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Surgical and Endoscopic Options in Patients with NAFLD/NASH

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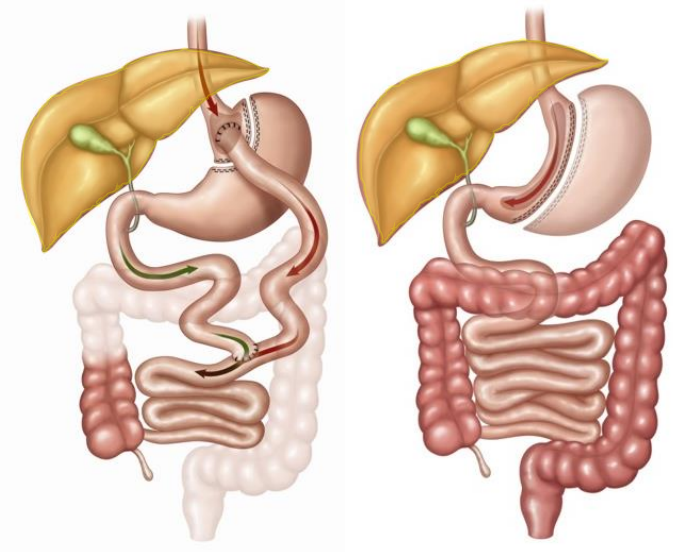
July 10, 2020



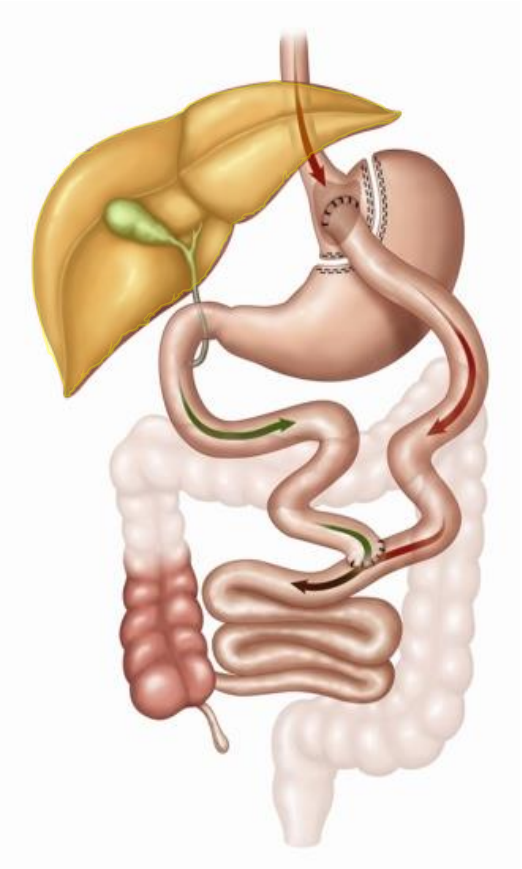
Disclosures

I am a paid consultant to the following companies and organizations:

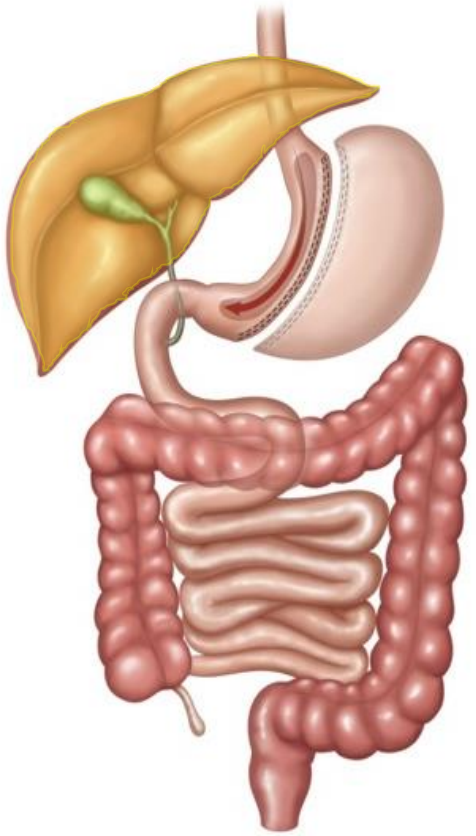
Amgen
Boehringer Ingelheim
Gelesis
GI Dynamics
Johnson & Johnson
Novo Nordisk
Pfizer
Rhythm Pharmaceuticals
U.S. Department of Defense
U.S. Department of State

