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Incretins (GLP-1 and GIP) and the Microbiome

CREATED IN COLLABORATION WITH DR. RACHEL BURNETT

Introduction

The use of incretin analogs is skyrocketing and is projected to continue. These medicines bind receptors for glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP), which are gut-derived hormones released primarily in response to ingestion of glucose and fat.[1] Although GLP-1 and GIP analogs may have caught fire due to their ability to promote rapid weight loss, the influence of incretins is vast – playing a vital role in blood sugar regulation, metabolic and cardiovascular health, and neurological health, with new areas of activity indentified continuously. Although GLP-1 was discovered almost 40 years ago, research on these vital hormones is in the early stages – akin to the discovery of the microbiome 20 years ago.

Odds are you are actively treating patients taking GLP-1/GIP agonists or will be asked to provide information on how to support internal production of incretins. Regardless of your role, a strategy for whole-body health must be utilized to garner lasting results.

Foundational to whole-body health, of course, is gut health. The microbiome plays a central role, as it sets the stage for nutrient absorption, healthy levels of inflammation, proper immune function (both competence and tolerance), and digestive health. In fact, the microbiome is responsible for signaling the production and release of several GI peptides, including GLP-1 and GIP – making it a central consideration in the conversation.

Recent research highlights the intricate interplay between these gut-derived peptides, gastrointestinal health, and the gut microbiome, deepening our understanding of the microbiome's pivotal role in the optimal production and release of incretin hormones and the myriad ways they influence physiology.

The following quote from *Cell* articulates the importance of the relationship between the microbiome, gut health, metabolic health, and GLP-1.

> "Enteroendocrine cells (EECs) are specialized hormone-producing cells in the gut epithelium that sense changes in the intestinal milieu... Accordingly, microbial metabolites interact with the EECs to stimulate or suppress hormone secretion, which act through endocrine and paracrine signaling to regulate local intestinal and diverse physiological functions and impact overall host metabolism. The remarkable success of glucagon-like peptide-1-based drugs for treatment of type 2 diabetes and obesity highlights the relevance to investigate microbial regulation of EECs to tackle metabolic diseases through novel microbiota-based therapies."
>
> https://www.cell.com/med/fulltext/S2666-6340(21)00120-3

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Epidemiology

Incretin-related disorders are associated with **metabolic syndrome**, a cluster of conditions including type 2 diabetes mellitus (T2DM), obesity, polycystic ovarian syndrome (PCOS), and metabolic-associated fatty liver disease (MAFLD), as well as **cardiovascular conditions** such as hypertension (HTN), dyslipidemia, heart disease, and stroke.

The prevalence of metabolic syndrome is estimated to be a quarter of the population or over 1 billion people.[2]

A recent survey done by KFF Health Tracking Poll found that one in eight (12%) adults have taken a GLP-1 agonist, and 6% of adults are currently taking one for diabetes or prevention of heart attacks or stroke.[3] Of the adults that take these drugs:

- 43% have diabetes
- 25% have heart disease
- 22% are overweight or obese

There has been an increase in public awareness and use of incretin medications; however, high costs and low coverage from insurance present a barrier to use for many people.

Physiology and Clinical Relevance

INCRETIN PHYSIOLOGY

GLP-1 and GIP are peptide hormones released from the gastrointestinal mucosa in response to a meal. GLP-1 originates in enteroendocrine L-cells, and GIP is produced and released from K-cells.

Both peptides play a primary role in regulating glucose homeostasis. Although both enhance pancreatic insulin secretion, these sister peptides work slightly differently:[4]

GLP-1	GIP
• Enhances pancreatic beta cell insulin secretion • Stimulates enteric and autonomic reflexes (slows gastric emptying, stimulates vagal sensory neurons that regulate appetite) • Inhibits pancreatic α-cell glucagon secretion	• Enhances pancreatic insulin secretion • Stimulates pancreatic α-cell glucagon secretion (more effectively in fasting states)

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INCRETIN PHYSIOLOGY, CONTINUED

Because of the breadth of activities initiated by GLP-1 and GIP receptors, their analogs are being studied for a wide range of conditions. While these medications are being utilized primarily for diabetes and weight loss, phase 3 clinical trials are currently underway for:

- Chronic kidney disease
- Alzheimer's disease
- Heart failure with preserved ejection fraction
- Obstructive sleep apnea
- MASH/NASH
- Cardiovascular health
- Parkinson's disease
- Cancer
- Skeletal muscle wasting.[6]

INCRETINS AND DIABETES

Type 2 diabetes mellitus (T2DM) is characterized by the loss of GIP receptor (GIPR) function in both pancreatic α and β-cells and leads to reduced postprandial insulin secretion and hyperglycemia.[7]

GLP-1 is glucose-dependent. It only helps to lower blood sugar in the presence of elevated glucose levels, as seen in a postprandial phase. Once blood glucose is back at fasting levels, GLP-1 is degraded by the enzyme dipeptidyl-peptidase-IV (DPP-IV), preventing a hypoglycemic state.[5] For this reason, GLP-1 receptor agonists (GLP-1R), as well as DPP-IV inhibitors, are being used as therapeutic agents for the control and treatment of T2DM. Additionally, research shows that GLP-1 and GLP-1R agonists have the capacity to improve insulin and glucose sensitivity by increasing the functionality of pancreatic β-cells.[5]

INCRETINS AND OBESITY AND WEIGHT MANAGEMENT

Obesity is defined as a BMI over 30 kg/m2 with an excess of adiposity throughout the body.[8] It is a global epidemic associated with increased risk for metabolic syndrome as well as osteoarthritis, obstructive sleep apnea, gastroesophageal reflux disease, liver disease, cancer progression, and death.

In addition to regulating blood sugar and insulin resistance, GLP-1 can lead to weight loss by acting on peripheral and central receptors in the gut and brain to reduce gastric emptying time, thereby stimulating satiety and reducing food intake.[7]

The role of GIP in weight loss is not clear. It has long been associated with weight gain and obesity as it is released after consumption of nutrients and leads to fat deposition in adipose tissue. Conclusions about GIP and weight gain are being reconsidered, as studies have demonstrated that both antagonism and agonism of GIP receptors (GIPR) can reduce body weight.[9]

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INCRETINS AND OBESITY AND WEIGHT MANAGEMENT, CONTINUED

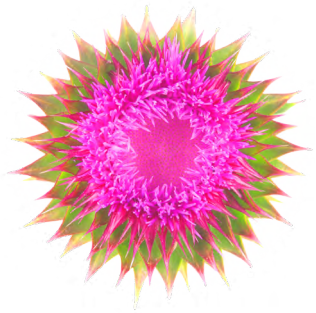
Further, the co-administration of GLP-1 and GIP receptor agonists (as seen with tirzepatide) acts synergistically on β-cell receptors and enhances weight loss, lowers BMI, waist circumference, postprandial and fasting blood glucose levels and reduces HbA1c more significantly than just using a GLP-1R agonist alone.[7]

INCRETINS AND CARDIOVASCULAR AND OTHER BENEFITS

GLP-1 and GIP have both direct and indirect effects on the cardiovascular system. GLP-1R and GIPR are found in cardiomyocytes and endothelial cells in the heart and blood vessels, while GLP-1R alone is found in vascular smooth muscle cells of blood vessels and the kidneys. They have cardioprotective, nephroprotective, and anti-inflammatory actions. Mechanisms linking GLP-1 and GIP to cardiovascular outcomes remain unclear. However, with their ability to reduce blood glucose, blood pressure, body weight, systemic inflammation, and post-prandial lipaemia, they influence favorable reductions in cardiovascular risks.

GLP-1 influences cardiovascular health in the following ways:

- Reduction of gut lipoprotein secretions
- Decreased platelet aggregation
- Reduced infarct size and improved ventricular function in those with myocardial infarction
- Diminished plaque burden and aortic inflammation
- Cardioprotective actions in those with ischemic cardiac injury[8]



GIP likely plays a role in the suppression of macrophage-driven inflammation and foam cell formation, leading to lower risks of atherosclerosis, hypertensive cardiomyopathy, and myocardial infarctions.[8]

