Hepatology Snapshot:

Endoscopic bariatric and metabolic therapies for non-alcoholic fatty liver disease

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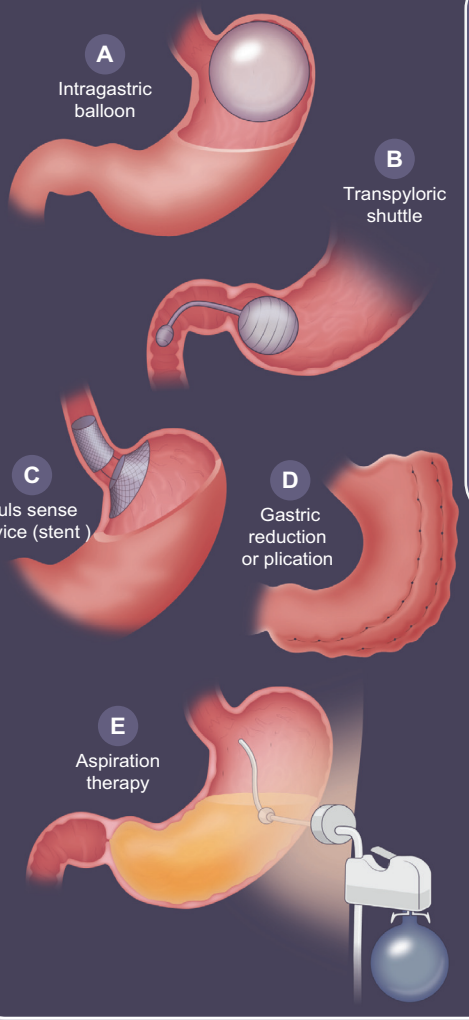
Gastric EBMT

Weight loss dependent pathways

Improved satiation; Improved satiety; Alteration in gastric accommodation; Alteration in gastric emptying; Improved insulin resistance