Bariatric/Metabolic Surgery

Gastric Bypass

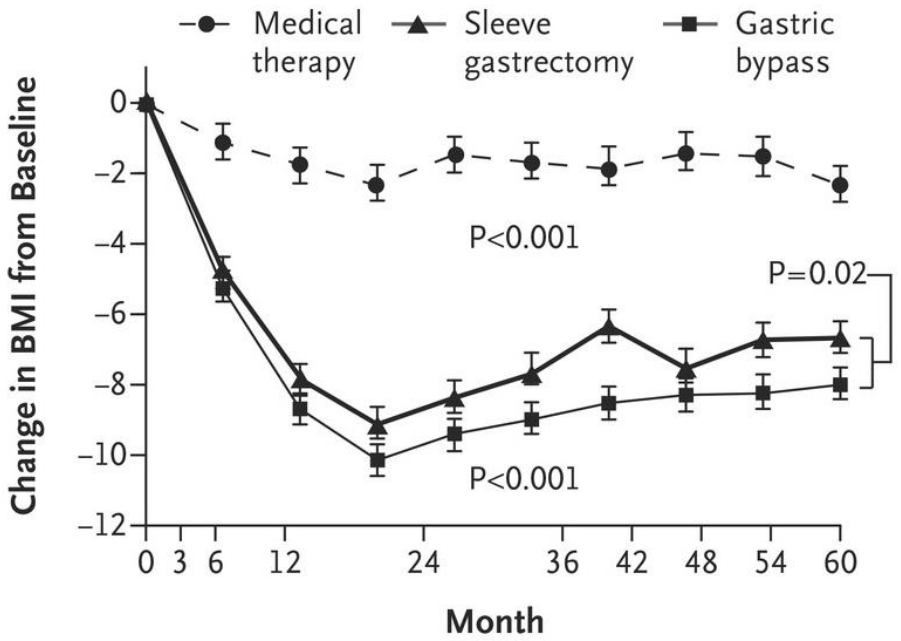


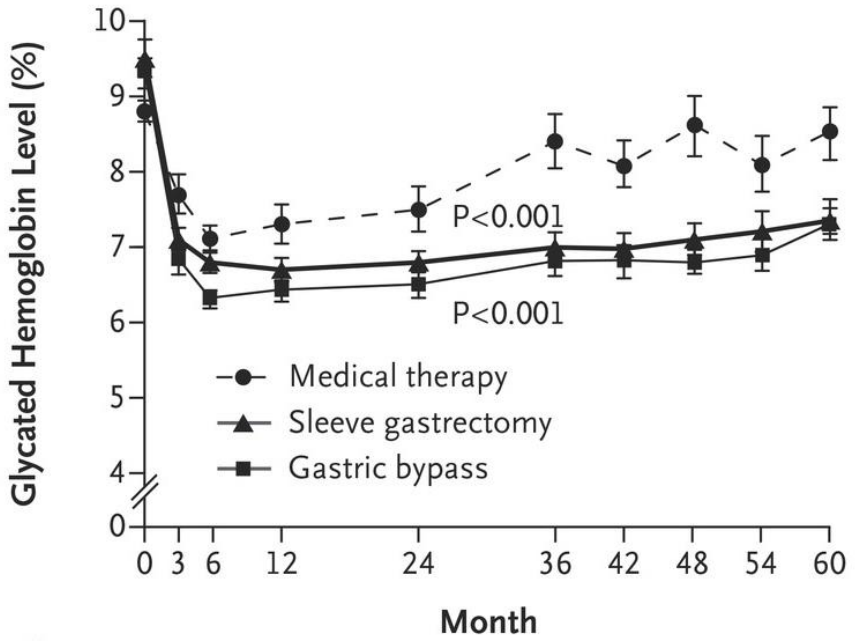
Sleeve Gastrectomy



Long-term Weight Loss after Bariatric Surgery

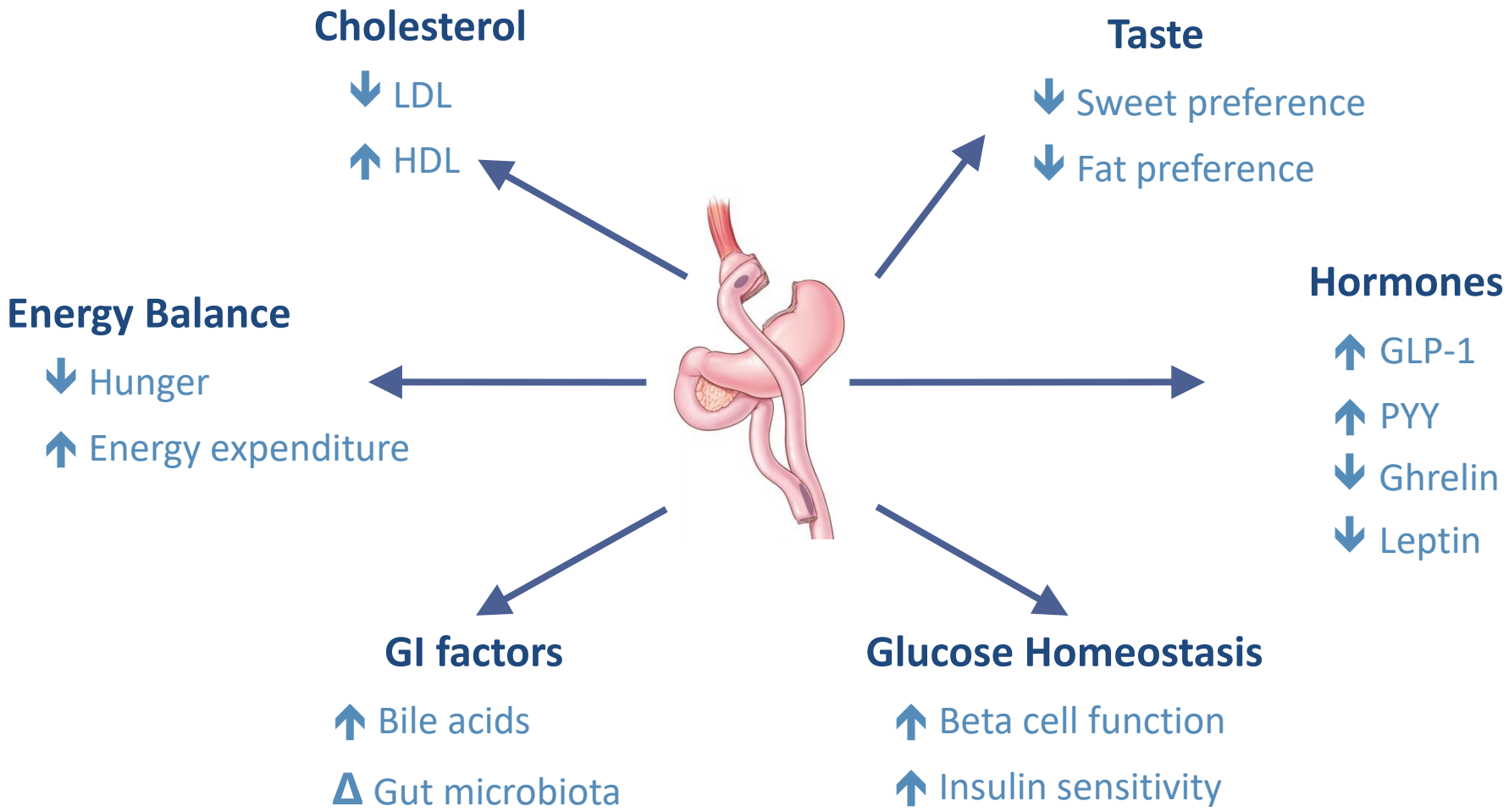
STAMPEDE Trial (RCT)