INCRETINS AND NEUROINFLAMMATION

Metabolic syndrome involving insulin resistance is a major contributory factor in the development and progression of neurodegenerative conditions such as Alzheimer's Disease (AD) and Parkinson's disease (PD).[9] Insulin resistance (with or without the presence of T2D) in the brain alters localized glucose metabolism, leading to elevated blood sugar levels and unbalanced lipids in the blood, conditions which cause chronic neuroinflammation and increase the permeability of the blood-brain barrier (BBB). In response to a damaged BBB, microglial cells are activated into a pro-inflammatory state, releasing cytokines and reactive astrocytes that further contribute to the vicious cycle of neuroinflammation and hyperglycemia in the brain. Other neuroinflammatory consequences of brain insulin resistance include:[9]

- Vascular dysfunction, which can impede blood flow and has been linked to dementia
- Excessive production of nitric oxide causing toxicity and leading to nerve cell death
- Oxidative stress, which causes neuron loss and increases risks for dementia and neurodegenerative diseases
- Excessive mitochondrial respiration in the brain leading to an increase in ROS and activation of NF-κB

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INCRETINS AND NEUROINFLAMMATION, CONTINUED

In addition to addressing metabolic conditions, GLP-1/GIP pharmaceuticals are being studied for the treatment of neurodegenerative and neuroinflammatory conditions. Incretin receptors are prominent in neurons, microglia, and astrocytes across the brain. They help with peripheral insulin regulation by controlling eating behaviors and have been shown to have anti-inflammatory, neurotrophic, and neuroprotective properties.[10]

Rat hippocampal neurons treated with GLP-1 were more resistant to glutamate excitotoxicity, showed reversed inflammation-induced synaptic impairments by LPS, and were protected against amyloid-β-induced neurotoxicity. Additionally, mice with higher levels of GLP-1 had enhanced neural growth and differentiation, reduced memory impairment, improved cognitive performance, and improved motor abilities.[9]

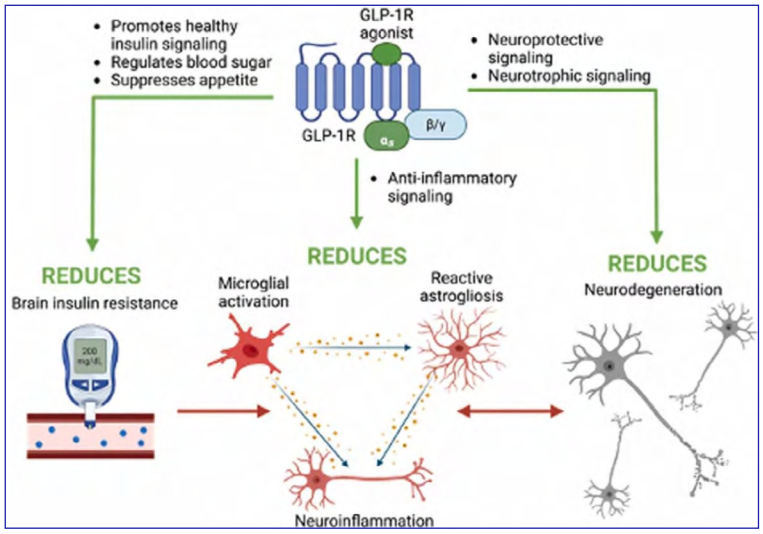

Figure 1. https://www.sciencedirect.com/science/article/pii/S1043661822004960

The Role of the Microbiome

The microbiome influences host GLP-1 production and release through a complex and dynamic combination of signaling pathways mediated by the EECs, shaping the gut-liver axis (GLA), production of short-chain fatty acids (SCFAs), and maintenance of the integrity of the intestinal epithelium.[10] The presence of a healthy microbiota affects L-cell differentiation and secretion of incretins and, as such, is required for normal GLP-1 production and release, in particular postprandial response.[11]

Research shows that the microbiome influences the physiology of incretins in several ways.

