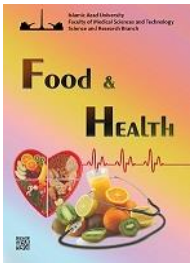

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Probiotics and glycemic control: A simplified interplay model for the pathways behind

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ABSTRACT

The link between gut microbiota composition, insulin resistance, and diabetes has been recently proposed. As such, the impact of probiotics on improving glycemic control has been reported recently. Although probiotics have attracted much interest as a complementary approach to improve glucose metabolism, the mechanisms underlying their actions remained to be determined. Hence, here we aim to review the mechanisms by which the probiotics might affect glycemic control. Probiotics improve glycemic control through diminishing fermentation of polysaccharides, suppressing inflammation, act as bile acid de-conjugate hydrolase, increase the bioavailability of Gliclazide drugs and changes in incretin secretion. However, the pathway behind the effect of probiotics on glycemic control is complex with many interplay interactions. The involvement of multiple mechanisms may explain the ambiguities in determining the exact mechanism that is behind this effect.

Introduction

Type 2 diabetes is a major metabolic disorder increasing worldwide. The mechanisms related to type 2 diabetes have been at the center of research in the last decade. In this regards, the gut microbiota is known to play a significant role in type 2 diabetes. The type and count of gut microbiota composition differ between type 2 diabetics and healthy individuals (1). The direct contribution among gut microbiota composition, insulin resistance, and diabetes has been recently proposed (2, 3). As such, the use of probiotics to improve hyperglycemia as an innovative therapeutic approach has been reported (4-6). To date, several randomized controlled trials have been conducted to assess the effects of probiotic on glycemic control (5, 7-9), however, results are controversial. Probiotics consumption demonstrated beneficial effects on improving glycemic control among pregnant women (5) and type 2 diabetics (9), while, another randomized controlled trial investigating the efficacy of probiotics (8, 10, 11) described no significant improvement. The impact of probiotics in modulating glucose homeostasis in animal and human studies has been well reviewed in systematic review and meta-analysis study before (4, 12). Altogether, it is well documented that probiotics are able to improve glycemic control at a modest level. Although probiotics have attracted much interest as a complementary approach to improve glucose metabolism, the mechanisms underlying their actions remained to be determined. Animal model studies and human clinical trials have attempted to elucidate the mechanism behind this effect (5, 9, 13). In this regard, several pathways were identified to attenuate glycemic control such as inflammation suppression (13, 14), changes in secretion of gut hormones (15) and changes in the harvest of energy (16). Yet, it is important to keep in mind that the glycemic modulation is affected by several key elements such as inflammation, insulin resistance and adiposity, which are linked and interact together. Hence, here we aim to review the mechanisms by which the probiotics might affect glycemic control. Moreover, we attempt to explore an interplay model on the possible interactions between these pathways. This will provide a framework to consider approaches that might help to improve the glycemic control in type 2 diabetic individuals. The main known mechanisms by which the probiotics affect glycemic control are as follows:

1. Suppressing inflammation

Type 2 diabetes is an inflammatory disease (17). The direct correlation between the low grade of inflammation and

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pathogenesis of type 2 diabetes was demonstrated (18). This hypothesis opens new horizons in the management of type 2 diabetes. Probiotic supplementation has been shown to suppress inflammation through in vivo studies (13, 14, 19). As such, inflammation suppression has been presented as the first step in recognizing a role for probiotics in managing glycemic control. Reduction in level of inflammatory mediators activates signaling pathways resulting in insulin sensitizer which subsequently leads to a decrease in insulin resistance and improve glycemic control (20-22). The effects of probiotics on glycemic control through modulation of inflammation are classified into two modes of action: a) indirectly, through improving the gut integrity, and b) directly by functioning as an antioxidant. These mechanisms are highlighted in the following paragraphs.

