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INTESTINAL ABSORPTIVE CAPACITY AS A MECHANISTIC DRIVER OF OBESITY AND TYPE 2 DIABETES: INTEGRATIVE FRAMEWORK AND DEVELOPMENT OF THE ABSORPTIVE CAPACITY INDEX

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ABSTRACT

Obesity and type 2 diabetes (T2D) are multifactorial disorders commonly attributed to excess caloric intake and insufficient expenditure. However, these paradigms overlook a critical determinant of systemic energy flux—the intestinal absorptive capacity (IAC). We hypothesize that IAC is a quantifiable, plastic, and modifiable biological trait that causally contributes to obesity and T2D by enhancing nutrient uptake and activating maladaptive endocrine, bile acid, and microbiome-mediated feedback loops.

We propose the development of an Absorptive Capacity Index (ACI) integrating nutrient uptake kinetics, transporter expression, gut hormone secretion, intestinal permeability, and microbial activity. Mechanistically, elevated IAC leads to increased glucose and lipid absorption, exaggerated incretin secretion with receptor desensitization, bile acid–FXR/TGR5 dysregulation, barrier dysfunction, and microbial reinforcement of absorptive function. Collectively, these processes amplify systemic nutrient flux and metabolic stress.

Therapeutic modulation of IAC—through transporter inhibition, bile acid sequestration, microbiome-directed therapies, or surgical interventions—offers a novel strategy to reduce effective energy absorption, restore metabolic balance, and redefine metabolic disease through the lens of intestinal energy efficiency.

Keywords: Intestinal Absorptive Capacity; Absorptive Capacity Index; Obesity; Type 2 Diabetes; Gut Hormones; Bile Acids; Microbiome; Metabolic Regulation

1 INTRODUCTION

Despite decades of progress in metabolic medicine, global rates of obesity and T2D continue to rise [1, 2]. The prevailing model of “calories in versus calories out” inadequately explains why individuals with similar diets and activity levels

exhibit markedly different metabolic trajectories. This discrepancy points to an unaccounted axis of energy regulation—the intestine's capacity to absorb and deliver nutrients into systemic circulation.

The intestinal absorptive capacity (IAC) represents the integrated efficiency of nutrient uptake, governed by structural, molecular, hormonal, and microbial determinants. Traditionally viewed as a passive process, absorption is now recognized as an active and adaptable function of the intestinal mucosa. Variations in IAC among individuals may determine why some people gain weight easily ("high absorbers") while others remain lean under equivalent caloric exposure.

Emerging studies link intestinal transporters, enteroendocrine signaling, bile acid metabolism, and microbial composition to systemic metabolic outcomes [3- 9]. However, these mechanisms have not yet been unified into a cohesive framework. We therefore propose that IAC is a modifiable metabolic trait that drives obesity and T2D through coordinated regulation of gut hormone secretion, bile acid signaling, barrier permeability, and microbiome ecology. As illustrated in (**Figure 1**), IAC functions as a central regulator integrating structural, transporter, hormonal, bile acid, and microbial inputs to determine systemic metabolic flux.

