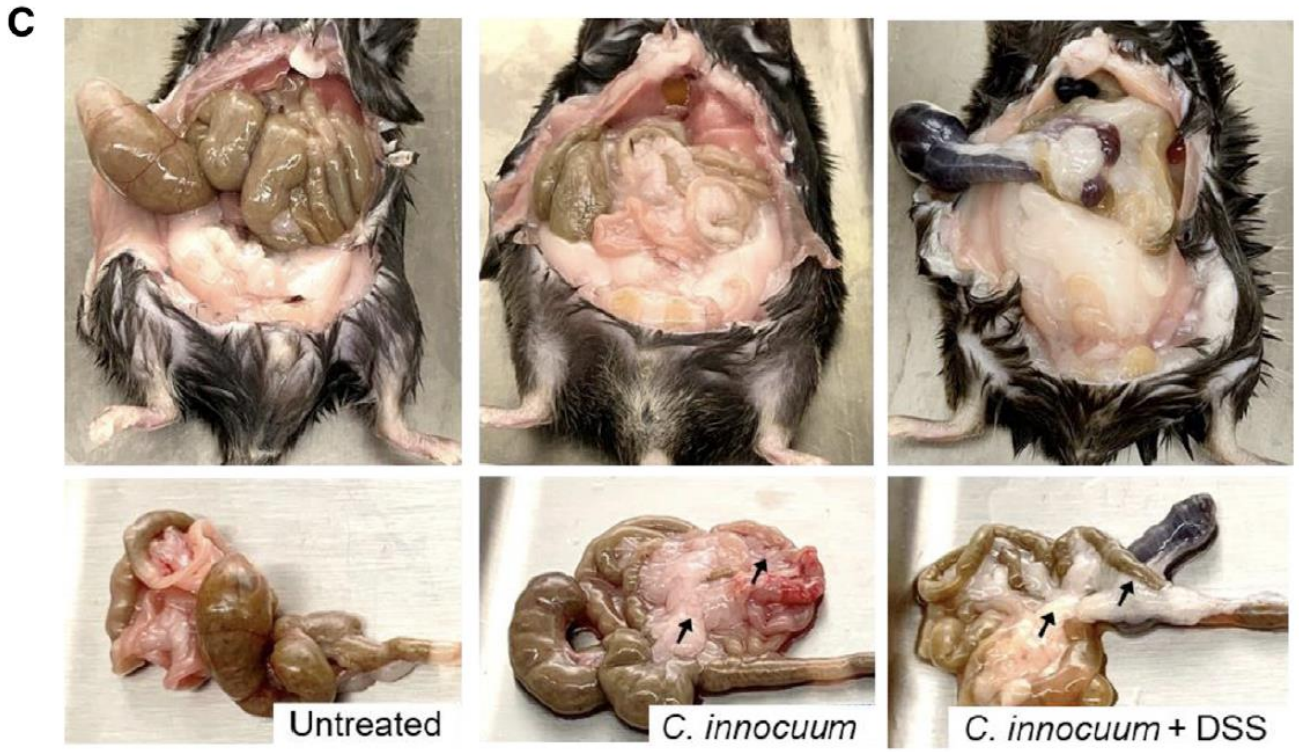
What is the link between creeping fat, microbiota and inflammation?

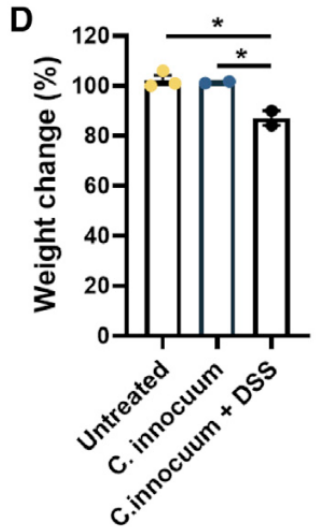


- Viable gut bacteria translocate into mesenteric fat (*C innocuum* dominant) and induces adipose tissue growth
- MF in CD becomes a hyperplastic, fibrotic, and adipogenic tissue
  - Single cell and bulk RNA-seq showed coordinated activation of adipocyte progenitors, fibroblasts, and innate and adaptive immune cells

Ha et al, Cell, 2020

What is the link between creeping fat, microbiota and inflammation?