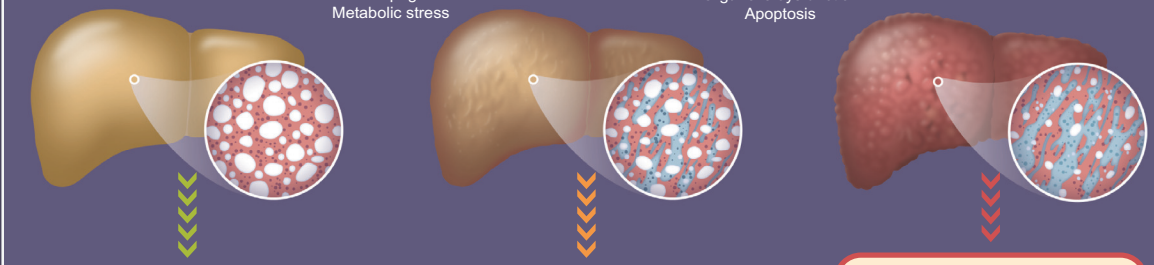


Non-alcoholic fatty liver disease

Fat deposition → Inflammation → Fibrosis/cirrhosis

Dietary
De novo lipogenesis
Metabolic stress

Oxidative stress
Organelle dysfunction
Apoptosis



Insulin resistance
+ High insulin level

Dysbiosis
Leaky gut
Metabolic endotoxemia

Bile acids
FXR/RXR inhibition
Altered FGF15/19 and
TGR-5 signaling

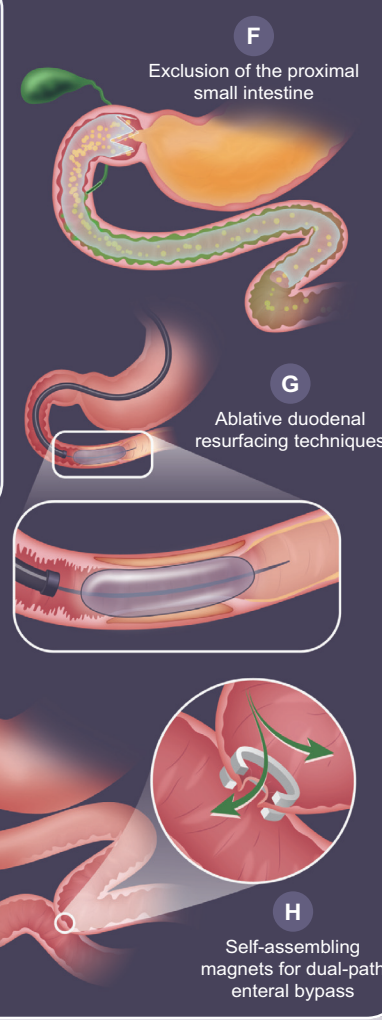
DEVICE	Gastric pathways		Small intestinal pathways			
	↓Bodyweight + ↑Insulin sensitivity	↓Ghrelin (fasting and post-prandial)	↓Bodyweight + ↑Insulin sensitivity	↑Insulin sensitivity (proximal intestinal pathways)[1]	↑Insulin secretion & sensitivity (distal intestinal pathways[2])	↑Energy expenditure[3]
Intragastric balloon (A)	++	+	-	+	-	-
Transpyloric shuttle (B)	++	+	-	+	-	-
Full sense device (C)	++	-	-	+	-	-
Gastric remodeling (D)	+++	+	-	+	+	-
Aspiration therapy (E)	+++	+	-	-	-	-
Duodenojejunal bypass liner (F)	-	-	++	+++	++	+
Duodenal resurfacing and rejuvenation (G)	-	-	+	+++	-	-
Dual-path enteral bypass by magnets (H)	-	-	+	-	+++	++

[1] ΔGUT Hormones; ΔGI Nutrient Sensing; ΔIntestinal Glucose Metabolism; ΔIron Absorption; ΔMicrobiome
[2] ΔGUT Hormones; ΔGI Nutrient Sensing; ΔDistal Intestinal Hyperstimulation
[3] ΔBile Acids; ΔGUT Hormones; ΔMicrobiome

Small bowel EBMT

Weight loss independent and dependent pathways

Improved satiety; Regeneration of gut mucosal barrier; Gut microbiome; Gut neurohormonal signaling; Improved insulin resistant; Bile acid signaling



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Non-alcoholic fatty liver disease (NAFLD) is a common chronic progressive parenchymal liver disease with strong pathophysiological underpinnings to adiposity-based chronic disease or obesity. One of the hallmarks of the disease is an insulin-resistant state driven by increased body fat promoting adipose tissue dysfunction, a chronic inflammatory state, altered gut mucosal barrier and microbiome, and permissive abnormal signaling between the central nervous system and peripheral metabolic organs. This results in the development of liver steatosis due to increased fatty acid delivery from the adipose tissue and hepatic *de novo* lipogenesis. The excess fat in the liver leads to oxidative stress and organelle dysfunction (mitochondria and endoplasmic reticulum) that produces a chronic inflammatory state within the liver known as steatohepatitis (a histopathological finding consisting of ballooning and lobular inflammation in the presence of fat). Finally, hepatocyte apoptosis and inflammation in the liver activate the fibrosis cascade, ultimately resulting in liver fibrosis and cirrhosis.[1]