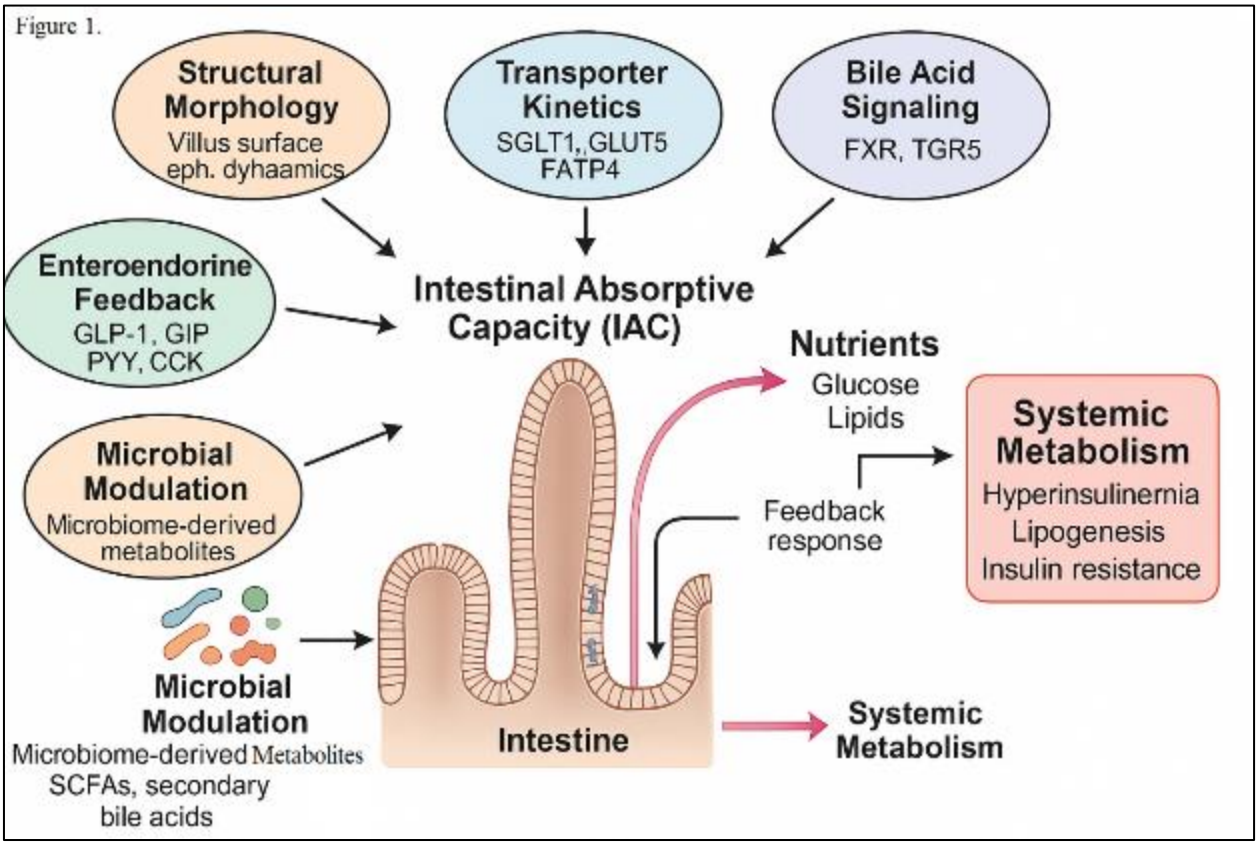

Figure 1: ***Conceptual Overview of Intestinal Absorptive Capacity (IAC) as a Central Regulator of Metabolic Homeostasis.*** **This schematic illustrates the proposed conceptual model in which intestinal absorptive capacity (IAC) serves as a central integrator of metabolic regulation.**

The small intestine acts as a dynamic energy gateway connecting five interacting regulatory domains: (1) Structural Morphology — villus height, crypt depth, mucosal surface area, and epithelial turnover that determine absorptive surface; (2) Transporter Kinetics — glucose and nutrient transporters (SGLT1, GLUT2, GLUT5, PEPT1, FATP4) that mediate luminal nutrient flux; (3) Enteroendocrine Feedback — secretion of gut hormones (GLP-1, GIP, PYY, and CCK) that modulate motility, insulin secretion, and systemic metabolism; (4) Bile Acid Signaling — FXR and TGR5 receptor networks that regulate lipid oxidation, transporter expression, and glucose homeostasis; and (5) Microbiome Modulation — microbial metabolites (short-chain fatty acids, secondary bile acids) that influence epithelial function and systemic energy balance.; Arrows indicate bidirectional feedback among these components. The figure conceptualizes how elevated IAC amplifies nutrient absorption, hormonal signaling, and microbial feedback, driving hyperinsulinemia, lipid accumulation, and insulin resistance.

1.1 Mechanistic Framework of Intestinal Absorptive Capacity (IAC) / Intestinal Absorptive Index (IAI)

Definition

IAC is defined as the integrated ability of the intestinal mucosa to import, process, and transfer luminal nutrients—carbohydrates, lipids, and amino acids—into systemic circulation. It is determined by structural morphology, transporter kinetics, endocrine feedback, bile acid signaling, barrier integrity, and microbial modulation. These

processes converge through multiple feedback loops involving nutrient uptake, hormonal resistance, and microbial reinforcement, as shown in Figure 2.