- Mice gavaged with *C. innocuum* developed mesenteric adipose expansion, recapitulating human creeping fat.
- In DSS-treated mice, there was MF expansion despite decreased weight

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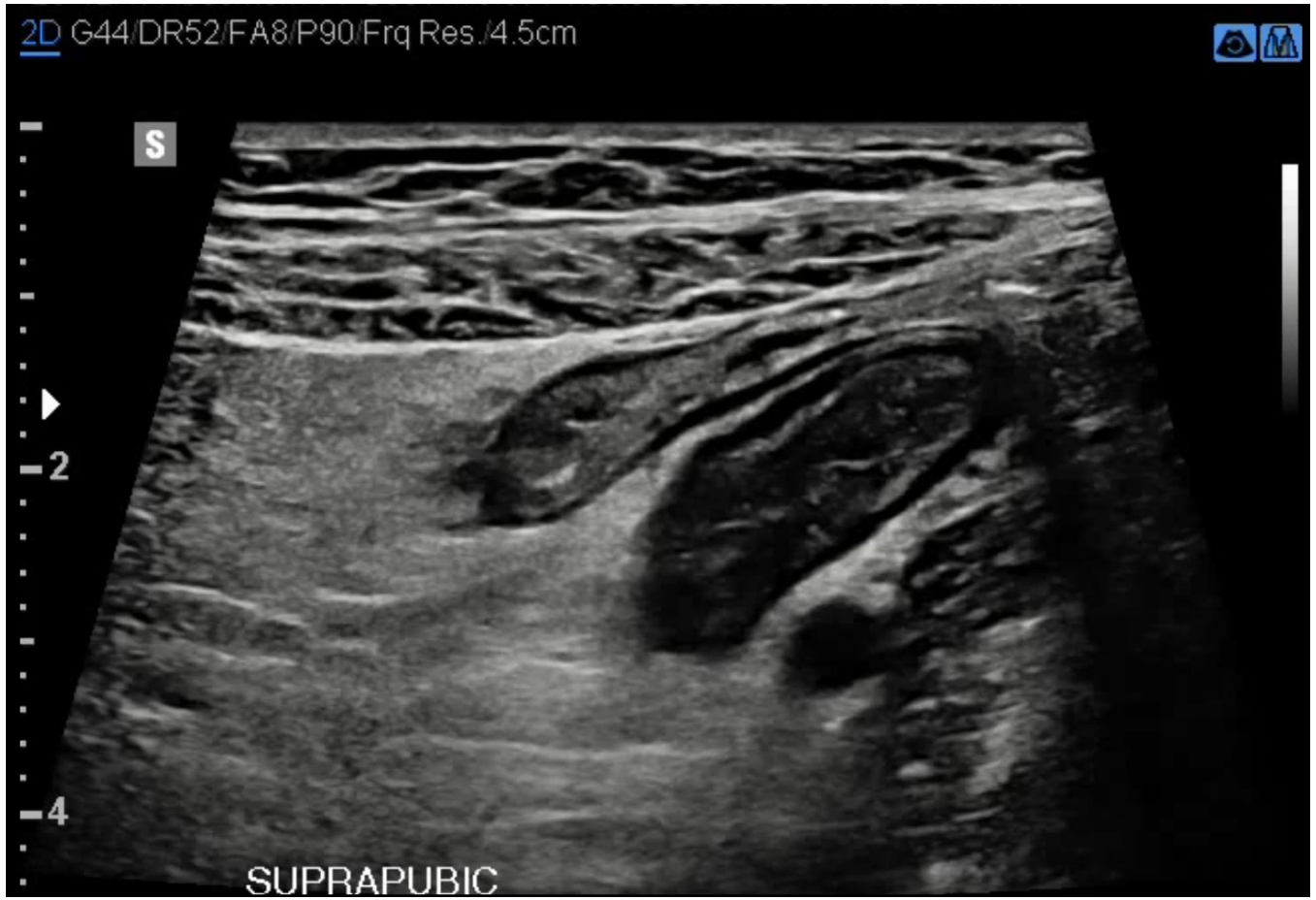
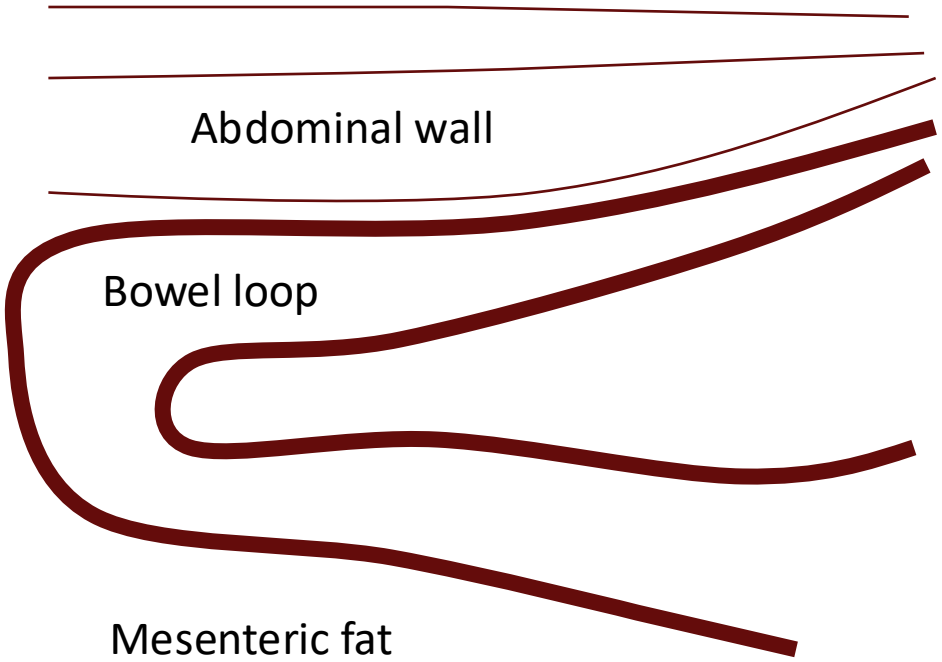
Mesenteric fat wrapping (Creeping fat)