Although there are many drugs under investigation in clinical trials for non-alcoholic steatohepatitis (NASH), some of them in phase III trials, there are no approved pharmacological options for the treatment of NASH.[2] Currently, lifestyle modification strategies targeting sustained weight loss are the only approach that has proven to be effective for NAFLD.[2] A sustained and long-term weight loss of ≥7–10% of body weight is needed in order to reduce steatosis, inflammation and fibrosis.[3] However, only between 10–20% of patients achieve this goal, so other strategies are clearly needed.[4] Bariatric and metabolic surgery targeting the gastrointestinal tract has shown the most promise in reversing steatosis and steatohepatitis, with regression of fibrosis in about 30% of patients.[5] The invasive nature and poor penetrance of surgery among patients with obesity limit its scalability as a universal management option for this chronic disease. Capitalizing on selective targeting of similar peripheral and central gastrointestinal pathways, endoscopic bariatric and metabolic therapies (EBMTs) can reproduce the benefits of surgical interventions in a minimally invasive and cost-effective manner.[6] The gastrointestinal anatomic manipulations resulting from EBMTs produce weight-loss dependent and independent physiological alterations conducive to improvement in obesity and its metabolic consequences; such as type II diabetes and NAFLD (Table 1).

Gastric EBMTs include space-occupying devices that most commonly take the form of temporarily placed prostheses. These include intragastric balloons (A). The TransPyloric Shuttle (BAROnova Inc, Goleta, CA) (B), which intermittently seals the pyloric channel and delays gastric emptying in the fed state to induce early satiation and prolonged satiety. The Full Sense Device (BFKW, Grand Rapids, MI) (C), is a modified fully covered gastroesophageal stent with a cylindrical esophageal component and a gastric disk connected by struts that exerts constant gentle pressure on the gastric cardia, triggering afferent vagal signaling to the central nervous system and a sensation of fullness, resulting in weight loss. Additional gastric devices include gastric remodeling techniques that reduce the gastric reservoir by endoscopically creating a tubular sleeve along the greater curvature of the stomach through transoral suturing (Overstitch, Apollo Endosurgery, Austin, Tx) or plication (POSE, USGI Medical, San Clemente, CA) (D). Finally, aspiration therapy (E) is a treatment approach for obesity that allows obese patients to dispose of a portion of their ingested meal via a specially designed percutaneous gastrostomy tube, known as the A-Tube (Aspire Bariatrics, King of Prussia, PA). Gastric EBMTs have shown weight loss dependent improvement in histologic and biochemical parameters of NAFLD.[7–10]

The proximal small intestine plays a central role in the pathogenesis of type II diabetes and NAFLD orchestrated through a variety of pathways, resulting in insulin resistance and chronic inflammation. These pathways include alteration of gut incretin to anti-incretin neurohormonal signaling, changes in the gut microbiome and mucosal barrier function, and activation of innate immune reactions caused by an excess of free fatty acids, bacterial lipopolysaccharides, chemokines, cytokines, and adipokines. Exclusion of the proximal small intestines by impermeable polymer duodenojejunal bypass liners (F) (EndoBarrier, GI Dynamics, Lexington, MA) (Metamodix, Minneapolis, MN) and ablative duodenal resurfacing techniques that regenerate the proximal small intestinal mucosal barrier by thermal ablation (G) (Fractyl Laboratories, Cambridge, MA) have shown promise, improving insulin resistance and NAFLD through weight loss dependent and independent pathways.[11–13]

Finally, primary and secondary bile acid concentrations and composition in the intestinal, portal and systemic circulation play an essential role in insulin secretion and resistance, metabolic rate, liver lipogenesis and inflammation, and liver fibrosis progression through FXR/FGF15 and 19/TGR5 signaling. Self-assembling magnets for endoscopy (H) (GI Windows, Boston, MA) create a dual-path enteral bypass between the proximal jejunum and ileum; thus, partially diverting bile to the terminal ileum, resulting in diabetes and NAFLD improvement.[14]

Conflicts of interest

BKA: Consultant for Boston Scientific, Metamodix, BFKW, USGI. Research support from Aspire Bariatrics, GI Dynamics, Apollo Endosurgery, Medtronic, Spatz, and Cairns. Speaker for Johnson and Johnson and Olympus. FB: Nothing to Disclose. IG: Speaker for Gilead and Novartis. AC: Consultant for Boston Scientific. Speaker for Mallinckrodt Pharmaceuticals.

Please refer to the accompanying ICMJE disclosure forms for further details.

Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jhep.2019.07.026.

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