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The effect of acarbose on the gut microbiota: an evidence-based review

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Abstract: *Acabose is wildly used in various disease treatments and could interact with the gut flora, while the gut flora plays a significant role in human body. This means that acarbose is able to be utilized to improve the efficacy and patient experience by measuring and regulating intestinal flora to achieve precise medicine intake. Moreover, it is also capable to be employed for treating and preventing more other diseases by targeting the gut flora to open up new uses. Based on this hypothesis, we summarized the reasons, methods and results of the interactions between acarbose and intestinal flora, as well as ways for health promotion according to existing experimental results and literature reviews.*

Keywords: *Acarbose, gut microbiota, Bacteria, type-II diabetes*

1. Introduction

Acarbose is a complex disaccharide (pseudotetrasaccharide) with cyclohexanol, amino sugar, and two molecules of dextrose in its structure. It can inhibit glycosidase in the intestines, thereby slowing down the decomposition of starch and disaccharides into glucose, delaying the digestion of ingested carbohydrates. Hence, the increase in blood glucose concentration after meal is small, and the side effects are also small. According biological and clinical researches, arcabose is wildly used in type-II diabetes medication. Compared with its weak inhibitory effects on α-amylase, it has stronger inhibitory activities on intestinal sucrase, maltase, dextrinase and glucoamylase. These properties with its specific pharmacokinetics and toxicology of the substance make it an ideal therapeutic agent [1]. In addition to diabetes, acabose as an α-glucosidase inhibitor plays an significant role treating polycystic ovary syndrome, hypertensive heart disease, cardiovascular disease, ulcerative colitis [2] and prolonging human life expectancy. As a product of bacteria, many experiments have proven that the therapeutic effects of acarbose are related to the intestinal flora.

The intestinal microbiota refers to the trillions of microorganisms living in our intestines. It can be considered as an independent endocrine organ [3], which provides amino acids and vitamins to the host. Another essential function of arcabose is to break down indigestible carbohydrates into short chains. Fatty acids (SCFA), mainly acetic acid, propionic acid and butyric acid, short-chain fatty acids are capable to directly or indirectly participate in the communication between the microbiota-gut-brain axis and help to broaden the metabolic potential of its host [4]. The composition and balance of this microbial ecosystem play a vital role in human physiology and health. This system helps to shape and regulate plentiful physiological processes of the host [5] [6], including the immune system, which can lead to the occurrence of disorders of metabolism and energy metabolism [7] [8]. Previous researches primarily focused on fields such as irritable bowel syndrome [9], inflammatory bowel disease [10] [11] allergy[12] diabetes [13], cancer[14] [15], asthma [16], and obesity [17]. Not only are many diseases related to microbial community disorders, but more and more studies have gone beyond correlation and pointed out their causality. Besides, based on human fecal transplant flora transplantation [18] [19] [20] [21] of the pathogenic effect of microbiota on certain diseases, proposed by researchers, the intestinal flora becomes a new object of health and disease.

Therefore, understanding the influence of acarbose on bacteria might be helpful to regulate the intestinal flora and improve physical and mental health of human [8]. Even for intractable diseases, such as cancer or mental illness [22] [23], acabose may have miraculous effects to change the flora structure, and the flora composition. Furthermore, acabose is also able to act as a flora regulator with lower side

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effects in the treatment on many other diseases.

2. How Acarbose affects

Acarbose is an α-glucosidase inhibitor, which competitively inhibits pancreatic α-amylase and various α-glycoside. It is able to restraints the hydrolysis of complex carbohydrates in the brush border of the intestinal epithelium, inhibits host digestion, and reduces intestines absorption of glucose. The tract absorbs glucose, resulting in an increase in the concentration of complex carbohydrates in the lower part of the intestine, leading to changes in the intestinal microbiota and its fermentation products [24] including SCFA.

α-glycosidase inhibitors prevent the digestion of carbohydrates, while indigestible carbohydrates usually provide the main energy source for the microbes that produces short-chain fatty acids in the large intestine. Higher levels of SCFA, a microbial by-product of carbohydrate fermentation, usually bring health benefits, such as increased anti-inflammatory effects in chronic inflammatory diseases. Among them, propionate, acetate and butyrate have different tissue fates and host responses [25]. The SCFA that is considered to have the greatest therapeutic potential is butyrate, which is the preferred energy source for colon cells and has effective effects on various colonic mucosal functions, such as inhibiting inflammation and carcinogenesis, strengthening various components of the barrier of colon and reducing oxidation stress [25] [26]. With immunosuppressive properties, butyric acid seems to improve the symptoms of graft-versus-host disease in mice after allogeneic bone marrow transplantation by enhancing the intestinal epithelial barrier by increasing the expression of tight junction proteins [27].