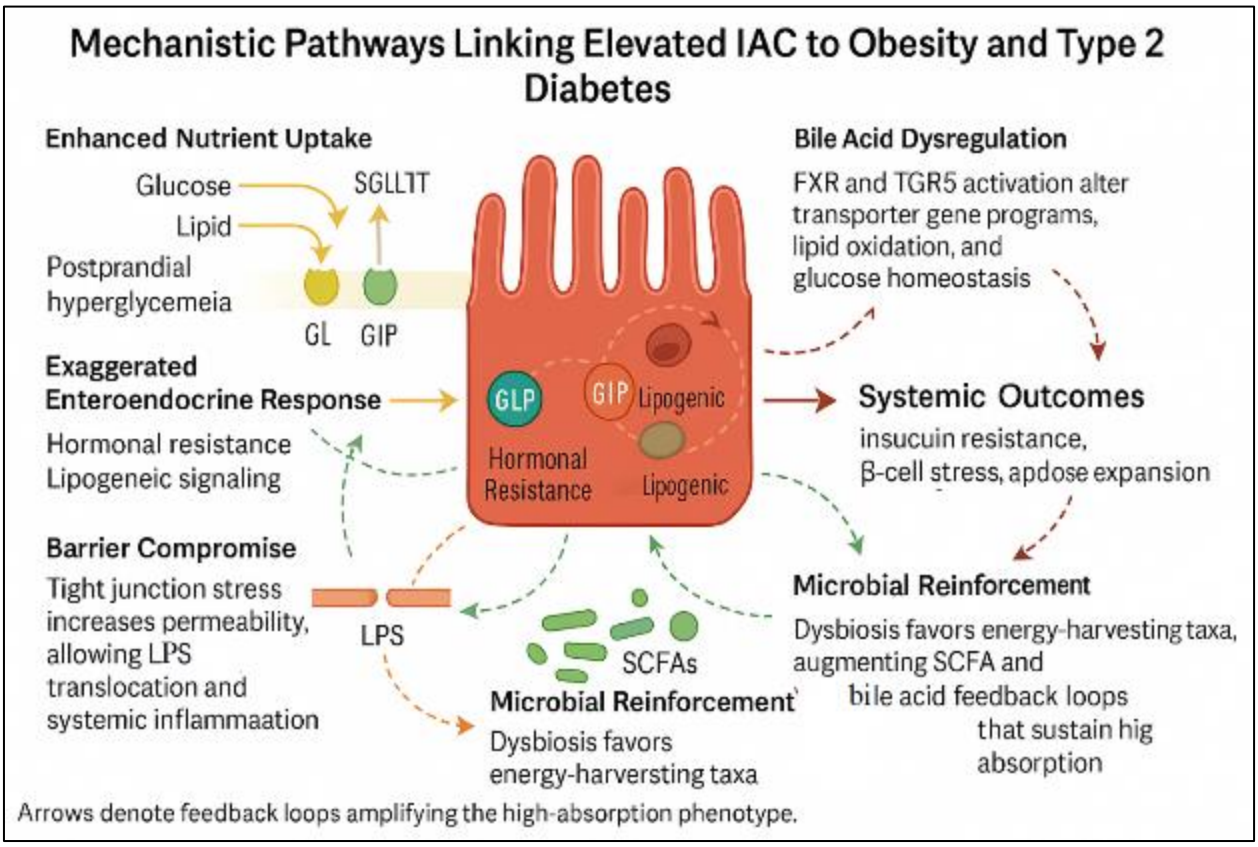

Figure 2: ***Mechanistic Pathways Linking Elevated IAC to Obesity and Type 2 Diabetes.*** **This diagram depicts the sequential and parallel mechanisms through which increased intestinal absorptive capacity (IAC) contributes to metabolic dysfunction.**

- Enhanced Nutrient Uptake: Elevated transporter expression accelerates glucose and lipid absorption, leading to postprandial hyperglycemia and chylomicronemia.
- Exaggerated Enteroendocrine Response: Chronic overactivation of GLP-1 and GIP pathways results in incretin resistance and adipogenic signaling.
- Bile Acid Dysregulation: Altered bile acid pools and FXR/TGR5 activation shift transporter gene programs, lipid oxidation, and glucose metabolism.
- Barrier Compromise: Tight junction stress increases permeability, allowing translocation of lipopolysaccharides (LPS) and systemic inflammation.
- Microbial Reinforcement: Dysbiosis favors energy-harvesting taxa, producing SCFAs and bile acid derivatives that sustain high absorptive states.
- Systemic Outcomes: These intestinal events converge on insulin resistance, β-cell stress, hepatic steatosis, and adipose tissue expansion, culminating in obesity and T2D.

Arrows denote feedback loops that perpetuate the high-absorption phenotype. The figure highlights how intestinal and systemic processes interlink to drive metabolic disease.

1.2 Structural Morphology and Epithelial Dynamics

- Villus length, crypt depth, and enterocyte mass determine mucosal surface area; high-fat diets and obesity induce villus elongation and mucosal hypertrophy [6, 7].
- Stem cell and progenitor dynamics are regulated by Wnt and Notch signaling, expanding absorptive lineages in obesity [3-5].
- Regional heterogeneity: The proximal intestine (duodenum/jejunum) shows the greatest remodeling under metabolic stress, correlating with transporter upregulation [6, 7].

1.3 Transporter/Carrier Capacity and Kinetics

- Apical uptake transporters (SGLT1, GLUT2, GLUT5, PEPT1) mediate glucose and peptide absorption [10].
- Lipid transporters (CD36, FATP4, NPC1L1) and MTP–ApoB48 pathways govern chylomicron assembly [11-13].
- Obesity upregulates duodenal SGLT1 and GLUT5 expression, correlating with BMI and insulin resistance [10].
- Pharmacologic evidence: SGLT1 inhibitors reduce glucose absorption, improving glycemia and preventing weight gain [14].

1.4 Enteroendocrine Feedback and Nutrient Sensing

- SGLT1 and GPCR nutrient sensing triggers secretion of GLP-1, GIP, and PYY [8].
- Incretin paradox: chronic high IAC causes hypersecretion yet reduced receptor sensitivity ("incretin resistance") [15-17].
- Microbial metabolites (SCFAs) stimulate L-cells via FFAR2/3, modulating hormone release [18-20].
- Neuroendocrine integration: Gut hormones act on vagal afferents to coordinate motility, appetite, and glucose control.

1.5 Bile Acid–Receptor Crosstalk and Absorptive Regulation

- Increased bile acid flux and microbial modification of the bile pool activate FXR/TGR5 signaling, shifting absorptive gene expression and altering metabolic setpoints [21].
- FXR overactivation (common in high-fat diets) suppresses GLP-1 secretion and promotes pro-absorptive gene programs, enhancing nutrient uptake [22, 23].
- TGR5 activation counterbalances by enhancing GLP-1 release and promoting energy expenditure.
- Microbiota-mediated modulation of FXR/TGR5 tone—via bile salt hydrolase and secondary bile acids—can amplify or suppress receptor signaling, thereby influencing both absorption and systemic metabolism [21, 24-26].

