VitaHash. Vol 1. No 1. (2026)
DOI https://doi.org/10.68919/vitahash.2026.00011
On-chain: STAMP-2026-1106-FFLQ47K7

Perspective

Beyond Digestion: The Gastrointestinal Tract at the Centre of Metabolic Regulation

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Traditionally, gastrointestinal (GI) and metabolic disease have been considered separate clinical entities with the GI tract viewed primarily as a conduit for digestion and nutrient absorption, while the metabolic regulation was largely attributed to the liver, pancreas, and adipose tissue. Recent evidence, has challenged this distinction and has demonstrated that the intestine functions as a major endocrine, immune, and metabolic organ playing a key role in metabolic health. The emergence of metabolic dysfunction-associated steatotic liver disease (MASLD), the success of incretin-based therapies, and the metabolic benefits of bariatric interventions highlight the increasingly interconnected nature of gastrointestinal and metabolic health. In this perspective, we propose a gut–metabolic network framework in which the intestine serves as a central integrator linking the metabolic system together. This framework extends beyond the conventional gut–liver axis and helps explain the multisystem effects of contemporary therapies. We discuss key mechanistic pathways, therapeutic convergence between gastroenterology and metabolic medicine, and important gaps in current clinical practice, including limited metabolic phenotyping and fragmented care models. Recognizing the gut as a central regulator of metabolic health may enable more integrated approaches to patient care, research, and training, and better align clinical practice with evolving biological understanding.

KEYWORDS: Gut-metabolic network, obesity medicine, enteroendocrine signaling, MASLD, metabolic disease

Why is it important

For better half of the twentieth century, the gastrointestinal (GI) tract was thought of as a conduit for digestion, absorption and excretion, while metabolism was governed by the pancreas, liver, and adipose tissue. This distinction is no longer accurate. The recent transition from nonalcoholic fatty liver disease (NAFLD) to metabolic dysfunction associated steatotic liver disease (MASLD) highlights the role of metabolic dysfunction in disease pathogenesis.[1] Gut hormone analogues are now used to treat type 2 diabetes and obesity.[2] Bariatric surgery has shown superior long-term glycemic control compared to intensive medical therapy in selected patients with type 2 diabetes.[3] As more therapies in metabolic medicine target the gut or act through it, the distinction between the two is becoming increasingly blurred. We propose a unified framework in which GI and metabolic health are viewed as interconnected components of a single physiological network, reshaping how phy-

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sicians view and assess patients, deliver care, and direct future research.

The GI tract as a metabolic organ

The GI tract is a major endocrine organ. Enteroendocrine cells sense nutrients within the intestinal lumen and release hormones such as glucagon like peptide 1 (GLP-1), glucose dependent insulinotropic polypeptide (GIP), peptide YY (PYY) and cholecystokinin, that regulate intestinal function, insulin secretion, nutrient absorption, and appetite.[4] Similarly, bile acids also act as hormones and activate ileal farsenoid X receptor (FXR) which in turn induces fibroblast growth factor (FGF19), which regulates hepatic bile acid synthesis and metabolism, while takeda G protein-coupled receptor 5 (TGR5) signaling promotes GLP-1 release.[5]

The gut microbes also influence metabolic function through the generation of bioactive metabolites. Fermentation of dietary fiber yields short-chain fatty acids that act through free fatty acid receptor 2 and 3 (FFAR2 and FFAR3([6], whereas gut microbes metabolize dietary phosphatidylcholine and produce trimethylamine N-oxide, whose plasma levels predict major adverse cardiovascular events.[7]

A bidirectional relationship

Emerging evidence supports a bidirectional gut-metabolic axis. Obesity is known to be associated with reflux disease, cholelithiasis, and colorectal cancer.[8] Similarly, metabolic dysfunction is increasingly associated with intestinal barrier dysfunction and with host-microbial interaction alteration.[9] Conversely, the GI tract regulates metabolism through hormone signaling, microbial metabolites, and immune pathways. This bidirectional relationship is well depicted in MASLD: Microbial products that cross a compromised intestinal barrier are delivered directly to the liver through the portal circulation, while the steatotic liver alters bile acid metabolism and enterohepatic pathways, further influencing intestinal and metabolic function.[9,10]

From gut–liver axis to gut–metabolic network

The gut-liver axis has significantly advanced our understanding of metabolic disease, but it captures only one component of a broader physiologic network. In our proposal the intestine serves as the central integrator of metabolic signaling in the gut-metabolic network [Figure 1]. The liver is the primary recipient of portal nutrients, bile acids, and microbial metabolites, while the pancreas responds to intestinal hormone signals. Adipose tissue is influenced by microbial and inflammatory signals, and skeletal muscle by nutrient availability and systemic inflammation. The brain integrates neural and hormonal signals originating from the gut to regulate appetite and energy balance, while the immune system serves as a regulator of interactions through this network.