Jejunum



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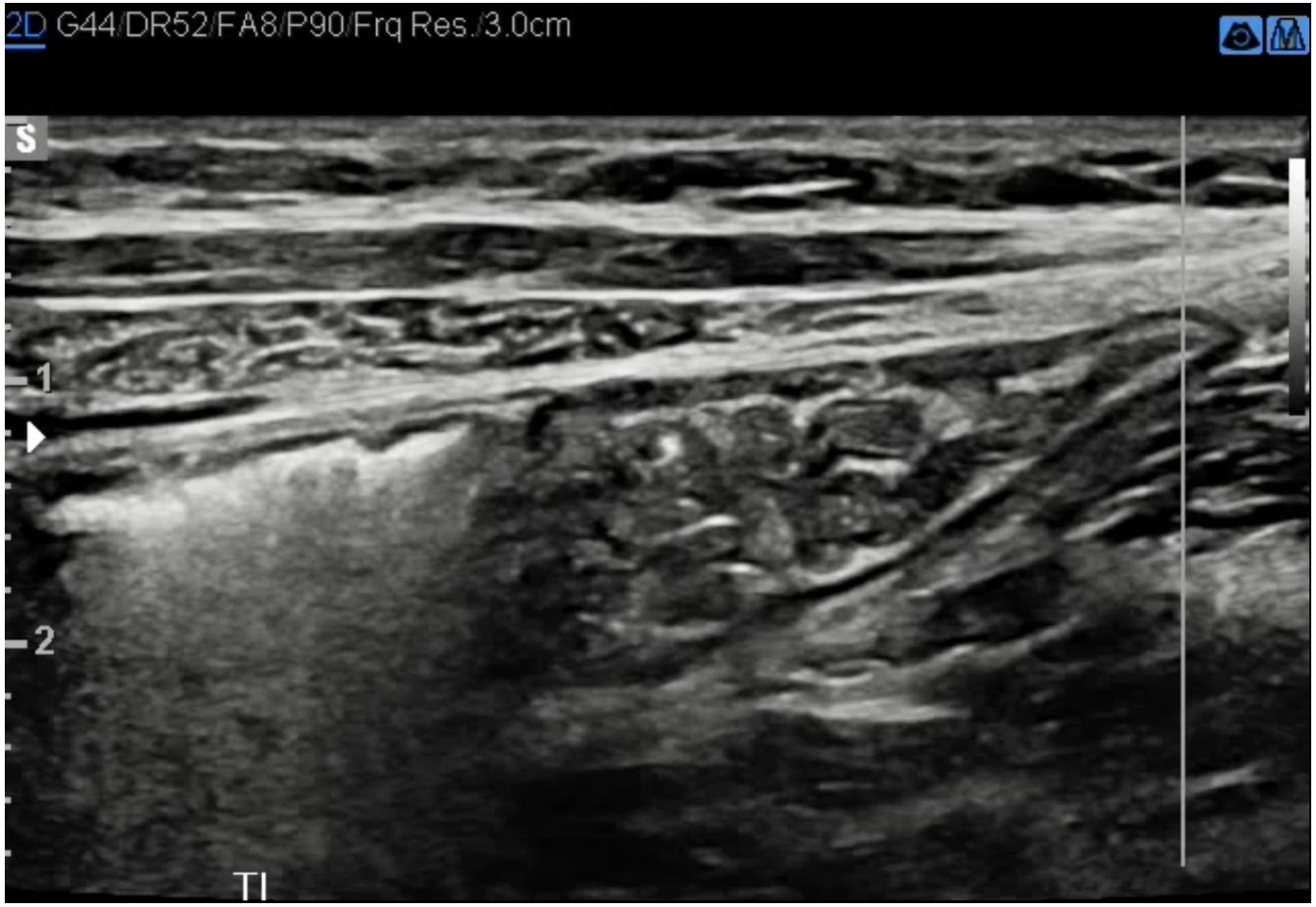
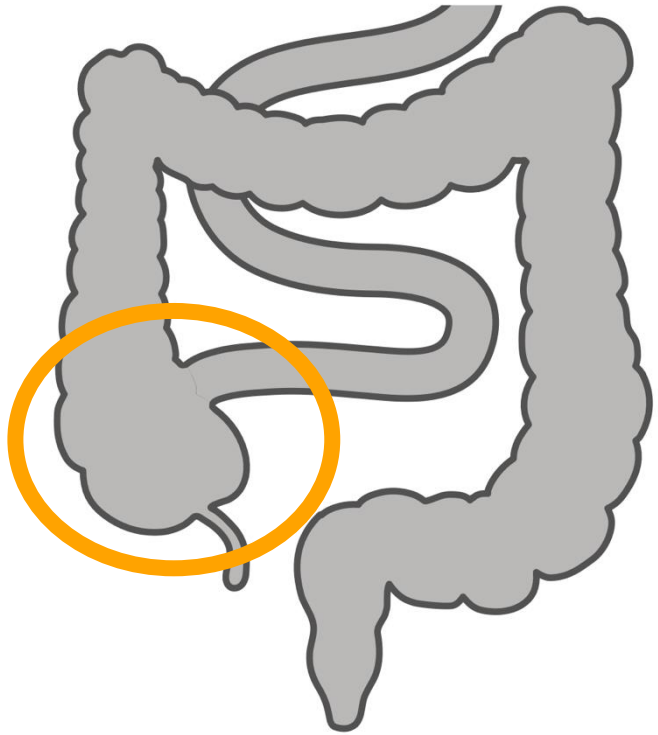
Normal terminal ileum