1.6 Intestinal Barrier Integrity and Metabolic Inflammation

- Elevated absorptive stress and mucosal turnover weaken tight junctions, allowing paracellular leakage of LPS and microbial products [27]
- LPS translocation activates TLR4–NF-κB signaling and cytokine release (IL-6, TNF-α), impairing insulin pathways in liver, muscle, and adipose tissue [28-30].
- This cascade links local gut absorption dynamics to systemic insulin resistance, positioning barrier health as a determinant of metabolic homeostasis.

1.7 Microbial Reinforcement and Positive Feedback

- Obesogenic diets favor Firmicutes-dominant microbiota that efficiently harvest energy and transform bile acids into forms promoting absorption [9, 24, 26, 27, 31-33].
- Dysbiosis reinforces absorption by inducing transporters (SGLT1, PEPT1) and mucosal proliferation, sustaining a high-IAC phenotype [9, 24, 26, 27, 32, 33].
- Over time, these interactions form a self-sustaining "high absorption–high storage" loop, perpetuating obesity and insulin resistance.

1.8 Adaptive Remodeling and Mucosal Plasticity

- Chronic high IAC drives mucosal hypertrophy**,** crypt proliferation, and expansion of stem/progenitor pools, increasing baseline absorptive potential [6, 7].
- Sustained nutrient exposure activates GLP-2, insulin, and Wnt signaling, promoting enterocyte proliferation and persistent absorptive upregulation [4, 5].
- Under normal physiology, feedback mechanisms (reduced nutrient flux, hormonal modulation) limit mucosal expansion, but in obesity, these controls fail, establishing a chronic hyperabsorptive state**.**

2 SUMMARY AND INTEGRATION

IAC functions as a multi-level integrator of structural, transporter, hormonal, bile acid, barrier, and microbial inputs. Its elevation initiates a cascade of metabolic perturbations—substrate overload, hormonal desensitization, inflammation, and reinforcing microbial feedback. Because each component is modifiable through dietary, microbial, or pharmacologic means, IAC represents a unifying mechanistic axis for both pathogenesis and therapy in metabolic disease.

2.1 Predictions, Quantification, and Experimental Assertions Derived from the IAC Framework

A major strength of the IAC hypothesis lies in its ability to yield falsifiable, measurable predictions. The proposed ACI integrates nutrient uptake kinetics, transporter expression, hormonal response, bile acid activity, permeability, and microbial function to quantify intestinal absorptive efficiency. If IAC is a modifiable determinant of systemic metabolism, measurable differences in ACI should precede and predict metabolic changes before conventional markers such as BMI or HbA1c shift. A proposed composite measure, the ACI, integrates six measurable domains reflecting intestinal absorptive efficiency (Figure 3).