The value of this framework lies in its ability to predict multisystem effects. An intervention targeting one component of the network often produces benefits, and occasionally unintended consequences, across multiple organ systems. The pleiotropic effects of GLP-1 receptor agonists exemplify this principle, with demonstrated benefits extending beyond weight reduction to cardiovascular disease, chronic kidney disease, and MASH, while also highlighting trade-offs such as loss of lean body mass during weight loss. Together, these observations suggest that metabolic therapies should be understood not as acting on a single organ, but as modifying an interconnected physiological network.[11,12,13,14]

Therapeutic convergence

Therapeutic advances are increasingly blurring the traditional boundaries between gastroenterology and metabolic medicine. In the ESSENCE trial, semaglutide achieved resolution of steatohepatitis without worsening fibrosis in 62.9% of patients versus 34.3% with placebo, and improved fibrosis in 36.8% versus 22.4%;[13] These findings resulted in its accelerated approval in the United States for non-cirrhotic MASH with moderate-to-advanced

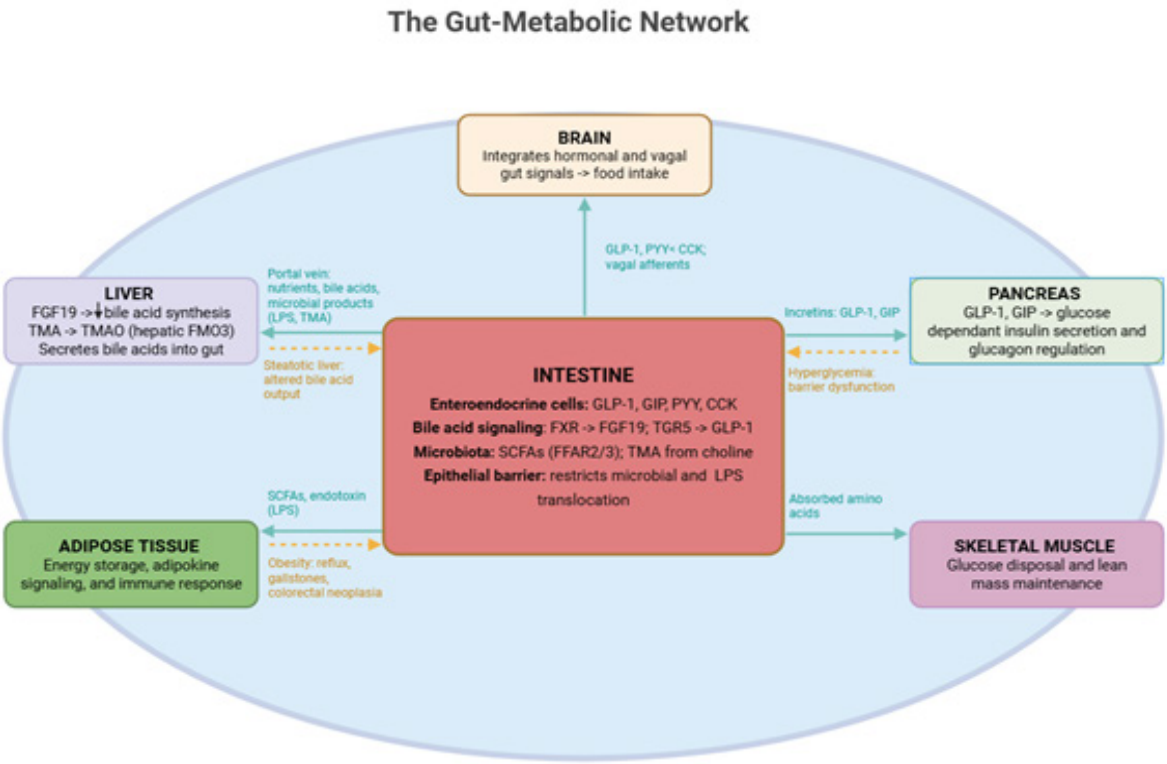


FIGURE 1. The gut–metabolic network. The intestine senses nutrients, bile acids and microbial products and signals to the liver, pancreas, brain, adipose tissue and skeletal muscle (solid arrows); metabolic dysfunction in turn alters the gut (dashed arrows). Low-grade inflammation mediated by the immune system links all nodes. Therapies acting on the network are shown below.[2,4,5,6,7,8,9,10,11,14,15,17,18,19,22,23,26] CCK, cholecystokinin; FFAR, free fatty acid receptor; FGF19, fibroblast growth factor 19; FMO3, flavin-containing monooxygenase 3; FXR, farnesoid X receptor; GI, gastrointestinal; GIP, glucose-dependent insulinotropic polypeptide; GLP-1, glucagon-like peptide-1; GLP-1 RA, GLP-1 receptor agonist; LPS, lipopolysaccharide; PYY, peptide YY; SCFA, short-chain fatty acid; TGR5, Takeda G protein-coupled receptor 5; THR-□, thyroid hormone receptor-□; TMA, trimethylamine; TMAO, trimethylamine N-oxide.

fibrosis in 2025.[15] Other agents have demonstrated similar cross-disciplinary promise. Tirzepatide and survodutide showed histological benefit in phase 2 MASH trials,[16,17] and the thyroid hormone receptor-□ agonist resmetirom was effective in a phase 3 study.[18] Beyond liver disease, newer incretin-based therapies continue to reshape obesity management; in topline phase 3 data not yet peer reviewed, retatrutide produced mean weight loss of 28.3% at 80 weeks,[19] and oral orforglipron became the first nonpeptide GLP-1 receptor agonist approved for weight management in 2026.[20] Procedural interventions also show the same principle, with bariatric surgery associated with lower risks of major adverse liver outcomes in biopsy-proven steatohepatitis and endoscopic sleeve gastroplasty producing greater weight loss than lifestyle mod

ification alone.[21,22]