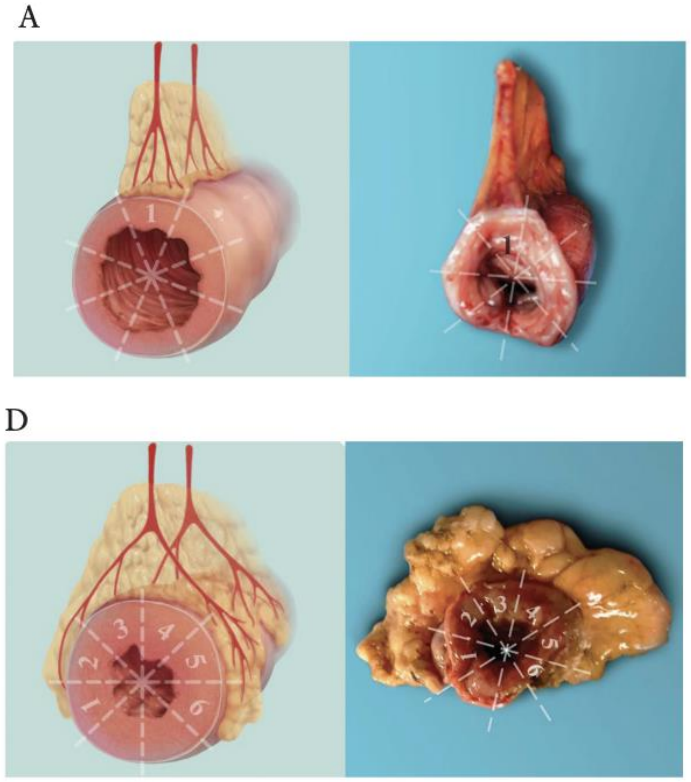




Terminal ileum

Assessing mesenteric fat wrapping by imaging

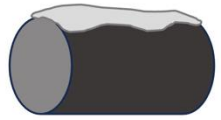
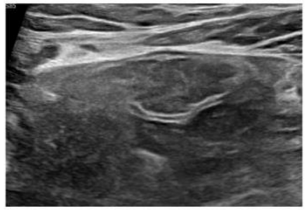
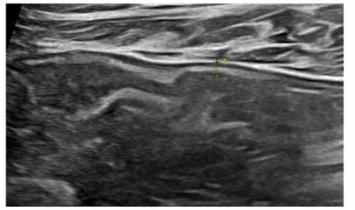
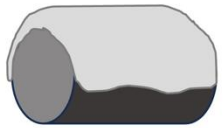
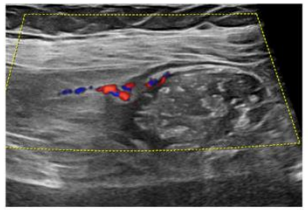
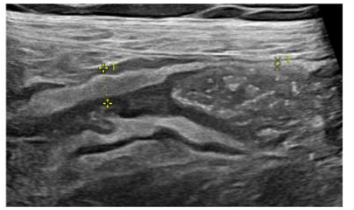
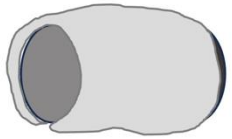
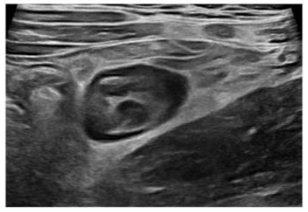
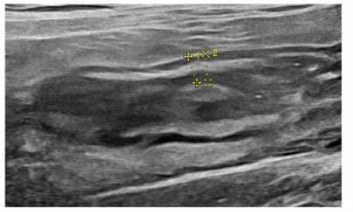
CT scan



Modified from Li et al, JCC, 2021

Intestinal Ultrasound

Figure 1. Proposed Chicago Mesenteric Fat Index

Mesenteric fat wrapping	Schematic	Cross-sectional	Longitudinal
None *Absence or minimal (<25%) fat wrapping*			
Incomplete *Incomplete circumferential, with skipped areas along the TI*			
Complete *Circumferential wrapping, continuous along the TI*			

St-Pierre et al, IBD J, *in press*; Kellar et al, IBD J, *in press*

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From pathophysiology to intervention: Rethinking adipose tissue as a therapeutic target

- VAT and creeping fat are not passive reservoirs -> they are active immuno-metabolic organs
- Chronic inflammation alters their phenotype, but these depots are *modifiable*

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Supporting healthy weight management in patients with IBD

- Nutritional Modifications[1,2]:
  - Focus on dietary adjustments that could benefit both IBD control and weight management (i.e. Mediterranean diet).
  - Encourage strategies for managing portion sizes and achieving caloric balance within the Mediterranean framework
  - Avoid ultra-processed foods
- Exercise and Physical Activity
  - Regular physical activity reduces fatigue and improves QoL[3]
- Behavioral and Psychological Support:
  - Address the psychological burden of living with both IBD and metabolic disease
  - Behavioral therapy and support groups improve adherence to lifestyle changes

[1]Hashash JG et al, Gastroenterology. 2024, [2]Gibson PR et al, Aliment Pharmacol Ther. 2024
[3]Van de Pol et al, DDS, 2025