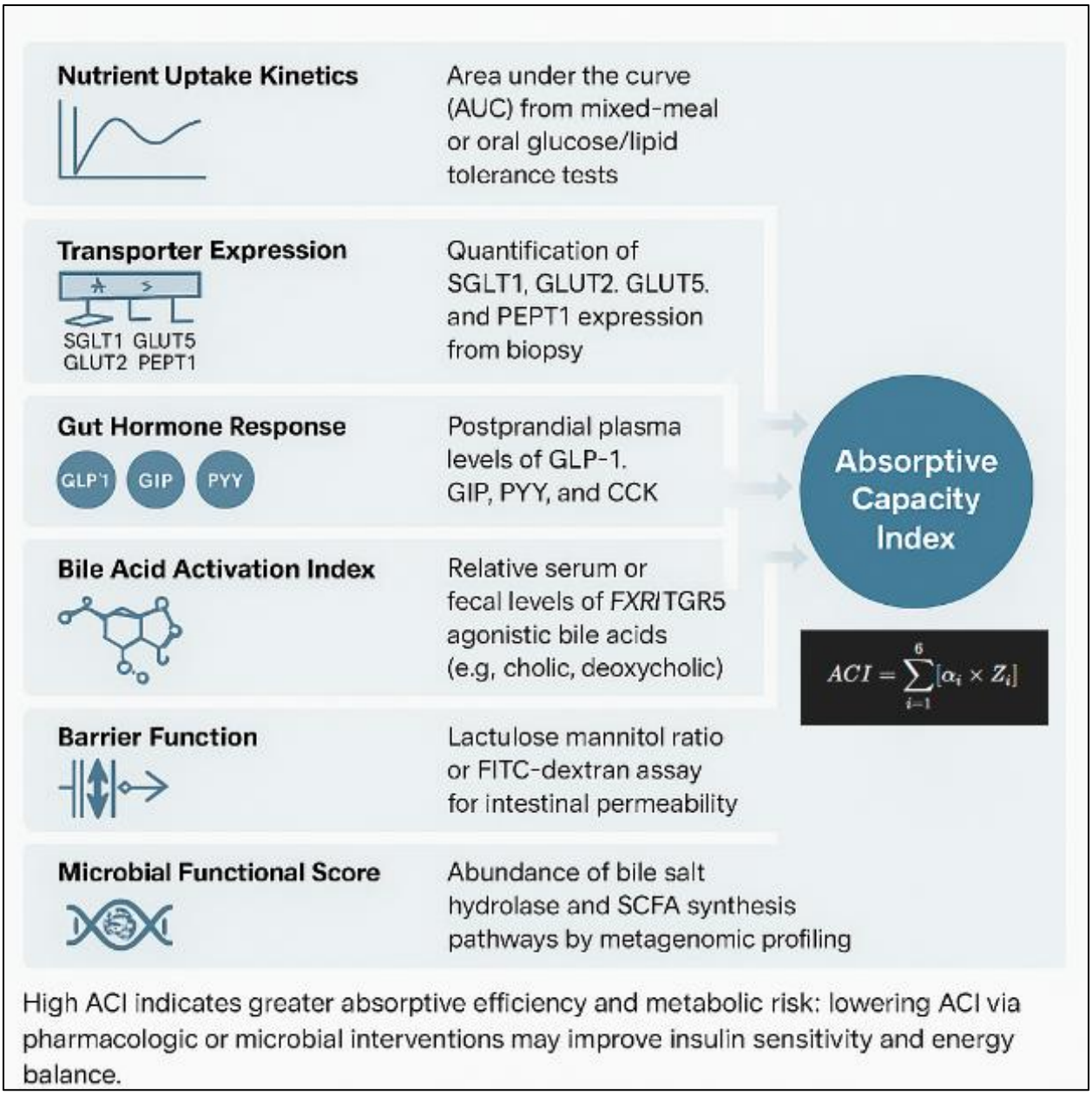

Figure 3: Design and Quantification of the Absorptive Capacity Index (ACI). This conceptual framework illustrates the composite design of the Absorptive Capacity Index (ACI), a proposed quantitative metric of intestinal absorptive efficiency.
The model integrates six measurable domains, each contributing to a standardized z-score weighted in the composite equation ACI = Σ [$\alpha_i \cdot Z_i$]:

1. Nutrient Uptake Kinetics — area under the curve (AUC) from oral mixed-meal, glucose, or lipid tolerance tests;
2. Transporter Expression — quantification of intestinal SGLT1, GLUT2, GLUT5, and PEPT1 from biopsy or transcriptomic data;
3. Gut Hormone Response — postprandial levels of GLP-1, GIP, PYY, and CCK;
4. Bile Acid Activation Index — serum or fecal concentrations of FXR/TGR5 agonistic bile acids (e.g., cholic, deoxycholic acids);

5. Barrier Function — intestinal permeability via lactulose: mannitol ratio or FITC-dextran assay;
6. Microbial Functional Score — metagenomic abundance of bile salt hydrolase genes and SCFA synthesis pathways.

Arrows indicate the integration of these domains toward the composite ACI. High ACI values represent greater absorptive efficiency and metabolic risk; lowering ACI predicts improved insulin sensitivity and energy balance.

2.1.1 Testable Predictions

- Prediction 1: Individuals with obesity or T2D will exhibit a higher ACI than lean, insulin-sensitive controls, reflecting greater absorptive efficiency.
- Prediction 2: Interventions lowering ACI (e.g., SGLT1 inhibition, bile acid sequestration, prebiotic therapy) will improve insulin sensitivity and metabolic profiles.
- Prediction 3: Early ACI changes will precede shifts in BMI, HbA1c, or lipid profile, positioning ACI as an early biomarker of metabolic transition.

2.1.2 Predictive Assertions and Supporting Evidences

The intestinal absorptive capacity (IAC) framework generates several testable predictions linking structural, molecular, endocrine, and microbial features to metabolic outcomes. Structurally, individuals with obesity or insulin resistance are expected to exhibit longer intestinal villi, expanded mucosal surface area, and higher crypt proliferation indices than lean counterparts. Histologic studies and duodenal or jejunal biopsies have shown increased villus height and elevated Ki-67 staining in obesity and high-fat diet (HFD) models, supporting the concept of mucosal hypertrophy and enhanced absorptive area [6, 7].

At the molecular transport level, obesity is predicted to associate with elevated expression of nutrient transporters such as SGLT1, GLUT2, GLUT5, and PEPT1, resulting in greater luminal nutrient clearance and higher postprandial glucose and lipid excursions. Indeed, duodenal SGLT1 and GLUT5 expression correlate positively with body-mass index and insulin resistance, and ex vivo uptake assays confirm increased transporter Vmax [10].

In the hormonal domain, fasting and postprandial concentrations of GLP-1, GIP, and PYY tend to be elevated in individuals with high absorptive capacity, yet these responses often display functional blunting—a state of "incretin resistance"—where hormonal secretion remains exaggerated but receptor signaling becomes desensitized [8].

Bile acid signaling is likewise expected to reflect heightened IAC, with increased circulating levels of 12α-hydroxylated bile acids (e.g., cholic and deoxycholic acid) and a bile-acid pool enriched in FXR-activating species. Such changes reinforce pro-absorptive gene programs and can suppress GLP-1 release [22, 23].

From a barrier-function perspective, higher IAC is predicted to coincide with greater intestinal permeability and low-grade endotoxemia. Elevated lactulose: mannitol ratios and plasma endotoxin concentrations have been observed in HFD-fed models, linking paracellular leak to systemic metabolic inflammation [29, 30].

Finally, microbiome ecology is expected to favor an energy-harvesting profile characterized by an increased Firmicutes-to-Bacteroidetes ratio and enrichment of bile salt hydrolase and short-chain-fatty-acid–producing genes. 16S and metagenomic sequencing demonstrate that such dysbiosis promotes bile-acid transformation, mucosal growth, and transporter induction, reinforcing the feed-forward nature of IAC expansion [9, 24, 26, 27, 31–33].