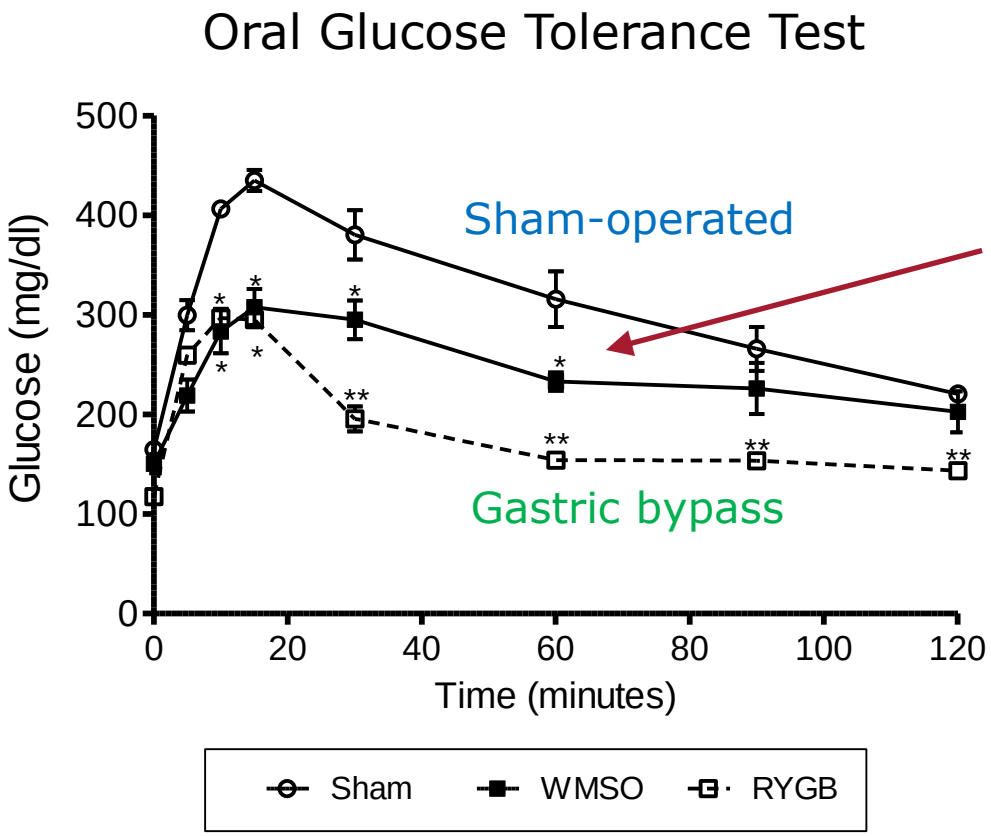


Schauer PR, *et al., NEJM* 2017

Surgery Induces System-wide Physiological Changes



Surgery Induces Weight-independent Metabolic Effects



Sham-operated, then underfed to match the weight of the bypassed animals

Carmody J, *et al., Am J Physiol* 2016

Bariatric Surgery Improves Several Aspects of NAFLD

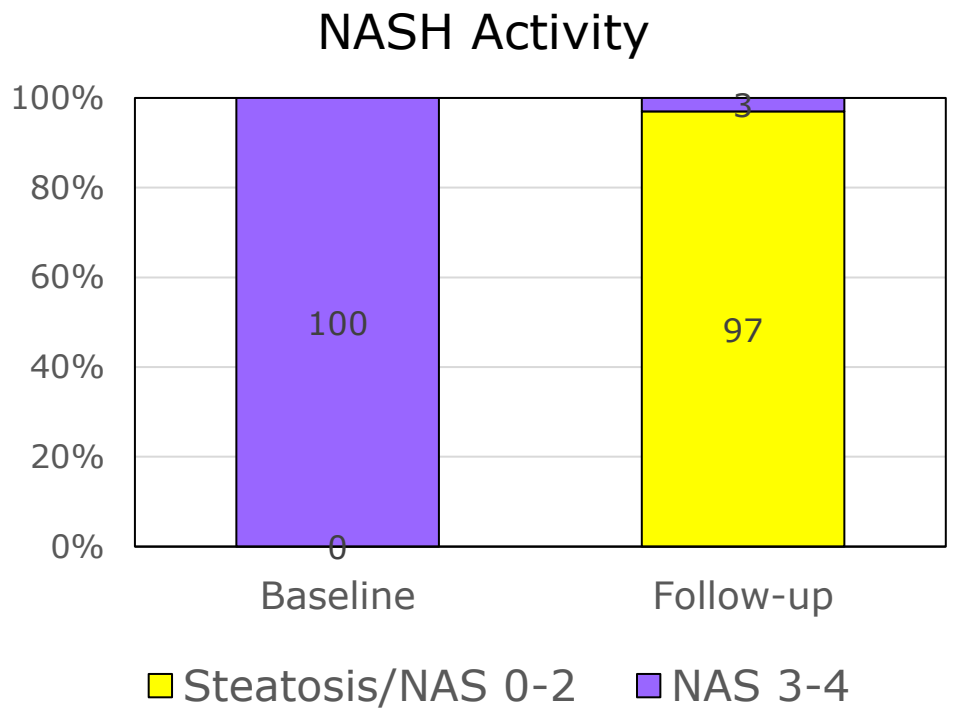
- Subjects: 65 adults with advanced NASH (F3-4 or NAS 3-4) and perioperative and follow-up liver biopsies

