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Letters to the Editor
https://doi.org/10.63501/r3s57m93

From Metformin to Microbiome: The Missing Links in Metabolic Modulation

Dear **Editor**,

Type 2 diabetes mellitus (T2DM) is a chronic condition characterized by insulin resistance and impaired glucose metabolism. Recent studies indicate that the gut microbiota might be a significant contributing factor to the pathogenesis of T2DM. Changes in microbial composition, known as dysbiosis, influence energy homeostasis, obstruct the intestinal barrier's operation, and promote low-grade inflammation [1]. Diabetic individuals usually have a lower microbiota of beneficial bacteria and a greater prevalence of detrimental bacterial species. The gut microbiota's modulation of bile acid metabolism, short-chain fatty acid (SCFA) production, and incretin hormone secretion affects insulin sensitivity [2].

Metformin, often given as a first-line medication for T2DM, mainly lowers blood glucose levels by boosting insulin sensitivity and reducing the production of glucose by the liver. However, recent evidence points to its hypoglycemic role via the modification of gut flora. Studies show that metformin promotes the growth of beneficial microorganisms in the gut wall. These microbial changes help improve glucose metabolism, boost gut barrier integrity, and reduce inflammation [3].

Since metformin accumulates in the intestine at concentrations 30–300 times higher than those in plasma, its therapeutic effect via microbiota modification cannot be overlooked. Metformin encourages the growth of bacteria such as Bifidobacterium and Akkermansia, producing short-chain fatty acids and upholding intestinal barrier integrity. These microbial changes also enhance the activity of GLP1, a pro-hypoglycemic chemical messenger produced in the intestinal epithelial cells [4]. Recent experiments on animals have proven that when a metformin-modified gut microbiota was transferred to the gut of a sterile mouse, it showed a marked reduction in glucose concentration in the plasma and insulin resistance [5]. Considering all factors, these data suggest that the benefits of metformin go beyond its conventional mechanisms and include a complex interaction with the gut microbiota.

Although metformin's impact on the gut microbiota is well known, most of the evidence available comes from animal models rather than human studies. Many conclusions are derived from mouse experiments, the results of which may not be entirely applicable to the human body. Human studies available in this regard are scant and small-scale. Moreover, protracted and regulated human trials assessing the effects of gut microbiome on the overall physiology of the body are still lacking [5]. Methodological differences between the studies make cross-study comparisons much more difficult. It is unknown which particular bacterial species is responsible for which beneficial or hazardous effect on the body.

To sum it up, variations in the gut bacteria are a contributing cause of metformin's impacts on T2DM. Though promising, there is a lack of excellent human evidence, and the bulk of supporting information originates from animal research. Future studies should primarily concentrate on protracted, thorough human tests. Multi-omics methods might help us to understand the functional host–microbiome interactions better. This could open a new horizon in the treatment of T2DM devoid of the nuances of conventional long-term pharmacotherapy and the associated adverse effects.

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Fahad Amin

King Edward Medical University, Lahore

Corresponding Author Email: fahadamin2003kemu@gmail.com