Collectively, these predictions provide a coherent experimental roadmap for validating IAC as a quantifiable and modifiable metabolic trait linking gut architecture, nutrient transport, enteroendocrine signaling, and microbial ecology to systemic insulin resistance and obesity.

2.1.3 Quantification: Development of the Absorptive Capacity Index (ACI)

To operationalize the IAC framework, we propose a composite Absorptive Capacity Index ACI integrating physiological, biochemical, and microbial domains:

$$ACI = \Sigma\ [\alpha_1 \cdot (\text{Nutrient AUC}) + \alpha_2 \cdot (\text{Transporter Expression Z-Score}) + \alpha_3 \cdot (\text{Gut Hormone Composite}) + \alpha_4 \cdot (\text{Bile Acid Activation Index}) + \alpha_5 \cdot (\text{Permeability Ratio}) + \alpha_6 \cdot (\text{Microbial Functional Index})]$$

$$ACI = \sum_{i=1}^{6} (\boldsymbol{\alpha i}\ x\ Zi)$$

where each Z_i is a standardized z-score for a domain, weighted by its relative contribution (α_i) to metabolic outcomes such as BMI, HOMA-IR, or hepatic fat fraction.

The proposed ACI integrates six functional domains that collectively quantify intestinal absorptive efficiency and its metabolic implications.

1. Nutrient Uptake Kinetics: The first domain captures systemic nutrient absorption dynamics, measured as the area under the curve (AUC) from mixed-meal, oral glucose, or lipid tolerance tests. Higher AUC values reflect more rapid and extensive nutrient absorption across the intestinal epithelium.
2. Transporter Expression: The second domain evaluates mucosal transport capacity through quantification of apical and basolateral transporter expression—specifically SGLT1, GLUT2, and PEPT1—at both mRNA and protein levels. Elevated expression denotes increased capacity for monosaccharide and peptide translocation.
3. Gut Hormone Composite: The third domain encompasses the magnitude of enteroendocrine output, assessed via postprandial plasma concentrations of GLP-1, GIP, and PYY. These values provide an integrated measure of nutrient-triggered hormonal signaling along the gut–brain–pancreas axis.
4. Bile Acid Activation Index: The fourth domain represents the degree of bile acid–receptor signaling, defined by the ratio of FXR- and TGR5-agonistic bile acids—such as the cholic-to-deoxycholic acid ratio—indicating how bile acid composition modulates metabolic receptor pathways.
5. Barrier Function: The fifth domain reflects intestinal permeability and low-grade inflammation, evaluated by the lactulose: mannitol ratio and circulating endotoxin (LPS) units. Higher values suggest compromised barrier integrity and metabolic endotoxemia.
6. Microbial Functional Index: Finally, the sixth domain quantifies microbial contributions to energy harvesting through analysis of short-chain fatty acid (SCFA) profiles and the relative abundance of bile salt hydrolase–encoding genes. Elevated scores within this domain indicate a microbiome configuration that supports enhanced nutrient recovery and intestinal energy flux.

Together, these six domains form a multidimensional framework for calculating the ACI, offering a quantitative index of intestinal absorptive efficiency that can be standardized, compared across individuals, and targeted for therapeutic modulation.

The ACI provides a quantitative phenotype of absorptive efficiency, enabling:

- Cross-sectional comparison among lean, obese, and diabetic groups.
- Interventional tracking of therapies that modulate absorption or microbiota.
- Longitudinal prediction of metabolic trajectories.

2.1.4 Validation Framework

- Cross-sectional studies: Compare ACI across lean, obese, and T2D cohorts using mixed-meal tolerance, transporter assays, and microbiome analysis.
- Interventional trials: Assess ACI changes following SGLT1 inhibitors, bile acid sequestrants, or prebiotic therapy.
- Longitudinal studies: Determine whether baseline ACI predicts subsequent weight gain, insulin resistance, or hepatic steatosis.
- Mechanistic models: • *Animal:* inducible SGLT1/GLUT2 overexpression or FXR/TGR5 modulation. • *Organoid:* human intestinal enteroids exposed to metabolic or microbial stimuli.

Expected outcomes:

- ACI positively correlates with metabolic impairment.
- Lowering ACI improves insulin sensitivity and energy balance.
- Absence of correlation would falsify the model, refining mechanistic understanding.

3 DISCUSSION

3.1 Redefining Metabolic Efficiency- IAC as a New Metabolic Dimension

The IAC framework challenges the traditional notion of "calories in, calories out." Instead, it introduces "calories absorbed" as a biologically variable determinant of metabolism. It unites epithelial physiology, gut–endocrine signaling, and microbial ecology into a single quantitative axis influencing systemic energy balance [3-5].

Traditional energy balance models assume that intake and expenditure determine weight, but interindividual variability in nutrient absorption efficiency can explain why some individuals gain weight more readily than others despite similar diets. This framework situates the small intestine as a dynamic metabolic gatekeeper, capable of amplifying or attenuating energy flux to peripheral tissues [3-7].

3.2 Hormonal and Bile Acid Crosstalk

The gut's endocrine functions are intimately coupled to its absorptive state. High nutrient flux amplifies secretion of incretins such as GLP-1 and GIP, yet sustained stimulation leads to hormonal desensitization, a hallmark of obesity and T2D [8, 15-17]. This paradox—elevated GLP-1 levels with reduced metabolic responsiveness—highlights a dysregulated alignment between intestinal nutrient sensing and systemic energy demand.