CD-FAST: Time-Restricted Feeding in CD

- CD-FAST is the first RCT evidence that a lifestyle intervention can directly reduce VAT and improve adipose-driven inflammation in CD

- 12-week RCT in adults with CD and overweight/obesity
- TRF (16:8) vs usual eating
- N = 35 (TRF 20; Control 15)
- Outcomes: BMI, VAT by DEXA, adipokines, cytokines, symptoms, microbiota

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Haskey et al, Gastro, in press

CD-FAST: Linking VAT, adipokines, inflammation and microbiota

- Meaningful VAT Reduction with TRF
- Adipokine Profile Improved
  - Leptin ↓ ($p < 0.001$)
  - PAI-1 ↓, Adipsin ↓ ($p < 0.05$)
- Cytokine Responses Linked to Weight/VAT Change
  - In those losing >1 BMI unit, reductions in adiposity correlated with IL-1RA & IL-4 (anti-inflammatory) and IL-2/IL-12 family (immune recalibration)
- Microbiota Shifts Supporting VAT Change
  - Enrichment of SCFA-producing bacteria

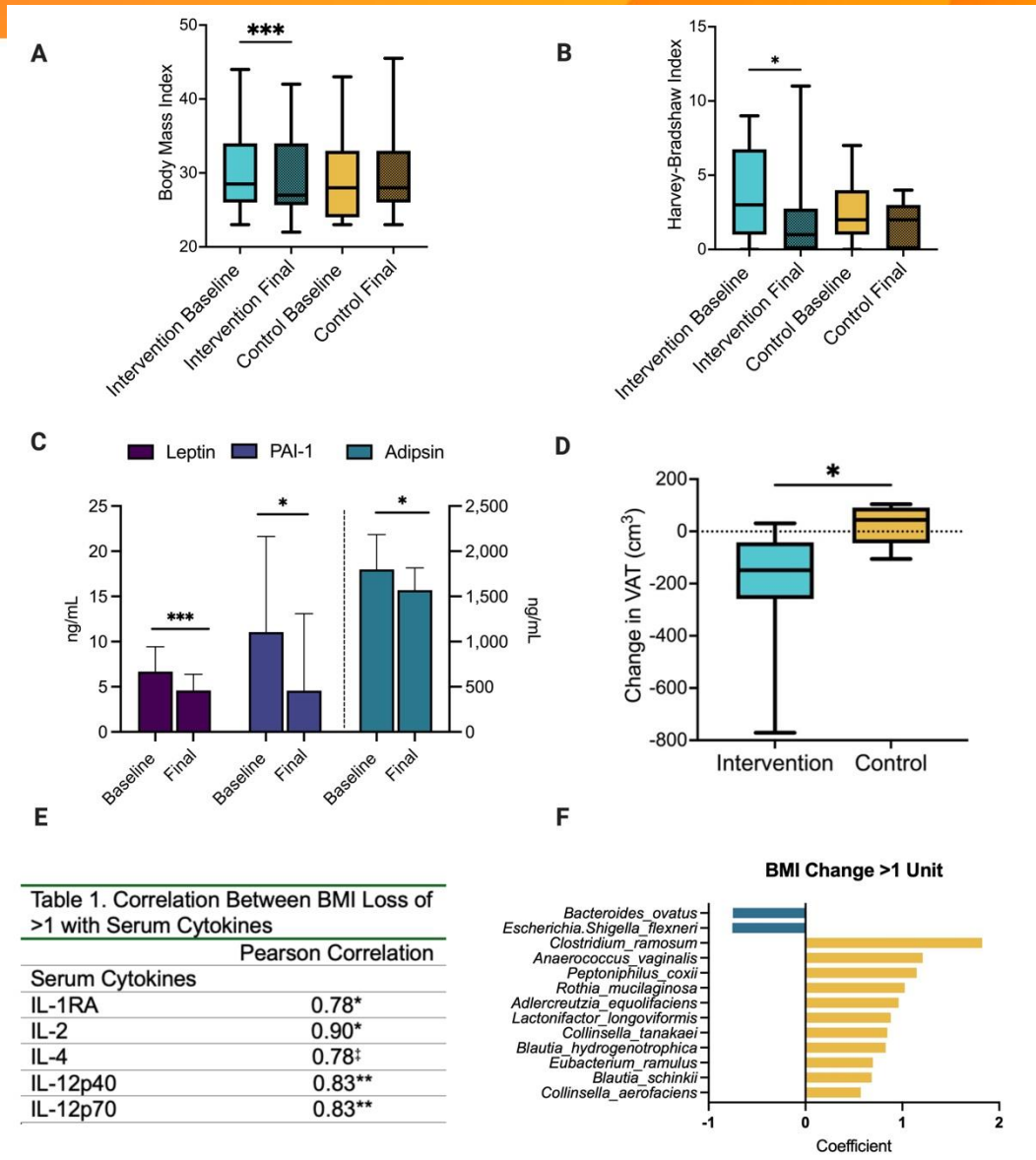

Table 1. Correlation Between BMI Loss of >1 with Serum Cytokines

Serum Cytokines	Pearson Correlation
IL-1RA	0.78*
IL-2	0.90*
IL-4	0.78‡
IL-12p40	0.83**
IL-12p70	0.83**

Haskey et al, Gastro, in press

GLP-1/GIP agents in IBD

14 studies up to date (as of September 2025)

- 13 retrospective cohorts (10 database, 3 chart review)
- 1 case-control study
- No RCTs

Populations:

- Countries: US (10), Denmark (2), Spain (1), Israel (1)
- N 16-61927 (≈75,000), UC & CD

Follow-up:

- Ranged 3 months to 7 years
- Median ≈12 months in most chart-based cohorts

Maracle et al, *submitted*