- **Bile Acids (BAs).** BAs are second only to ingesting macronutrients in stimulating the release of GLP-1. The microbiome modifies the GLA via cross talk and is essential for healthy bile production and release. BAs released by the liver into the small intestine are one way the GLA homeostasis is preserved.[12] They emulsify fats and act as antimicrobial agents to help control bacterial overgrowth in the small intestine. Unchecked overgrowth results in the overproduction of proinflammatory metabolites that drive many chronic diseases. In excess levels, secondary BAs can contribute to inflammation, cholestasis, gallstone formation, and carcinogenesis. In the presence of a healthy microbiome – which also acts upon xenobiotics and other endogenous toxins – the effects of secondary BAs are mitigated through the production of SCFAs, which exert an anti-inflammatory effect.[13]

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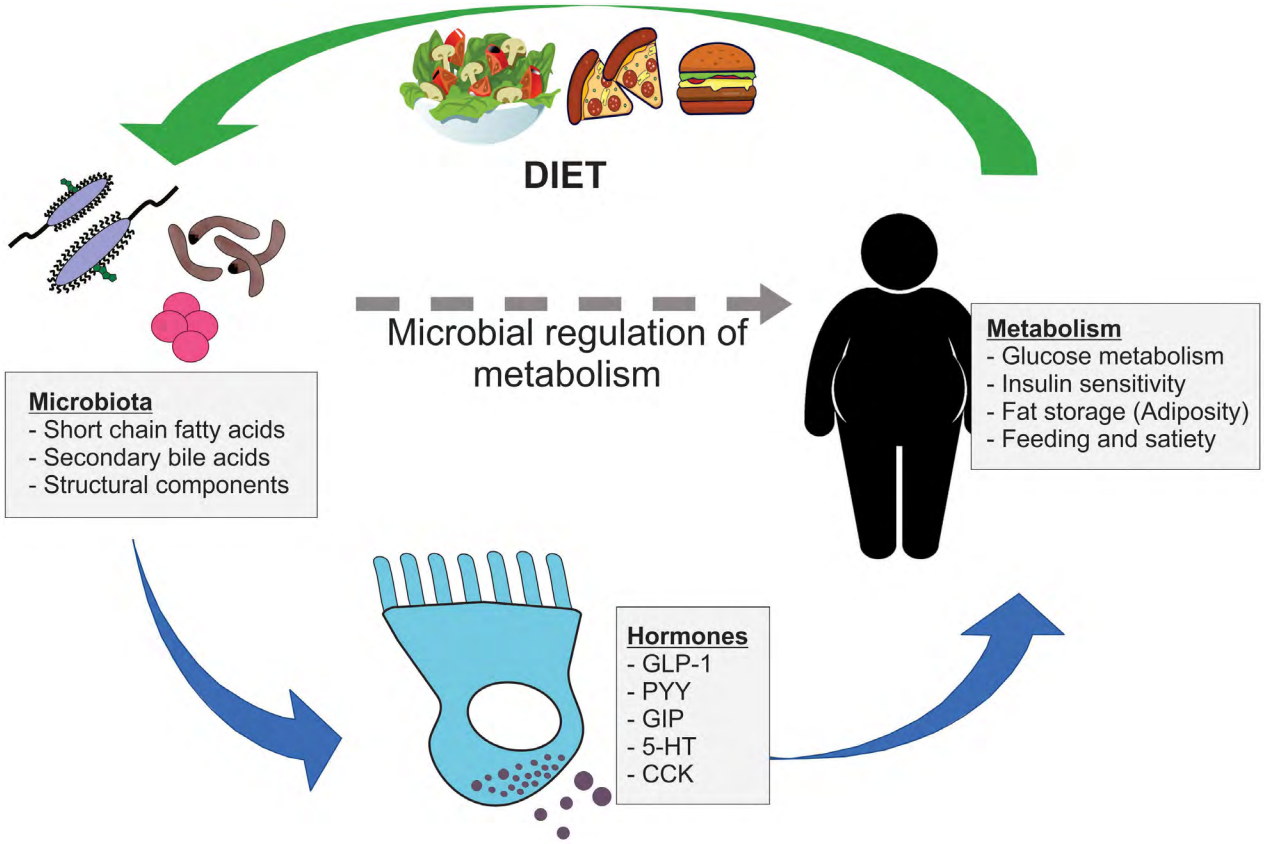
The Role of the Microbiome, continued