Gut hormones and bile acids operate within a bidirectional regulatory network, wherein absorption efficiency modifies hormonal tone, and hormones reciprocally govern absorptive machinery. Chronic activation of GIP and FXR pathways fosters hyperinsulinemia, lipogenesis, and pro-absorptive gene expression, while GLP-1 and TGR5 signaling counterbalance these effects by promoting energy expenditure and metabolic resilience [8, 22, 23].

3.3 Microbiome as a Dynamic Amplifier

The intestinal microbiome is both a determinant and a product of intestinal absorptive capacity (IAC). It adapts to host diet while simultaneously shaping mucosal physiology and nutrient handling. Enrichment of Firmicutes and bile salt hydrolase–producing taxa in obesity enhances caloric extraction, bile acid deconjugation, and short-chain fatty acid (SCFA)–driven upregulation of nutrient transporters—thereby reinforcing a hyper-absorptive phenotype (9, 24, 26, 27, 31-34). Conversely, microbial depletion or transplantation can reverse metabolic phenotypes in animal models, underscoring the microbiome's causal influence on host energy balance. Metabolic interventions such as dietary fiber supplementation, prebiotics, or probiotics can remodel microbial ecology toward a lower-energy, metabolically favorable state, attenuating IAC and improving systemic metabolism [31].

3.4 Barrier Integrity and Systemic Inflammation

Elevated intestinal absorptive capacity (IAC) may come at the cost of epithelial fragility, transforming localized absorptive hyperactivity into systemic metabolic inflammation. Disruption of tight junction proteins increases intestinal permeability, permitting lipopolysaccharide (LPS) and other microbial products to translocate into circulation, where they activate TLR4–NF-κB inflammatory pathways and impair insulin signaling [28-30]. This leaky gut–driven endotoxemia links heightened absorption to chronic low-grade inflammation and insulin resistance. Thus, maintaining the delicate balance between nutrient absorption efficiency and epithelial barrier protection is essential to prevent maladaptive metabolic outcomes.

3.5 Therapeutic Implications

Potential therapeutic interventions targeting specific nodes of the IAC network are summarized in **Figure 4,** illustrating pharmacologic, microbial, and procedural strategies to normalize absorptive dynamics.

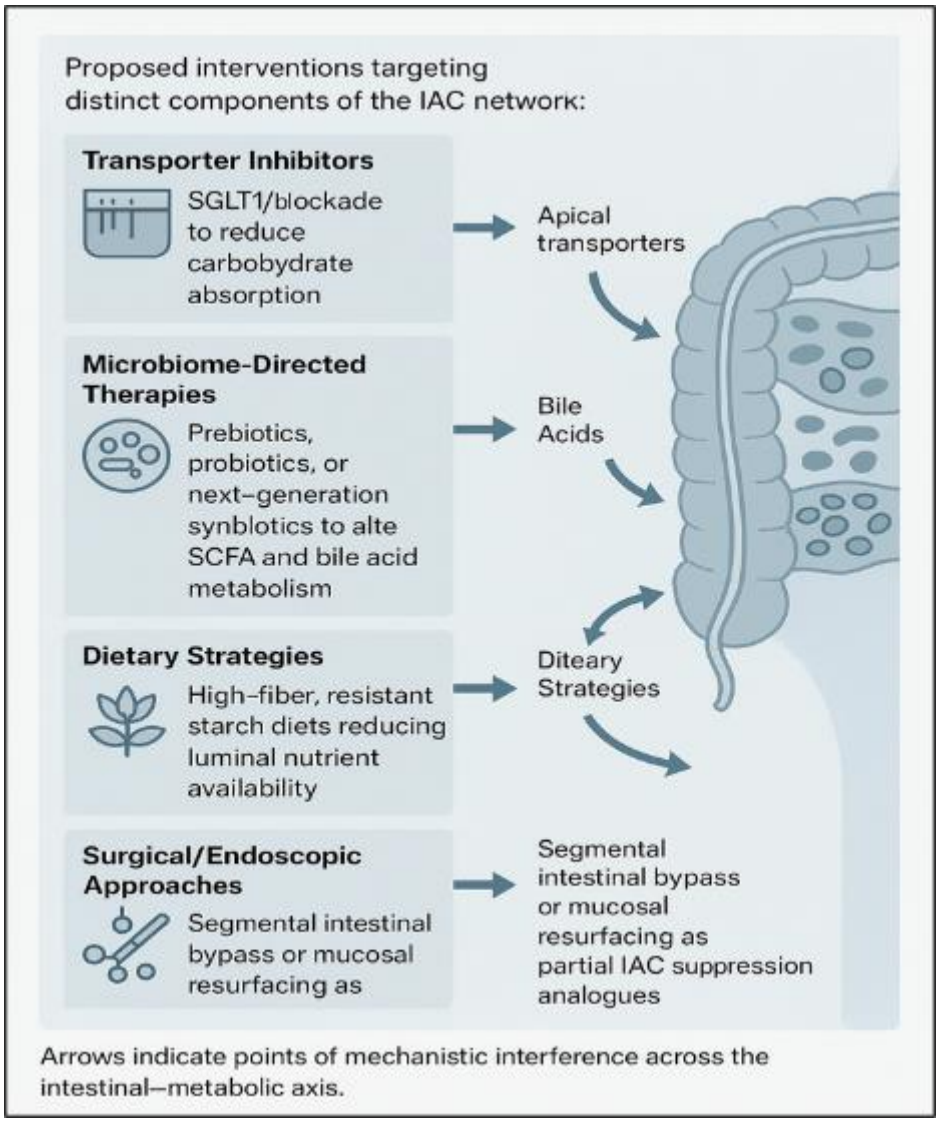

Figure 4: *Therapeutic Modulation of IAC.* This schematic summarizes proposed therapeutic interventions targeting different components of the IAC network to rebalance metabolic homeostasis:

1. Transporter Inhibitors: SGLT1/2 blockade to reduce carbohydrate absorption and postprandial hyperglycemia.
2. Bile Acid Modulators: FXR antagonists and bile acid sequestrants to normalize receptor signaling and reduce lipid absorption.
3. Microbiome-Directed Therapies: Prebiotics, probiotics, and next-generation synbiotics designed to alter SCFA and bile acid metabolism.
4. Dietary Strategies: High-fiber and resistant starch diets that lower luminal nutrient availability and improve barrier integrity.
5. Surgical/Endoscopic Approaches: Segmental intestinal bypass or mucosal resurfacing procedures that partially suppress IAC while preserving nutrient sufficiency.

Arrows indicate mechanistic points of interference along the intestinal–metabolic axis, linking IAC modulation to improved insulin sensitivity, reduced lipid accumulation, and restored energy balance.

1. Pharmacologic: SGLT1/2 inhibitors, FXR antagonists, and bile acid sequestrants to reduce absorption and signaling overload.
2. Microbial Modulation: Prebiotic and probiotic therapies or next-generation microbial consortia to modulate SCFA and bile acid metabolism and reduce energy harvesting.
3. Nutritional: High-fiber diets and resistant starches to blunt nutrient flux and enhance SCFA-mediated barrier reinforcement.

4. Procedural: Endoscopic mucosal resurfacing or segmental bypass as partial IAC suppression analogues of bariatric surgery without full bariatric remodeling.

3.6 Integration into Personalized Medicine

The proposed Absorptive Capacity Index could become a clinical biomarker to stratify patients according to their metabolic absorptive phenotype. Combining ACI with genomic and microbiome profiles would enable precision metabolic therapy—personalized modulation of nutrient flux rather than blanket caloric restriction.

Limitations and Future Directions

- Measurement complexity**:** Quantifying true absorption in vivo remains challenging.
- Compensatory mechanisms**:** Chronic reduction of IAC might induce appetite or transporter compensation.
- Causality**:** Determining whether high IAC precedes or results from obesity requires longitudinal designs.
- Translational hurdles**:** Most data arise from animal models; human validation is essential.

Nevertheless, the IAC paradigm offers a coherent mechanistic scaffold linking intestinal biology with systemic metabolic disease.

4 CONCLUSION

The intestinal absorptive capacity is a modifiable, quantifiable determinant of metabolic health. Its integration with hormonal, microbial, and bile acid signaling creates a self-reinforcing network that drives energy efficiency and metabolic overload. Development and clinical validation of an Absorptive Capacity Index (ACI) can transform the way we conceptualize, predict, and treat obesity and T2D.

By targeting IAC, we move from managing caloric intake to engineering intestinal energy efficiency—a paradigm shift in the prevention and treatment of metabolic disease.

Abbreviations

T2D – Type 2 Diabetes
IAC – Intestinal Absorptive Capacity
ACI – Absorptive Capacity Index
FXR – Farnesoid X Receptor
TGR5 – Takeda G Protein–Coupled Receptor 5
GLP-1 – Glucagon-Like Peptide-1
GIP – Glucose-Dependent Insulinotropic Polypeptide
PYY – Peptide YY
CCK – Cholecystokinin
SCFA – Short-Chain Fatty Acid
SGLT1 – Sodium–Glucose Cotransporter 1
GLUT2 – Glucose Transporter 2
GLUT5 – Glucose Transporter 5
PEPT1 – Peptide Transporter 1
FATP4 – Fatty Acid Transport Protein 4
CD36 – Cluster of Differentiation 36 (fatty acid translocase)
NPC1L1 – Niemann–Pick C1-Like 1 Protein
MTP – Microsomal Triglyceride Transfer Protein
ApoB48 – Apolipoprotein B48
LPS – Lipopolysaccharide
TLR4 – Toll-Like Receptor 4
NF-κB – Nuclear Factor Kappa B
IL-6 – Interleukin-6
TNF-α – Tumor Necrosis Factor-Alpha
BMI – Body Mass Index
HOMA-IR – Homeostatic Model Assessment of Insulin Resistance
GLP-2 – Glucagon-Like Peptide-2

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

Disclosure of conflict of interest

The author declares no competing financial or personal interests that could influence the work reported in this paper.

Author Contributions (CRediT Taxonomy)

Conceptualization: Tilahun Senbeto; Methodology: Tilahun Senbeto; Formal Analysis: Tilahun Senbeto; Visualization: Tilahun Senbeto; Writing – Original Draft: Tilahun Senbeto; Writing – Review & Editing: Tilahun Senbeto

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