3. Results of the effect of acarbose on the intestinal flora

Acarbose significantly increases the relative abundance of beneficial bacteria for patients with type 2 diabetes, while its diversity is also reduced [28] [29]. The specific changes in the abundance of each flora are shown in the chart (human). (Mouse) After high intake of the acarbose, the most significant changes take place on the bacterial Bacteroides family (P 4.4 107) and Bifidobacteria family (P 4.1 107), throughout the eight most abundant bacterial families [30]. (Human) Acarbose treatment causes an increase in the abundance of species with high Bsh activity (mainly Bifidobacterium longum, Lactobacillus gasseri), and a decrease in the abundance of SBA producer, B. plebeius, B. vulgatus/dorei and C. bolteae [29]. During the acabose treatment study by Zhang et al. [31]found that the diversity and composition of the individual intestinal flora of T2DM patients changed in the early stage, and the abundance of Enterobacter, Prevotella, and Lactobacillus in the intestine increased. In addition, the study of Su et al. [32] point out that acarbose increses the abundance of intestinal bifidobacteria and decreased some inflammatory factors in patients with T2DM. The experiment from Zhang et al. argues that [31] taking acarbose treatment significantly affects the intestinal flora that produces SCFA which increase the abundance of Enterobacter, Prevotella and Enterococcus faecalis. Other Studies [33] [34] have also claims that acarbose infuences the release of hormones and insulin in the intestine, and changes the abundance of microbial genes involved in bile acid metabolism by increasing the relative abundance of Lactobacillus and Bifidobacterium. The changes of some important strains are as follows.

Table 1 Effects of Acarbose on relative abundance of gut bacteria taxonomic groups.(human studies)

Increased relative abundance	**Decreased relative abundance.**
SCFA-producing bacteria [35][28]	*Butyricicoccus* [28]
Clostridiales (order) [28]	*Clostridium* [35]
Faecalibacterium [28]	*Ruminococcus* [28]
Dialister [28]	*Phascolarctobacterium* [28]
Lactobacillus [35][28]	Bacteroidaceae (family) [35]
Prevotella [28]	Enterobacteriaceae(family)[35][36]
Bifidobacterium [35][36][32]	

In bold: phylum, in italic: genus.

1) (T2DM patients) the effect of acarbose on Lactobacillus: Lactobacillus is the most gram-positive bacteria in the intestinal tract and can produce large amounts of lactic acid from carbohydrate. Lactobacillus is capable to tolerate the low pH environment in the intestine, reduce the permeability of the intestinal mucosa, and improve the plasma endotoxin level to resist inflammation. Moreover, it could improves IR and lowers blood sugar. The extract of Lactobacillus is able to inhibits α and β-glucosidase

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activity and lower blood sugar. Acarbose dramatically increases the abundance of lactobacilli in the intestine, the content of lactic acid in the intestine, and the decomposition of cholesterol to reduce the cholesterol content [24].

2) Acarbose treatment boosts the relative abundance of Actinomycetes, and reduces the relative abundance of wart microbes and Proteus [37]

3) (Zucker diabetic high-fat rats) Acabose rises the relative abundance of Firmicutes and the ratio of Bacteroides. The ratio of Firmicutes to Bacteroides phylum is positively correlated with fecal SCFAs [38] , from research conducts by Fernandes et al. Although the results of Larsen et al. [39] are contrary to this, the facts still demonstrate that the ratio of Firmicutes to Bacteroides in diabetic rats is declined [40]. After 4 weeks of treatment with metformin, acarbose, and sitagliptin, the ratio was reversed in a study by Zhang M et al [37].

4) Acabose give rise to the abundance of bifidobacteria [37]. (Zucker diabetic high-fat rat) As the number of unclassified Lactobacillus decreases, the relative abundance of Luminococcus 2 and Bifidobacterium is considerably higher than other. Furthermore, Bifidobacterium also has anti-inflammatory effects. High carbohydrate intake may lead to a higher content of bifidobacteria [41]. Therefore, the increase in the abundance of bifidobacteria may due to acarbose which exposes more carbohydrates to the distal intestine [37].

5) (Zucker diabetic high-fat rats) Acarbose intake rises the carbohydrates in the distal intestine and specifically promotes the growth of rumen cocci 2. Blaubia (rumen cocci) obeum shares the same clostridia and rumen cocci 2 and express α- glucosidase (Ro-αG1) [37]. A theory indicates that α-glycosidase inhibitors (acarbose, voglibose, miglitol) are able to impact human intestinal bacteria Ro-αG1 and play an anti-diabetic effect or produce adverse gastrointestinal symptoms [42]. In addition, SCFA-producing rumen cocci mainly produces acetate and propionate [25] to improve metabolic abnormalities and intestinal inflammation [43].

6) Acarbose reduces the relative abundance of Proteus [37]. The abnormal expansion of Proteus phylum plays an crucial role in inflammation.