- **SCFAs.** In addition to exerting both local and systemic anti-inflammatory effects, SCFAs influence the production and release of GLP-1 and GIP. Butyrate has been shown to cause a transient increase in both of these incretins, while other SCFAs have mixed effects. More research is needed to identify the intricacies involved. Still, it is clear that a healthy microbiome plays a central role in maintaining healthy incretin signaling, mediated in part by the production of SCFAs.
- **Dysbiosis.** Damage caused by proinflammatory mediators generated in the presence of dysbiosis can affect the integrity of the GI epithelium, including enteroendocrine cells (EECs) responsible for the production of GLP-1 and GIP.[14]



https://www.frontiersin.org/journals/physiology/articles/10.3389/fphys.2019.00428/full

Figure 2. Microbial regulation of host metabolism via gut hormone release. Gut microbiota signal to nearby EECs via a range of microbial metabolites, including SCFAs and secondary bile acids, and structural components. These EECs release important metabolically active hormones, such as GLP-1, PYY, GIP, 5-HT, and CCK, which influence key metabolic processes including glucose metabolism, insulin sensitivity, adiposity, and feeding behavior. In turn, dietary components impact the composition of gut microbiota, which may have further downstream consequences on gut hormone secretion and host metabolism.[16]

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Clinical Pearl #1 – Help patients use appetite changes to establish a new and healthier relationship with food

Many patients show up having already tried to lose weight "the old-fashioned way." They may have a complex relationship with food, including yo-yo dieting, intense cravings, and/or disordered eating. Some have had years or even decades of restrictive eating and intense exercise – to no avail. They have likely experienced ongoing physical discomfort, bias, and/or shaming for carrying excess weight and may be experiencing punishing internal dialogue. This can result in extreme frustration, mental health issues, and doubt or despair. For this population, quieting the "food noise" can be an extraordinary relief – and this is one strength of working with GLP-1 agonists and/or increasing endogenous GLP-1.[16]

Research suggests that GLP-1 receptor binding in the brain results in neuroplasticity, showing neuroprotective, neurotrophic, and neuroregenerative activities.[17] Neuroplasticity creates an opportunity to shed entrenched signaling and create new neurological connections. That means that working with GLP-1/GIP agonists could help lift mental struggles related to diet and set the stage for redefining patients' relationship with food. Helping patients learn to focus on eating foods that nourish the body and the microbiome during this time could help to rewire the neurological pathways so that long-term diet and lifestyle changes – and health – are sustainable. For more information about nutrition to support a healthy gut, see our Microbiome Diet.

Clinical Pearl #2 – Support gastric motility, gallbladder, and pancreatic function

Slowed digestive function – whether originating in the stomach, the gallbladder, or the pancreas – can be an underlying contributor to, or even the root cause of, a myriad of diseases. The resulting inflammation and irritation of the intestinal epithelium can disrupt the EECs responsible for producing and releasing incretins.

Patients taking GLP-1/GIP analogs, especially at a high dose, often experience delayed gastric emptying and cholestasis – making matters worse. These activities are the cause of the most common side effects of these pharmaceuticals, including nausea, vomiting, diarrhea, and constipation.[18]

One of the benefits of botanicals and nutrients is their ability to support healthy physiology through multiple pathways. A single herb may offer relief from nausea, promote the release of bile, and support healthy motility. Utilizing a combination of botanicals with synergistic and complementary activities can further augment their therapeutic effect.

Including select botanicals to support the production and release of bile and pancreatic enzymes may help mitigate the side effects of incretin mimetic therapies. They simultaneously support the GLA and a healthy gut lining for those looking to promote the natural production of GI peptides across the spectrum.

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Clinical Pearl #3 – Addressing "Non-Responders" by Identifying and Treating Underlying Causes

BY DR. RACHEL BURNETT

Clinical studies indicate that approximately 13% of participants using semaglutide[19] and 9% using tirzepatide[20] are classified as non-responders, defined as individuals who do not lose 5% or more of their body weight within the first three months of treatment. While this metric may not align with the endpoints we prioritize for our patients, it underscores the variability in individual responses to these therapies.

Further research is necessary to elucidate the factors contributing to this variability. However, as clinicians, we can enhance patient outcomes by focusing on overall wellness and tonifying underlying systems in conjunction with GLP-1/GIP agonist therapy.