2. Suppressing inflammation through the improving gut barrier

Several aspects of the modern lifestyle such as high fat diet (23), high carbohydrate diet and sedentary lifestyle have the potential to change the composition of gut microbiota toward being Firmicutes-dominant (24, 25). These phenotypes decrease gut integrity and increase gut permeability, promoting freeing lipopolysaccharides (LPS) and free fatty acids (FFA) in the blood and peripheral tissues (26, 27). LPS and FFA are detected by toll-like receptors (TLR) at the surface of immune cells including T lymphocyte, monocyte, and macrophage (28). TLR comprise a family of cell surface protein receptors that their activation leads to induction of inflammatory responses and this interaction promotes the release of inflammatory markers such as Tumor Necrosis factor α (TNF-α) and interleukins from immune cells (28). Inflammatory cytokines, especially TNF-α has been shown to inhibit the insulin signaling pathway and supposed to be the primary trigger for insulin resistance mechanism (25). Moreover, blood FFA is being transported in adipose tissue and leads to either hypertrophy or hyperplasia of adipose cells. The hypertrophic/hyperplasic adipose tissue has been shown to express high levels of biochemical substances. These substances have the ability to recruit monocyte-macrophages toward the hypertrophic fat tissue and attenuate local inflammatory mechanisms (17). Administration of probiotics has been shown to regulate gut permeability by stimulating the secretion of host gut peptides such as glucagon-like peptide 2 (GLP-2). GLP-2 is responsible for the effective protection of gut integrity (29). Selective gut microbiota structure controls and increases endogenous GLP-2 production, which consequently improves gut barrier functions by a GLP-2-dependent mechanism and contributes to the improvement of gut barrier functions (27). Improving gut permeability through probiotic administration has been associated with decreased serum levels of TNF-α and other cytokines such as interleukin-6 (30, 31). Reducing the levels of inflammatory markers decreases insulin resistance and improves insulin sensitivity, which is inversely related to B-cells function. β-cell function improvement promotes insulin secretion and resulting in better glycemic control (32).

3. Suppressing inflammation through antioxidant-like activities

Oxidative stresses play essential roles in the pathogenesis and progression of diabetes (33). The total antioxidant status of type 2 diabetes is lower than healthy individuals (34). Free radicals are produced in an excessive amount in type 2 diabetic individuals. Free radicals cause lipid peroxidation and produce inflammatory cytokines (35). Different strains of probiotics have been reported to act as antioxidant and repress oxidative stress (36-38). The antioxidative mechanisms of probiotics can be contributed to reactive oxygen species scavenging, metal ion chelation, enzyme inhibition, and the reduction activity and inhibition of ascorbate autoxidation (39). In the human model of type 2 diabetes, multistrain probiotic supplementation has shown to increase total antioxidant status, as well as serum levels of different antioxidants such as erythrocyte glutathione, reeducates, erythrocyte superoxide dismutase and glutathione peroxidase (37, 38). Hence, probiotics can scavenge free radicals and suppress inflammation, which leads to improving insulin resistance and glycemic control.

4. Changing the gut hormones

It has been well established that the structure of gut microbiota is directly related to the secretion of GLP-1 (40, 41), and GLP-2 (27, 40). GLP1 is a peptide which originates from enteroendocrine cells of the gut and usually circulating in the blood in the form of GLP17-36 amide (42). GLP1 exerts multiple physiological actions include stimulation of insulin secretion, decreasing hunger and controlling energy intake, as well as decreasing gluconeogenesis which lead to control energy intake and glycemic control. These functions (42). GLP2 is a 33–amino acid peptide secreted with GLP1 from enteroendocrine cells in a nutrient-dependent manner. GLP2 rapidly induces hexose transport in jejunal basolateral membrane vesicles leading to the expansion of the mucosal epithelium in the small bowel (43), making it a suitable candidate for maintaining the gut integrity. Considering the link between gut microbiota structure and secretion of gut hormones, manipulation of gut microbiota by probiotics could efficiently alter the secretion pattern of the gut hormones. The pathway in which GLP-2 hormone is involved was earlier discussed in improving gut barrier function and suppressing inflammation. Here, we continue to explore the role of GLP-1 in affecting glycemic control. Short chain fatty acids (SCFAs) driven from gut microbiota affect proliferation, differentiation, and modulation of gene expression in colonic epithelial cells (44). In addition, SCFAs can regulate gene expression by binding to the G-protein-coupled receptors. Signaling through these receptors affects the secretion of the GLP-1 which improves insulin secretion (15, 45). Improving insulin secretion directly will affect glycemic control. In addition, GLP-1 decreases hunger and increasing satiety which leads to