  (from 868 who had undergone bariatric surgery)
- Intervention: gastric bypass (53) or sleeve gastrectomy (12)
- Average time to follow-up biopsy - 6 years
- Average weight loss 23%
- Average change in NAS Score -3.12

Pais R et al., Hepatology 2019; 45(Suppl 1):45

Bariatric Surgery Improves High Activity NASH

(N=30)



Predictors of **Improvement** of High Activity NASH:

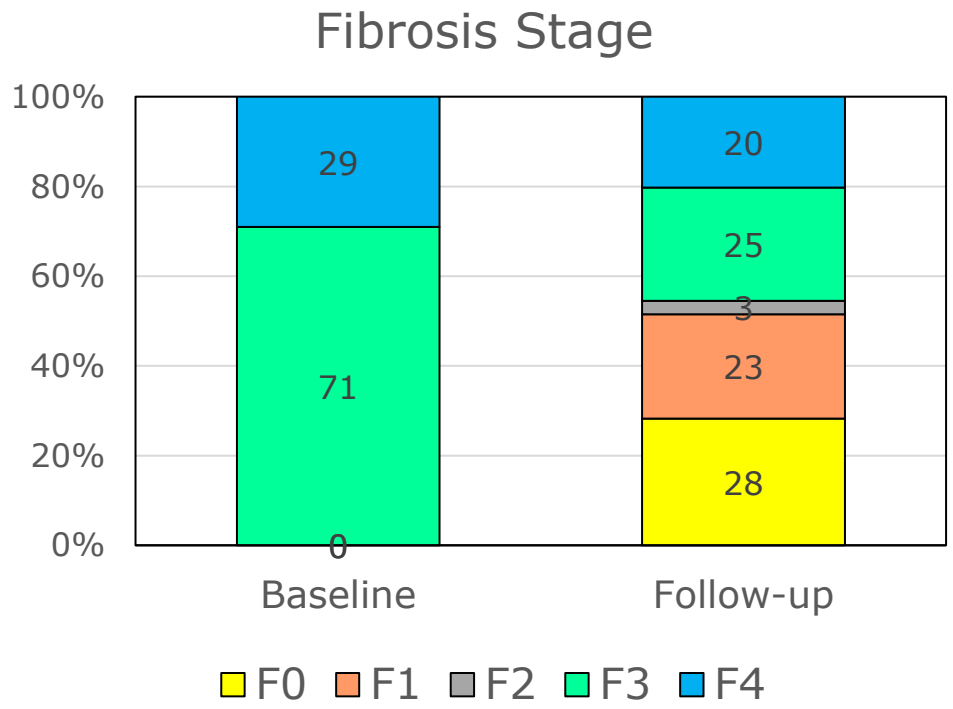
Shorter diabetes duration
Greater weight loss

Absence of severe fibrosis was a predictor of a normal follow-up biopsy (seen in 29%)

Pais R et al., Hepatology 2019; 45(Suppl 1):45

Bariatric Surgery Improves Severe Fibrosis

(N=35)



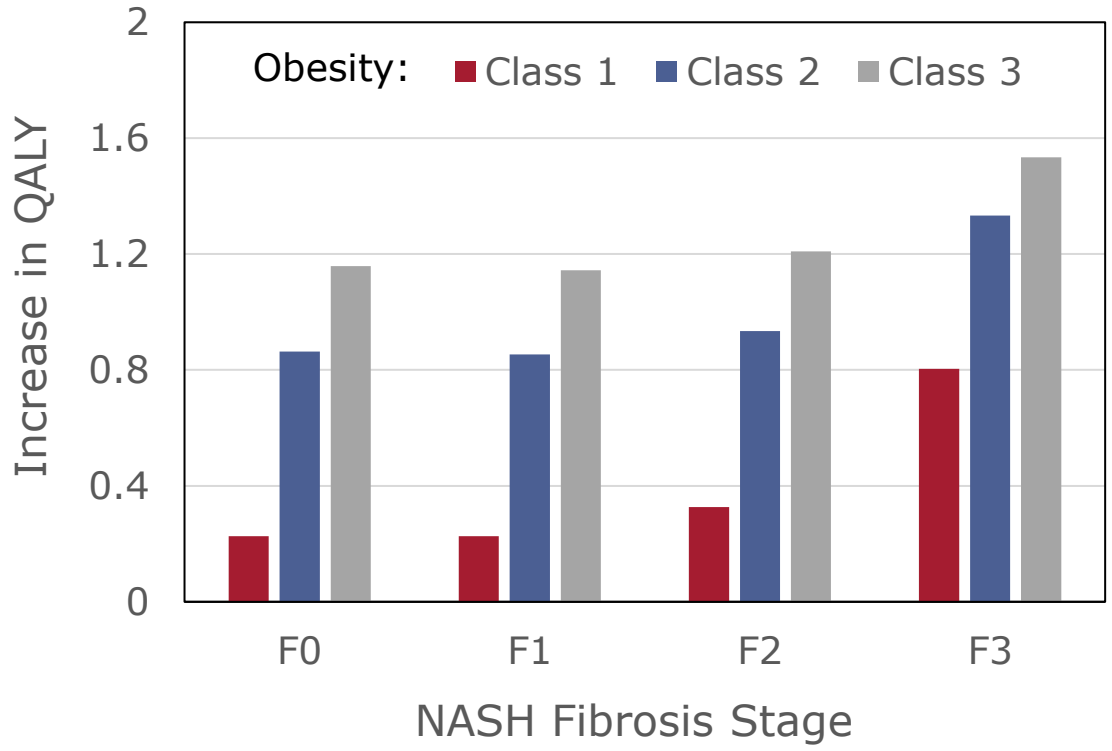
Predictors of **Improvement** in Severe Fibrosis:

Younger
Improved T2D
Longer time until follow-up biopsy
Underwent **gastric bypass**

Pais R et al., Hepatology 2019; 45(Suppl 1):45

Cost Effectiveness of Bariatric Surgery for NAFLD

Surgery vs. Intensive Lifestyle Therapy



Surgery: Cost/QALY

All fibrosis stages (F0-F3):

Class 1 obesity: $ 48,836
Class 2 obesity: $ 24,949
Class 3 obesity: $ 19,222

F3 only:

Class 1 obesity: $ 18,309
Class 2 obesity: $ 13,869
Class 3 obesity: $ 12,439

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Klebanoff MJ, *et al., Hepatology* 2017; 65:1156-1164

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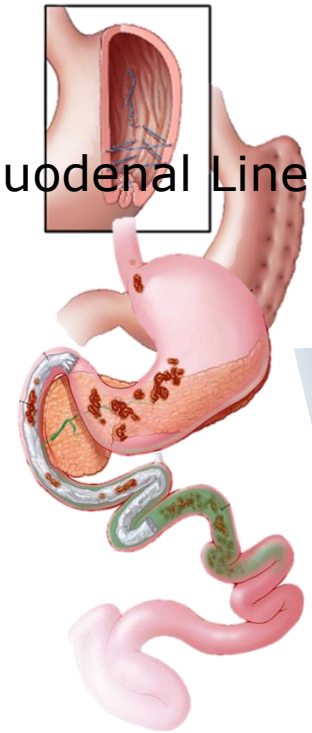
Endoscopic Metabolic Therapies

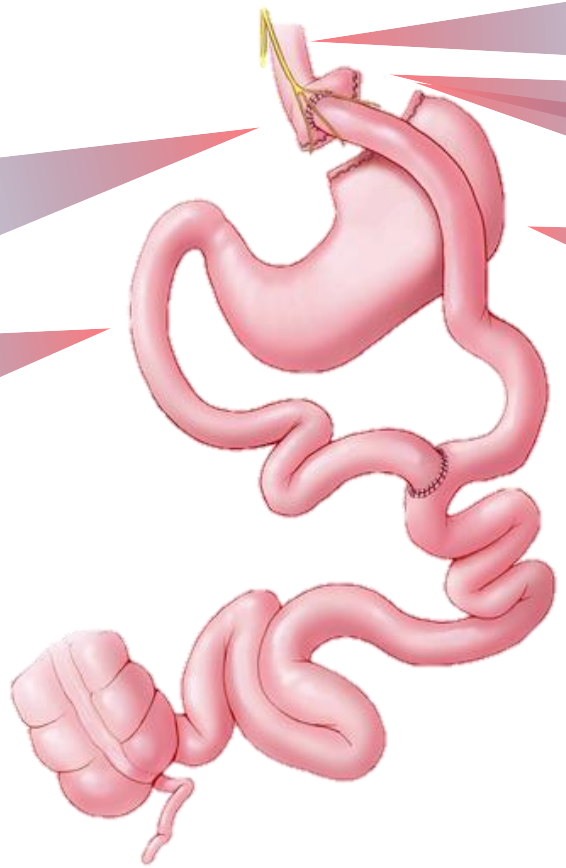
Harnessing the Power of Bariatric Surgery

Gastric Plication

Duodenal Liner



Roux-en-Y
Gastric Bypass



Adjustable

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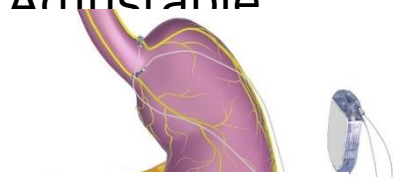
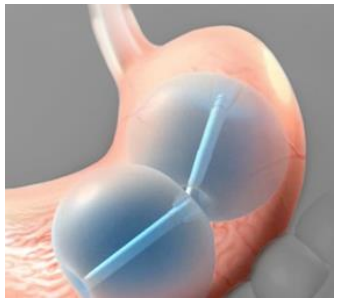