Current studies are exploring the effects of higher dosing regimens,[21] but the adage "bigger is better" may not always apply. It is crucial to listen to our patients, understand their unique challenges, and identify individual obstacles to success. Addressing these factors can also mitigate common side effects associated with these medications, such as nausea and sarcopenia.

For treatment details, please see "Key Strategies for Supporting Patient Outcomes" on page 11.

Clinical Pearl #4 – Include Detoxification Support

Incretin analogs result directly in delayed gastric emptying and reduced food intake.[22] Because ingestion of food and the deposition of stomach contents into the small intestine initiate a multitude of digestive processes, these therapeutics may disrupt the regulation of gastrointestinal hormones[23] – including activity in the biliary tract such as the release of bile and pancreatic enzymes. The release of toxins in bile is one major route of toxin excretion from the body.

Additionally, adipose tissue serves as a reservoir for fat-soluble toxins. Rapid weight loss may mobilize toxicity at a rate that overcomes the physiological threshold of the innate detoxification pathways in the liver, kidneys, and GI tract. It is plausible that these phenomena may contribute to the serious side effects experienced by some people when using incretin medications.

Microbial dysbiosis can be a major contributor to total toxic load, negatively impacting the physiology of detoxification in a number of ways – disrupting the GLA and SCFA production and increasing microbial metabolites such as lipopolysaccharides.

In addition to restoring microbial balance, supporting optimal toxin elimination during weight loss is advisable. This can be achieved through the use of nutritional support for detoxification pathways, as well as binders to eliminate toxins and microbial debris through stool excretion.

For more information, see our Detoxification Protocol.

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Treatment Recommendations

- **Bioclear® Microbiome Detoxification Program** contains three products designed to provide a microbial reset. This program acts to remove harmful organisms, bind microbial debris and toxins, and restore beneficial species to the GI tract.
- **G.I. InnerCalm®** contains botanicals and nutrients to support health in the upper and lower GI tract with immediate soothing effects, as well as long-term rebuilding of the GI mucosa. It includes ginger, which can reduce nausea, assist gastric emptying/ healthy motility, and promote healthy gallbladder function.
- **Biotonic®** contains two ancient Chinese formulas to tonify immune and digestive chi. It can be used acutely for nausea and slowed digestion that sometimes results from the use of incretin analog therapy.

Therapeutic Plan Suggestions

Support for Endogenous Incretin (GLP-1/GIP) Production		
Bioclear® Microbiome Detoxification Program **Choose Biocidin® Liquid, Capsules, or LSF to use in your program.**		
Biocidin® Liquid Titrate to 10 drops 2x/day per booklet instructions	Biocidin® Capsules Titrate to 2 capsules 2x/day per booklet instructions	Biocidin® LSF Titrate to 2 pumps 2x/day per booklet instructions
G.I. Detox®+	2 capsules at bedtime. 1 hour away from food, supplements, and medications. Temporarily increase dose to 2 capsules 2-3x/ day if Herxheimer reaction observed/worsens.	
Proflora® 4R	1 capsule any time of day	
ADDITIONAL SUPPORT (sold separately)		
G.I. InnerCalm®	1 stick pack mixed in water, 1-2 times daily, taken any time	

*These statements have not been evaluated by the Food and Drug Administration. These products are not intended to diagnose, treat, cure, or prevent any disease.

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Support for Those Using GLP-1/GIP Agonists	
CORE PROTOCOL	
G.I. Detox®+	2 capsules at bedtime. 1 hour away from food, supplements, and medications. Temporarily increase dose to 2 capsules 2-3x/ day if Herxheimer reaction observed/worsens.
Biotonic®	40-60 drops with meals and as needed for nausea/diarrhea
G.I. InnerCalm®	1 stick pack mixed in water, 1-2 times daily, taken any time
Proflora® 4R	1 capsule any time of day

Botanicals and Nutrients to Support Digestion and GLP-1 Therapy

Botanical/Nutrient	Key Actions*
Artichoke	Stimulates bile flow, enhances fat digestion, supports detoxification and liver health
Milk Thistle	Enhances absorption, protects the liver, supports detoxification and digestion
Turmeric	Helps support & stimulate bile flow, protects and supports the liver
TUDCA	Supports healthy bile flow and gallbladder health, protects and supports the liver, thins bile
Ginger	Improves production and flow of bile, promotes gastric emptying and reduces intestinal transit time, helps ease indigestion, belching, gas and feelings of fullness after eating