decreasing energy intake and improving glycemic control (40, 46). The GLP-1 hormone also improves glycemic control by inhibiting the gluconeogenesis leading to reduction of monosaccharide flow into the bloodstream which ultimately improves glycemic control (47). In conclusion, probiotic administration modulates gut microbiota composition in favor of GLP-1 and GLP-2 secretion. Secretion of these hormones affects glycemic control via different pathways. Modulation of other types of gut peptides involved in appetite regulation, such as leptin and peptide YY, could be another mechanism by which the gut microbiota might control energy and glucose homeostasis (29). However, there is limited evidence regarding this link in the context of metabolic modulation of glucose control.

5. Manipulation of the harvest of energy

Carbohydrates are important sources of energy for human and microbial cells. Human enzymes cannot degrade more complex carbohydrates and plant polysaccharides. These carbohydrates are fermented in the colon by its microbiota to yield energy for microbial growth and end products such as SCFAs (48). Animal model studies revealed that the gut microbiota capacity for energy harvest is higher in obese as compared with lean (49). For example, fermentation of dietary fructans increases when mice have been colonized with probiotics from Bacteroides phylum (50). Colonization of germ-free mice with obese microbiota results in a significantly greater increase in total body fat than colonization with a lean microbiota (49).

These interactions promote carbohydrate fermentation more efficiently and increase energy absorption from the gut, resulting in more adiposity. In a human study, the fecal microbiota of obese individuals has an increased capacity to harvest energy (49). The role of the gut microbiota in promoting energy harvest from diet and fat deposition has been demonstrated in mice (16), but most of the evidences in humans have come from indirect studies. Therefore, it can be hypothesized that manipulating the gut microbiota by probiotics changes the harvest of energy in favor of decreasing adiposity (16). Less adipocyte means less inflammation and insulin resistance, which leads to better glycemic control. However, changes in the harvest of energy can affect glycemic control through a more direct pathway. The new gut microbiota structure developed by beneficial microbes has less capacity for fermenting dietary polysaccharides, indigestible by human enzymes. So, less polysaccharide will be added to the pool of gastrointestinal absorbable glucose and will positively affect glycemic control (51). Although many theoretical hypotheses proposed the role of probiotics in the harvest of energy, the changes in the energy elucidation pattern after probiotic consumption in the context of a clinical trial remained to be determined. Thus, whether the subtle theoretical explanation can translate to clinically meaningful outcomes remains elusive.

6. Bile acid deconjugation and activation of Farsenoid X receptor

It is well recognized that some members of the gut microbiota, mostly Lactobacilli and Bifidobacteria, are known to possess the bile salt hydrolase enzyme and have the ability to de-conjugate bile salts (52, 53). The action of de-conjugated bile acids activates several bile acid signaling pathways, most importantly, nuclear Farsenoid X Receptor (FXR) (54). The FXR is a member of the nuclear receptor family, which is primarily expressed in liver, kidney, and intestine. FXR has a predominant regulatory role in glycemic control. FXR- null mice demonstrated high blood glucose and insulin resistance while activation of it suppressed gluconeogenesis and decreased blood glucose (55). Activation of FXR improves glycemic control through three different ways. (a) Repressing expression of gluconeogenic genes and increasing glycogenesis, which results in serum glucose reduction (55, 56). (b) Decreasing FFA and improving peripheral insulin resistance (55, 57) that ultimately lead to improved glycemic control. (c) Bile acids also are responsible for the secretion of incretins including GLP-1 and GLP-2 (58) which can modulate glycemic control through controlling hunger, stimulating insulin secretion, suppressing gluconeogenesis as well as reducing inflammation (These mechanisms have been discussed in detail earlier in “changing gut hormones” session).