Gastric
Aspiration

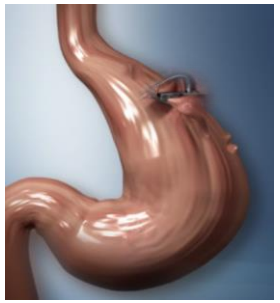
Metabolic Endoscopy

Metabolic Benefits Limited to Weight Loss

Gastric Balloon



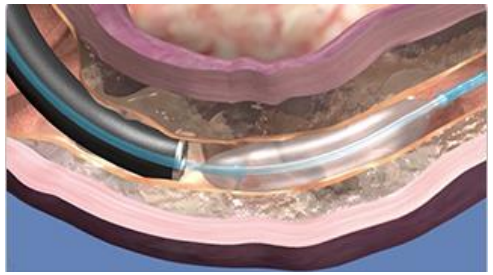
Gastric Plication



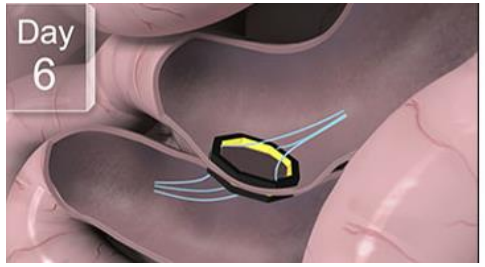
Gastric Aspiration

Weight-independent Metabolic Benefits

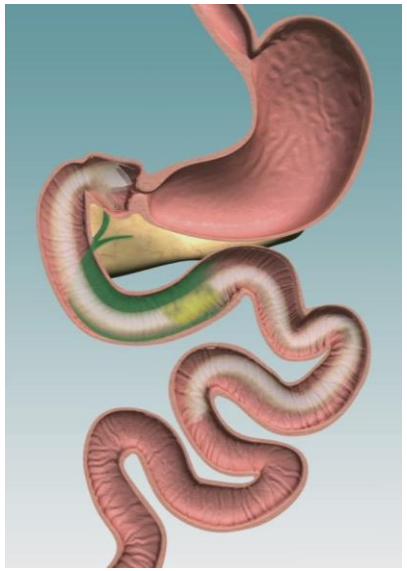
Duodenal Mucosal Resurfacing



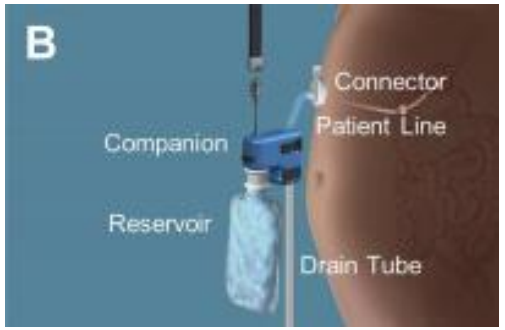
Self-assembling Magnets

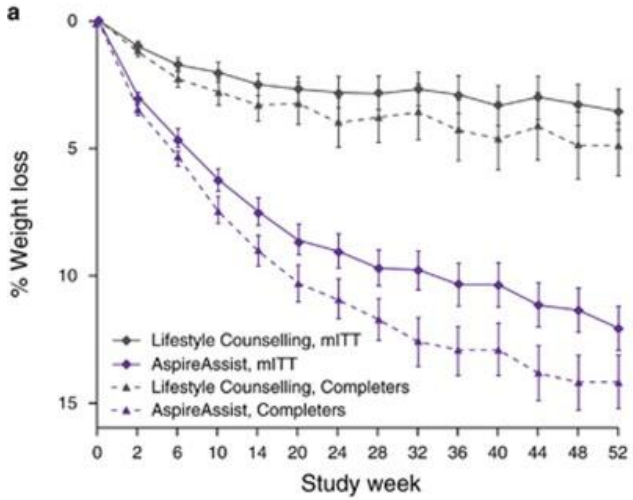


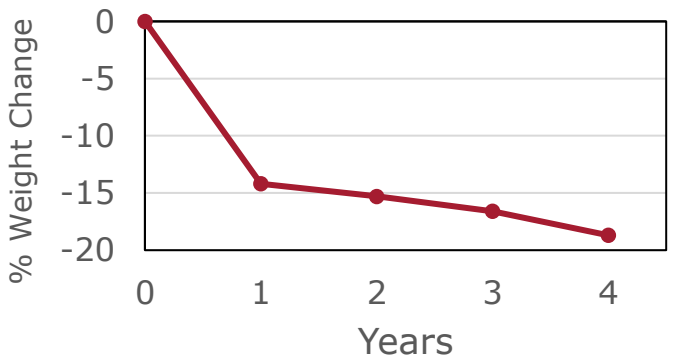
Endoluminal Duodenal Liner

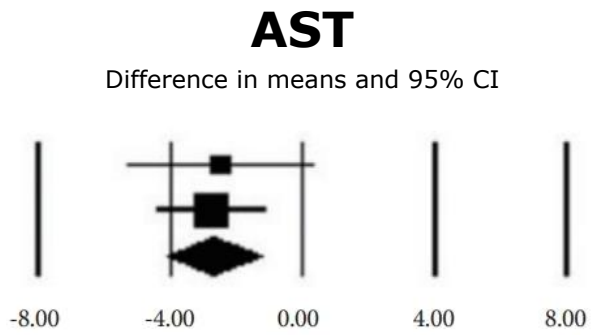


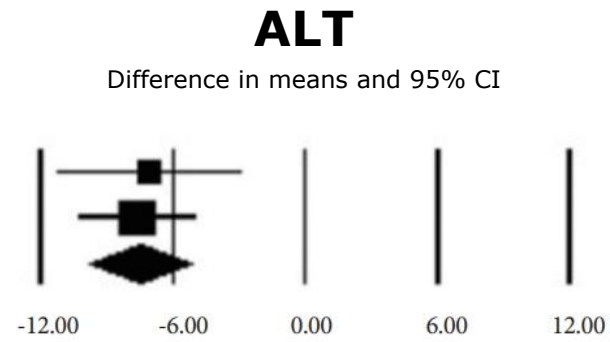
Aspiration Therapy (Aspire Assist®)