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Key Strategies for Supporting Patient Outcomes

BY DR. RACHEL BURNETT

- Adopt a "start low, go slow" approach and closely monitor patient responses. Their reactions provide valuable insights into how best to support their treatment journey.
- Consider utilizing GLP-1/GIP analogs as an adjunct to foundational lifestyle modifications rather than as stand-alone solutions. The combination can significantly improve outcomes. This aspect of care is often overlooked, and by highlighting lower-force interventions, we can help patients overcome the "non-responder" barrier.
- The following diet, lifestyle, and supplementation suggestions can support the endogenous production of GLP-1 and GIP. They are helpful for anyone with concerns about metabolic health and can also be used to support patients using incretin analogs in optimizing outcomes or to achieve results at a lower dose.

Nutrition. At mealtime, sit down, chew your food, and surround yourself with people you love. As well as reducing stress, this helps modulate some of the side effects experienced with the use of incretin therapies.

Information to help patients tailor diet choices for success:

- Protein and fat improve satiety.
- Fat and carbohydrates stimulate the release of GLP-1. Make them healthy fats and carbs!
- Carbohydrates should be:
    - Complex rather than simple.
        - These take longer to digest and absorb, have a lower glycemic index, and tend to be higher in fiber than simple carbohydrates.
    - High in fiber.
        - Carbohydrates high in fiber provide prebiotics for beneficial microbes in the gut, and the production of SCFAs, which stimulate the release of GLP-1.
    - Nutrient dense.
        - In addition to being a source of vitamins and minerals, fruits and vegetables contain phytonutrients such as polyphenols, an important category that includes phenolic acids, lignans, stilbenes and tannins, and flavonoids such as catechins, anthocyanins, quercetin and hesperidin. These nutrients have prebiotic, anti-inflammatory, immune supportive, and antioxidant effects, all of which support metabolic as well as overall health. Many of them stimulate the release of GLP-1 through a variety of mechanisms.

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Key Strategies for Supporting Patient Outcomes, continued

Exercise. Exercise increases the same hormones that these medications mimic in the body. Get daily movement – if only for 10 minutes. Include resistance and strength training 3 days/week to maintain muscle mass.

Sleep Optimization. Ensure adequate and regular sleep habits for an optimal sleep window.[24]

Address Gut Health. The gut microbiota plays a critical role in regulating obesity. Interventions aimed at improving gut health enhance the efficacy of incretin therapies through regulation of energy absorption, appetite, fat storage, chronic inflammation, and circadian rhythms.[25]

Hormone Replacement Therapy (HRT). Consider the use of HRT when appropriate, as studies have shown that hormone replacement in postmenopausal women is associated with improved weight loss outcomes with a GLP-1 analog.[26]

Supplement Recommendations

RECOMMENDED BY DR. RACHEL BURNETT

Product/Ingredient	Key Actions*
Berberine	Increases GLP-1 and makes positive changes to the microbiome for weight loss[27]
Polyphenolic compounds	Consider additional supplementation to augment dietary intake[28]
Prebiotics and/or probiotics	To support *Bifidobacteria infantis, Akkermansia mucinophila* and *Clostridium butyricum*[29]
Butyrate	A SCFA (postbiotic) that stimulates the release of GLP-1, can be supplemented[30]
GABA	Can reduce glucagon secretion and stimulate GLP-1[31]
Allulose	A natural sugar replacement, stimulates GLP-1 and activates neurons that respond to GLP-1. Use as a 1:1 substitute for sugar in recipes or exactly how you would use sugar.[32]
Yerba Mate	May induce satiety by stimulating GLP-1 secretion and modulating serum leptin levels[33]

Questions?

For clinical questions, email clinical@biocidin.com

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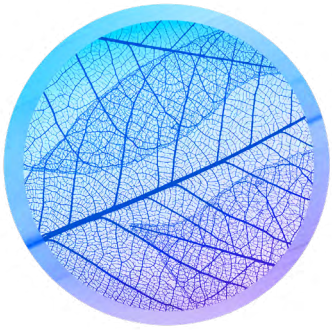

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