Despite these advances, some important limitations remain. Weight reduction with GLP-1 receptor agonists is accompanied by loss of both fat and lean muscle mass.[14] Delayed gastric emptying has raised concerns regarding retained gastric contents and aspiration risk during sedated endoscopy.[23] Discontinuation of semaglutide resulted in substantial weight regain, with participants recovering approximately two-thirds of lost weight within one year.[24] Likewise, microbiome-directed therapies have produced variable and often transient benefits; in one study, lean-donor faecal microbiota transplantation improved insulin sensitivity at 6 weeks but not 18 weeks, with response influenced by the recipient's baseline microbial composition.[25] Long-term liver outcomes and durability data for many emerging

therapies remain unavailable.

What is missing from clinical practice

Clinical practice has yet to fully capture the convergence of gastrointestinal and metabolic disease. Gastroenterologists routinely manage patients with obesity, diabetes, and MASLD, yet metabolic phenotyping remains inconsistent. Measures such as waist circumference, glycemic status, lipid profiles, body composition, and muscle function are not systematically incorporated into routine care, and fibrosis risk stratification often remains confined to hepatology settings. Referral for obesity pharmacotherapy or surgery is inconsistent. Sarcopenia assessment is largely limited to cirrhosis, and nutritional assessment is often omitted. At the same time, the gastrointestinal consequences of incretin-based therapies are increasingly encountered in clinics and endoscopy units, often without integrated care pathways. A practical first step would be the adoption of a minimum GI-metabolic dataset that can be collected routinely across outpatient practice.

Future directions

Key gaps remain in our understanding of the GI–metabolic interface. First, integrated phenotyping approaches that combine metabolic, hepatic, microbial, nutritional, and body-composition assessments may improve disease characterization and treatment selection. Second, future trials should incorporate hard clinical endpoints, including liver-related, cardiovascular, and functional outcomes, while evaluating strategies to preserve muscle mass during weight loss. Finally, training programs should evolve to incorporate obesity medicine, clinical nutrition, and body-composition assessment into routine clinical education. Implementation research and real-world data platforms will be equally important in determining whether integrated GI–metabolic care models improve treatment delivery, patient outcomes, and healthcare utilization.

Conclusion

The gut is not merely a target of metabolic disease; it is a central regulator of metabolic health. Viewing gastrointestinal and metabolic disease as components of an interconnected network represents more than a change in terminology. It reframes the questions gastroenterologists ask, the measurements they collect, and the therapies they consider. The emergence of incretin-based therapies has brought this interdependence into sharper clinical focus; the next challenge is to align clinical practice, research, and training with that reality.

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