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GLP-1/GIP agents in IBD

Clinical Efficacy	• **Consistent weight loss** (-6 to -12% TBW across most studies). • **HbA1c reduction** and some improvements in lipids (esp. HDL, triglycerides). • **Benefits similar in IBD and non-IBD** patients.

IBD-related Outcomes	• No increase in flares, hospitalizations, or surgeries in pre-post studies.
	• Several large cohorts show **reduced risks**:
	  • ↓ Steroid dependence (HR ~0.66)
	  • ↓ IBD hospitalizations (HR ~0.74)
	  • ↓ Obstruction/ileus (HR ~0.57)
	  • ↓ Surgeries in CD and UC subgroups

Safety and Tolerability	• GI side effects (nausea, constipation, diarrhea) common, but **rates comparable to non-IBD.** • SAEs (pancreatitis, gallbladder disease, ileus) rare, **no excess risk** vs controls. • Discontinuation mainly due to GI intolerance or cost, not IBD flares.

GLP-1RAs appear safe and effective in IBD, with early evidence of protective benefit.

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Maracle et al, *submitted*

GLP-1/GIP agents & muscle: what actually changes?

- Quantitative effects on lean vs fat mass
  - ≈25% of total weight lost is lean mass with GLP-1/GIP agents (22 RCTs, n=2,258)
  - Ratio of lean-to-fat loss relatively consistent across studies
- Molecule-specific differences
  - Liraglutide: minimal or no significant change in lean mass on DXA
  - Semaglutide and tirzepatide: greatest fat reduction, modest but measurable lean decrease (0.8-1.5 kg)
  - Weight loss magnitude (not the molecule) predicted lean-mass change.

