Editorial

Interaction of anti-diabetic medications and gut microbiota

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TABLE OF CONTENTS

The human gut microbiota is a complex microbial community that has about 10^{13} to 10^{14} microorganisms residing in the intestinal mucosa [1]. This large microbial community forms a symbiotic relationship with the human body and plays various essential roles in food digestion and intestinal homeostasis of the host. Studies have suggested that the intestinal microbiota may correlate with host metabolic status, and intestinal dysbiosis has been linked to the development of type 2 diabetes (T2D) [2, 3]. Because of these associations, medical interventions can in turn largely affect the composition of gut microbiota [4]. In a recent issue of this journal, Xourgia E *et al.* [5] provided a comprehensive review discussing the current understandings on the effects of anti-diabetic drugs on gut microbiota, and possible mechanisms of current anti-diabetic drugs acting on gut microbiota.

Gut microbiota has a major metabolic role in the gut lumen, including nutrient, xenobiotic and drug metabolisms, and these microbial metabolites may significantly influence human health and diseases [6]. As such, the normal gut microbiota ecosystem is pivotal in maintaining human metabolic homeostasis and regulating glucose metabolism. Imbalance in the microbiota composition or bacterial metabolic activities can cause dysbiosis, which could profoundly affect the physiopathology of various metabolic diseases, including T2D. The study by Xourgia E *et al.* [5] summarized two potential mechanisms by which gut microbiota could contribute to the pathogenesis of T2D, i.e., through the dysregulation of mucosal integrity and via bacterial metabolites.

The integrity of intestinal mucosa is maintained through mucus secretion and a monolayer of epithelial cells with intercellular tight junctions. During intestinal dysbiosis, the mucosa integrity may be compromised and become leaky, enabling the invasion of macromolecules (such as bacterial lipopolysaccharides (LPS), antigens and other endotoxins) into systemic circulation. When LPS cross over the mucosa barriers and enter the circulation, it can act through CD14 and toll-like receptor 4 (TLR4) to promote the secretion of pro-inflammatory cytokines, thus triggering low-grade chronic inflammation and oxidative stress that can deteriorate the conditions of T2D.

Another mechanism linking intestinal dysbiosis and T2D is through bacterial metabolites that participate in glucose metabolism, including short-chain fatty acids (SCFA), secondary bile acids, and branched chain amino acids (BCAAs). In normal gut microbiota, microbes can perform fermentation on non-digestible polysaccharides into SCFAs (including acetate, propionate and butyrate). SCFAs are beneficial to the gut health through maintenance of intestinal barrier integrity, mucus production, and protection against inflammation [7]. In addition, SCFAs can bind to G protein-coupled receptors to stimulate secretion of glucagon-like peptide 1 (GLP-1), peptide YY, and insulin, all of which can regulate energy homeostasis and glucose metabolism [7]. The gut dysbiosis associated with T2D has lower abundance of butyrate-producing bacteria, which may negatively impact the mucosa barrier functions and glucose metabolism. An important function of the intestinal microbiota is converting primary bile acids to secondary bile acids. These bile acids are involved in regulating the secretion of GLP-1 and expression of farnesoid X receptor (FXR), thus affecting glucose and fat metabolism. Gut microorganisms are a potential source of circulating BCAAs through both microbial biosynthesis and modification of nutrient absorption [8]. Consequently, dysbiosis of the microbiota is likely to affect the microbial amino acid metabolism and thereby contribute to the development of

insulin resistance [9]. Studies have demonstrated that both dietary intake of BCAAs and high plasma levels of BCAAs are associated with an increased risk of T2D [10].

Gut microbiota play indispensable roles in drug metabolism. Several classes of anti-diabetic drugs may have possible effects on gut microbiota [5]. The first line treatment for T2D is metformin, which is thought to activate adenosine monophosphate-activated protein kinase in the liver, causing hepatic uptake of glucose and inhibiting gluconeogenesis to exert its glucose-lowering effect. Recently, emerging evidence have suggested that part of the glucose-lowering effect of metformin is mediated by the gut microbiota through reshaping the composition and activities of the intestinal bacteria [5].

Several recent studies have found that metformin modified the gut microbiota composition and improved T2D related dysbiosis. Metformin treatment was associated with compositional and functional microbiome shifts in T2D patients [11]. Patients treated with metformin had considerably higher abundance of SCFA-producing bacteria (*Escherichia spp*.), which can produce butyrate and propionate, improve glucose homeostasis, and result in glucose-lowering effect [11]. By reshaping the gut microbiota, metformin may exert glucose-reducing effects through multiple mechanisms, including; (1) regulating the intestinal glucose uptake and glucose homeostasis; (2) promoting the SCFA producing bacteria; (3) promoting the mucin-degrading bacteria; (4) increasing the gut hormone GLP-1 secretion; (5) regulating the bile acids metabolism; (6) maintaining the integrity of the intestinal barrier [12].

In addition to metformin, there are several other classes of medications with different mechanisms of action for pharmacologic management of T2D. The interaction of these anti-diabetic drugs with gut microbiota have been less studied. Similar to the findings from metformin, a few available studies also implicated the involvement of gut microbiota as a likely mediator for drug action [5].

In summary, the human gut microbiota has recently been emerging as an important environmental factor in a wide array of diseases. It is now well-accepted that the intestinal dysbiosis contributes to the pathogenesis of T2D. Moreover, there is also evidence that T2D can induce dysbiosis of gut microbiota. The cause-effect relationships of dysbiosis and T2D are complex and remain to be elucidated. It is very likely that this is a two-way interaction. Similarly, anti-diabetic medications could also act on the gut microbiota to improve glucose homeostasis, and thus the gut microbiota may further affect the efficacy of drug treatment. Future research should examine the specific mechanisms of action of the drugs to understand how drugs induce gut microbiota modulation and how such modulation leads to improvement of glucose homeostasis.

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RC and SP wrote the manuscript; all authors approved the final version of the article.

2. Ethics approval and consent to participate

Not applicable.

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5. Conflict of interest

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