7. Improving the bioavailability of Gliclazide drugs

Another pathway for the hypoglycemic activity of probiotics can be attributed to their ability to increase the bioavailability of Gliclazide drug (59). Al-Salami et al., measured Gliclazide serum concentration on healthy and Alloxan induced type 1 diabetic rats supplemented with probiotics (59). They found that probiotic supplementation increased the bioavailability of Gliclazide in diabetic rats -with an unknown mechanism- when compared with the control group. Increased bioavailability increases the time of action for Gliclazide. Although in their study this increase did not lead to glycemic control, the changes in Gliclazide bioavailability potentially may improve glycemic control. However, the manipulation of Gliclazide bioavailability by probiotics should be interpreted with caution and considered hypothesis-generating results rather than a firm indication of the beneficial effects of the probiotic treatment. It is worth to mention that, there is no data to show whether probiotic supplements directly affect the bioavailability of Gliclazide or this effect is modulated by the bile acid hydrolase function of probiotic. In addition, it is unclear whether data obtained from an animal model of Alloxan induced type 1 diabetes can be extrapolated to human type 2 diabetes.

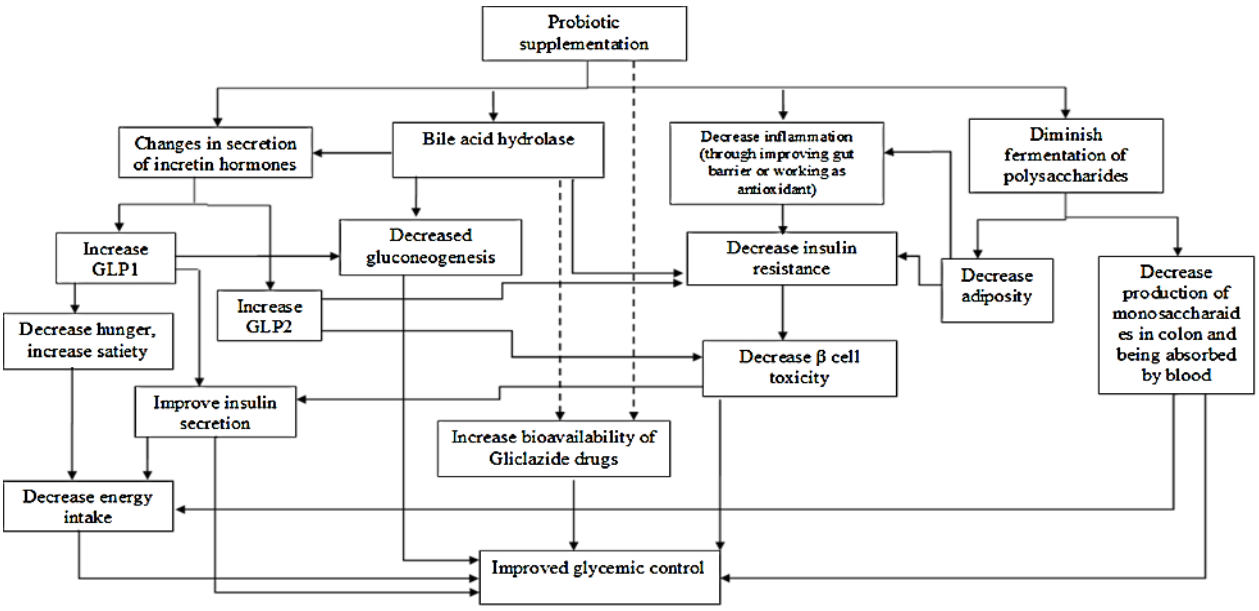

Fig. 1. Proposed mechanism of action. GLP1: Glucagon-like peptide 1, GLP2: Glucagon-like peptide 2, Dash lines has been proven in animal model of type 1 diabetes.

Conclusion

According to the above data, the pathway behind the effect of probiotics on glycemic control is complex with various interactions. These interactions are demonstrated in Fig. 1. As this pathway includes numerous interactions at the cellular and molecular level which most of them are still enigma, we attempted not to get involved at this level. The involvement of multiple mechanisms may explain the ambiguities in determining the exact mechanism that is behind this effect. There is also another mechanism involve such as changes in gene transcription which all remains to be elucidated by the future researches. However, focusing on this model will help researchers to clarify and investigate more precisely the underlying mechanisms of actions.

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