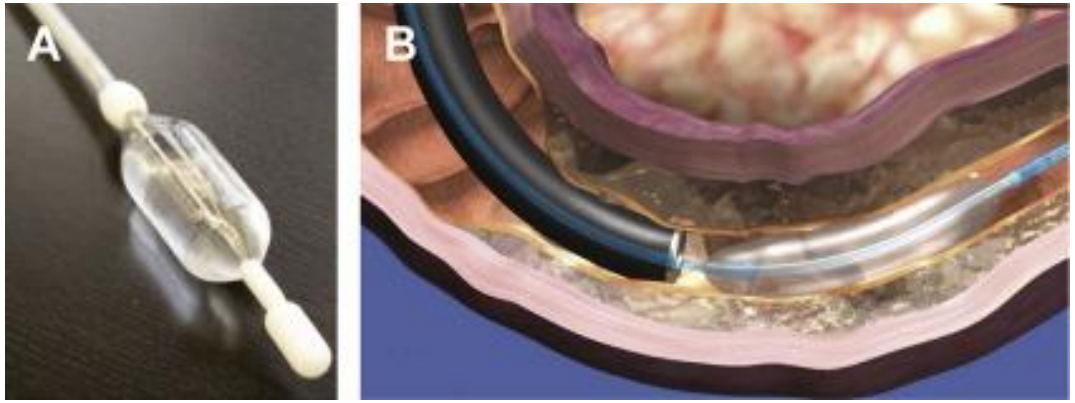


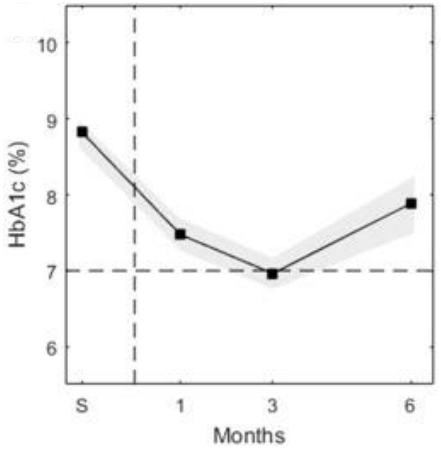


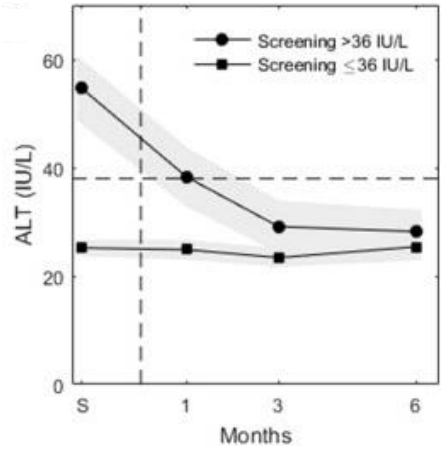


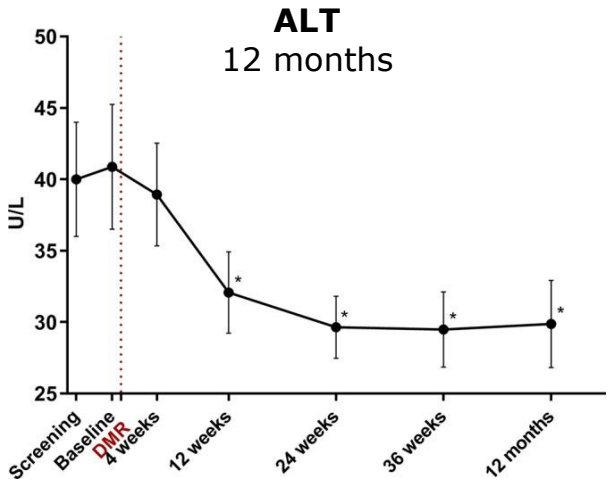
Thompson CC, *et al. Surg Obes Relat Dis* 2019; 15:1348-1354
Jirapino P, *et al., Clin Endosc* 2020; doi.org/10.5946/ce.2019.181

Duodenal Mucosal Resurfacing (DMR)







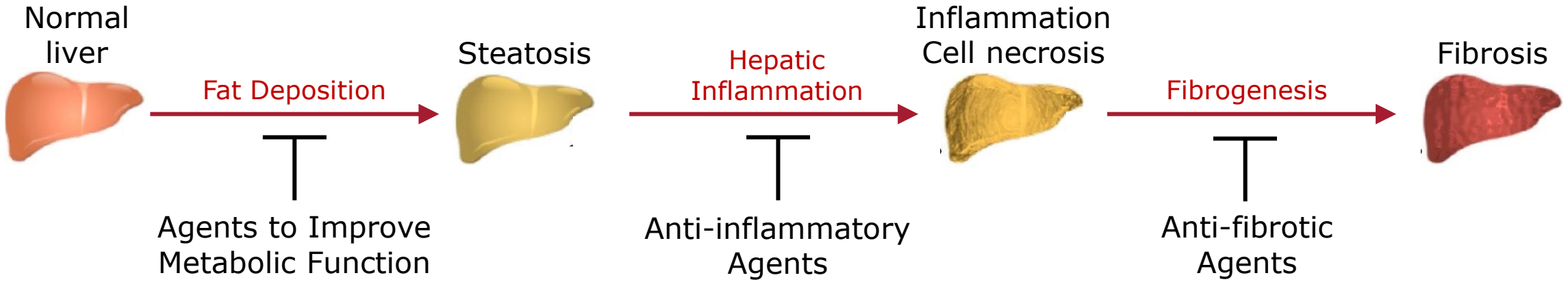


- Mean FIB-4 score decreased from 1.18 to 0.99
- In patients with baseline FIB-4 >1.30, 56% fell below 1.30
- No liver biopsies or imaging or elastography-based assessments were done

