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Twincretins and the Gut Microbiome: The Missing Link

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The novel treatment for type-II diabetes mellitus (T2DM), obesity, and associated metabolic dysfunctions is based on the insulinotropic actions of the two gut incretin hormones, glucagon-like peptide-1 (GLP-1) and the gastric inhibitory polypeptide (GIP), together known as twincretins. GLP-1 is primarily secreted by the small intestine and colon. While GIP is secreted from the duodenum and proximal jejunum. Both are secreted in response to a meal [1].

The human microbiome is composed of healthy bacteria, viruses, and microbes that boost metabolism and immunity and protect against pathogenic organisms. These also break down dietary fibers into metabolites that directly stimulate the endogenous release of incretins, which further regulate appetite and blood sugar [2].

Few studies demonstrate that twincretins promote a healthier microbial ecosystem. This results in an abundance of healthy gut bacteria like *Bifidobacterium, Akkermansia muciniphila,* and *Bacteroides*. This regulates appetite and blood sugar [3]. However, it is unclear how the gut microbiome may regulate insulin resistance, glucose control, and metabolic health. This is such an interesting and very beneficial link in many ways. Twincretins strengthen the gut lining, decreasing its permeability, which results in less penetration of harmful bacterial endotoxins into the body and hence lowers inflammation [4]. Twincretins also enhance gut microbiota and affect the adipokine pathway, altering fat metabolism [5]. Twincretins also alter bile acid metabolism, which helps reduce liver lipid deposition, thus helpful in managing Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD) [6].

This bidirectional relationship between the gut microbiome and twincretins is far more beneficial in patients with obesity, diabetes, and metabolic dysfunctions. While twincretins suppress inflammation and alter bacterial diversity, gut microbes are responsible for drug metabolism and the release of endocrine hormones [1-3].

Recent limited studies correlate poor metabolism with a decrease in bacteria. The most missing healthy bacteria include *Akkermansia muciniphila, Faecalibacterium prausnitzii, Bacteroides,* and *Bifidobacterium* [1-5].

The dynamic triangular relationship among twincretins, microbial composition, and metabolism is the basis for future therapies on obesity, associated metabolic dysfunction, and diabetes. In the future, routine microbiome profiling could predict a patient's response to incretin drugs, allowing clinicians to tailor treatments using targeted prebiotics or probiotics. Your baseline microbial composition dictates how effectively your body responds to twincretins. The people with healthy bacteria will have improved insulin sensitivity as well as GLP-1 secretion. Individuals with fewer healthy bacteria may show "GLP-1 resistance". This severely affects weight-loss and glucose-lowering potential [1, 2].

The future of weight loss therapies lies in the emerging field of pharmacomicrobiomics. A personalized treatment approach will work for every patient rather than one approach for all patients, like microbiome profile, which should be checked in every patient to predict the exact response to twincretins. Secondly, twincretins should be combined with precise prebiotics or probiotics to potentiate the gut's healthy microbiome in advance. This will surely increase twincretin's effect and hence personalized metabolic dysfunction, diabetes, and weight management [1-5].

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