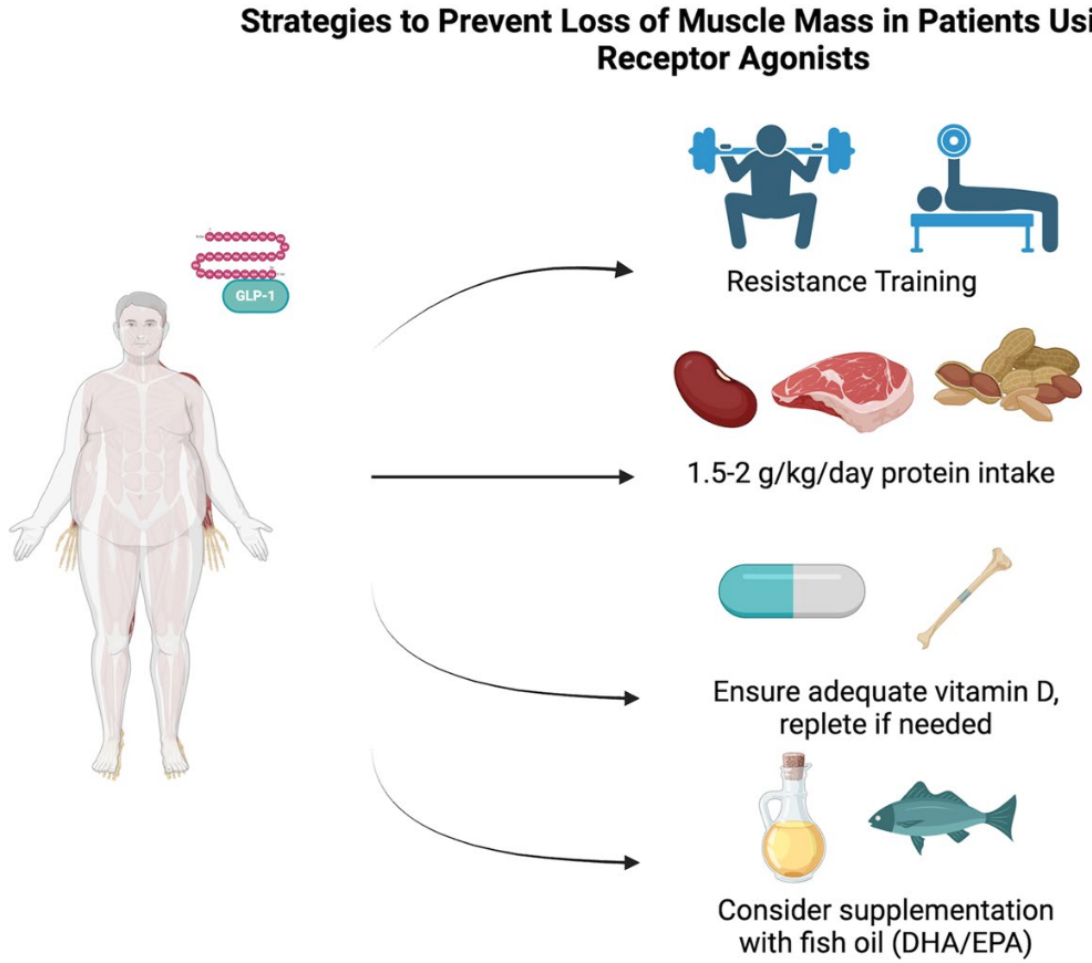
Preserving lean tissue is mainly about rate and context, not the drug itself

Karasakis et al, Metabolism, 2025; Neeland et al, Diabetes Obes Metab, 2025

GLP-1/GIP agents & muscle: Considerations in IBD

- Up to 50 % of IBD patients show altered body composition, with coexistence of sarcopenia and visceral adiposity
- Inflammation, dysbiosis, and malnutrition drive muscle catabolism
- What are the consequences of GLP-1/GIP agents in patients with IBD?

- **GLP-1/GIP use ≠ set-and-forget**



Memel et al, Curr Nutrition Reports, 2025

GLP-1/GIP trials in IBD

- COMMIT-UC (NCT06937086, Phase 3b) COMMIT-CD (NCT06937099, Phase 3b)
  - Design: Mirikizumab ± tirzepatide, 61 weeks
  - Population: Moderate-to-severe UC + BMI ≥ 27 or moderate-to-severe CD + BMI ≥ 27
  - Primary endpoint: Simultaneous clinical remission + ≥ 10 % weight loss at Week 52.

- Why it matters
  - First prospective attempt to co-target inflammatory and metabolic axes
  - Explores if GLP-1/GIP-mediated weight loss enhances anti-IL-23 efficacy
  - May inform how metabolic modulation influences disease activity, treatment response, and muscle preservation

Take home

- Body composition matters in IBD
  - IBD is no longer defined by undernutrition alone -> obesity, sarcopenia, and visceral adiposity now coexist and modulate outcomes.
  - VAT and muscle are immunologically active tissues, influencing both inflammation and therapeutic response.
- GLP-1/GIP therapies are reshaping the landscape
  - Early real-world data show safety, metabolic benefit, and possible anti-inflammatory effects in IBD.
  - Lean-mass loss is typically modest (~25% of total weight loss) but effect unknown in patients with IBD
- Integration with IBD care is key

Thank you!

UNIVERSITY OF CALGARY