Van Baar ACG, et al., JHEP Rep 2020; doi.org/10.1016/j.jhepr.2019.10.006

Challenges in Treating NAFLD

Interventions dependent upon stage of liver disease



- ☑ Availability of agents
- ☒ Number needed to treat
- ☑ Efficacy
- ? Impact on important clinical outcomes

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Toward a Treatment Algorithm for NAFLD

	Anti-Obesity Therapy	Metabolic Therapy	Anti-inflammatory Therapy	Anti-fibrotic Therapy
Steatosis 	**Lifestyle-based** **Anti-obesity meds** Bariatric surgery?	Diet-based **CV risk reduction** **GLP-1 RA** Bariatric surgery?		
NASH 	**Lifestyle-based** **Anti-obesity meds** **Bariatric surgery**	Diet-based **CV risk reduction** **GLP-1 RA** **Bariatric surgery**	Bile acids? GLP-1 RA? Bariatric surgery?	Bile acids? Bariatric surgery?
Advanced Fibrosis 	Lifestyle-based **Anti-obesity meds** Bariatric surgery	Diet-based **CV risk reduction** **GLP-1 RA** Bariatric surgery?	Bile acids? **Bariatric surgery**	Bariatric surgery?

Effect of bariatric surgery on NAFLD and NASH

- Immediate improvement in steatosis
- Effects on inflammation, cellular necrosis, and fibrosis less clear
  - Weight loss and other metabolic improvements after surgery provide hope of a benefit
  - No large or well-controlled studies; first well-controlled studies only recently started
- Effect of surgery to prevent progression to cirrhosis or hepatocellular carcinoma is currently unclear
- Mechanisms of benefit – weight loss alone vs. weight loss-independent metabolic effects – are not yet known

Laursen *et al. J Hepatol* 2019

Conclusions 1

- Metabolic surgery (bariatric surgery that also induces weight loss-independent metabolic benefits) appears to improve NAFLD by **multiple mechanisms**
  - Dramatically **decreasing hepatocyte fat** deposition
  - **Decreasing the inflammatory and cytotoxic response** associated with progressive NAFLD, with a likely decrease in hepatic fibrogenesis
  - Potentially **decreasing** (i.e., reversing) some **pre-existing** hepatic **fibrosis**
- The primary mechanism of its effects on NAFLD appears to be the profound associated **weight loss** (average long-term weight loss approx. 25-35%)
- Other potential mechanisms include weight loss-independent improvement in insulin sensitivity, changes in lipid handling and disposition, and decreased obesity-associated inflammatory and autoimmune responses

Conclusions 2

- The effect of bariatric/metabolic surgery on important cardiovascular outcomes (e.g., major adverse cardiovascular events; MACE) has not been determined
  - Well-designed studies have demonstrated improved CV risk, but not (yet) hard outcomes
- Better understanding of the physiological mechanisms of action of the major forms of bariatric surgery has led to the development of endoscopic interventions to treat obesity and diabetes
  - Some of these approaches appear to induce substantial, long-term weight loss (e.g., aspiration therapy, duodenal-jejunal bypass liner)
  - Others appear to selectively target metabolic regulatory physiology (e.g., DMR)
  - Evidence of their efficacy for the treatment of NAFLD is very limited
- These surgical and endoscopic approaches likely complement one or more of the emerging classes of anti-obesity / anti-diabetes medications

Unanswered Questions 1

- What components/stages of the NAFLD spectrum are most effectively – and cost-effectively – treated by bariatric/metabolic surgery
- To what degree does bariatric surgery improve macrovascular outcomes (i.e., MACE)
- To what degree does bariatric surgery reduce major adverse liver outcomes, including cirrhosis and hepatocellular carcinoma
- To what degree are each of the beneficial effects of bariatric surgery on NAFLD mediated by the associated weight loss alone
- What degree of weight loss is required to achieve a significant and sustained improvement in steatosis, NASH activity, fibrosis and hepatocellular carcinoma
- Where in the spectrum of NAFLD is/are the optimal point(s) of intervention
- Can we find useful predictors of who will respond to bariatric surgery and other therapies
- What are the benefit-cost-risk relationships in using bariatric surgery to treat patients with NAFLD

Unanswered Questions 2

- To what degree do currently available endoscopic therapies reproduce the long-term beneficial effects of bariatric surgery
- In treating NAFLD, are the benefit-risk-cost profile of any endoscopic therapies sufficient to compete effectively with either bariatric surgery or the emerging pharmacological treatments targeted to obesity, diabetes, immune/inflammation injury, and hepatic fibrosis
- Is there sufficient **mechanistic complementarity** among current surgical, endoscopic and pharmacological treatments to favor their **combined use**
  - To induce weight loss
  - To induce weight loss-independent metabolic effects
  - To reduce inflammation and hepatic cell injury
  - To reduce fibrosis
  - To reduce the risk of hepatocellular carcinoma

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