7) Although some undesirable digestive side effects are existing, they not dangerous [44]. One of the) main side effect of flatulence is the formation of gas due to the fermentation of undigested carbohydrates by colonic bacteria. The cause of flatulence is thought to be through competitive inhibition of enzymes that act on the small intestine. These enzymes delay the release of glucose from complex carbohydrates, and therefore particularly reduce the migration of glucose after meals [2]. After that, the human body ferments undigested carbohydrates through intestinal flora to produce H2 gas [45].

8) Hepatic encephalopathy in liver cirrhosis is caused by toxic products produced by the degradation of dietary nitrogen related to the proteolytic bacterial flora. Acarbose inhibits the absorption of glucose in the intestinal tract and promotes the growth of intestinal saccharification flora, while sacrificing the growth of proteolytic flora. Acarbose has a beneficial effect on hepatic encephalopathy and postprandial hyperglycemia in patients with low-grade hepatic encephalopathy and cirrhosis of type 2 diabetes [46].

9) Acarbose can be used to increase the delivery of carbohydrates to the colon. By breaking down digestible carbohydrates into absorbable monosaccharides, this agent can transport undigested carbohydrates to the colon for fermentation by resident bacteria [47]. Evenepoel et al. [48] According to the research from Evenepoel et al., the administration of acarbose greatly drops the levels of p-cresol in urine, plasma and feces of a group of people with normal renal function. Based on these observations, they believe that the use of acarbose can reduce (they believe the application of acarbose treatment will lower) the burden of uremic toxins derived from gut microbes in patients with CKD (chronic kidney disease).

4. Bacteria affect acarbose

1) Different diets can cause changes in the intestinal flora, and patients with different types of intestinal flora will have different effects of SCFA with acabose intake. Supplementing acetate (a short-chain fatty acid) is able to reverse intestinal damage, and this reversal effect is independent from the influence of the composition in the microbial community. The therapeutic potential of butyrate has also been fully established. Therefore, dietary components or treatments that increase this short-chain fatty acid may prevent the development of colorectal cancer, inflammatory bowel disease, or systemic inflammatory diseases [26][49][50]. For high-starch (HS) or high-fiber diets rich in plant polysaccharides

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(PP), the high dose of acarbose in the PP diet results in a unique community structure, increasing the representativeness of Bifidobacteria and Mysticaceae. Acarbose is used in both diets, and the short-chain fatty acids (SCFA) measured in stool samples is increased, especially for butyrate [30].

Plentiful data shows that acarbose has the potential to change the intestinal community structure and increase the production of beneficial SCFA in a diet-dependent manner. The increased abundance of butyrate-producing organisms are related to the host diet with high dietary fiber content. The host diet is defined as polysaccharides that is not available to the digestive enzymes of the host [49] [51].

Changes in the intestinal flora of mice depends. In the experiment conducts by Nielson T. Baxter et al which utilize acarbose as part of a high-starch (Western-style) low-fat diet, they observe that a large amount of acarbose is required to shift the gut microbial community structure dramatically. Moreover, this effect is directed in a large extent by a significant change in five bacterial operational taxonomic units (OTUs), while incorporating high doses of acarbose into typical high-fiber, low-fat rodents in the food. A huge change in the community was (is) observed, which is different from the structure of a high starch diet plus acarbose. For both diets, it shows an increase in butyrate, but only the high fiber plus acarbose diet causes a significant positive change in acetate output. Therefore, the ability of acarbose to increase the acetate output of the microbiota is related to diet, while butyrate has no relation with diet [30]. Regardless of the exact changes in the intestinal flora, studies of human volunteers supplemented with acarbose have reported the elevation of serum butyric acid levels [52] [53]. Therefore, regardless of the exact changes in the community structure, the observed metabolic footprint has a certain retention. And noticed that the largest increase in butyrate output was(is) observed in the background of plants polysaccharide diet [30].

These data indicate that acarbose feeding changes the structure of the gut microbiota in a reversible and diet-dependent manner [30], which may have an impact on how these drugs are ideally used in humans to enhance therapeutic potential.

2) Acarbose have different therapeutic effects on different intestinal types, and have the potential for stratification of T2D patients according to the intestinal flora before treatment. In one study [29], the baseline microbiota of patient could be clearly divided into two gut-like clusters. One is driven by Bacteroides (cluster B), and the other is by Prevotella (cluster P). Compared with patients with the intestinal flora of Propionibacterium, patients with rich Bacteroides have greater changes in plasma BAs and better improvements in metabolic parameters after acarbose treatment. Furthermore, the clinical efficacy of acarbose is more obvious in cluster B patients than in cluster P patients. A close relationship is detected between the acarbose-dependent changes of intestinal microbes and the composition of plasma BA. Among patients whose baseline microbiota belong to an intestinal-like cluster driven by Bacteroides, the discovery of in plasma BA composition and the clinical benefits of acarbose treatment further support the intestinal microbiota of acarbose potential therapeutic effects of plasma BA axis. Although acarbose treatment resulted in a similar improvement in HbA1c levels, the G0 (FBG), insulin levels, and C peptide levels of cluster B patients are significantly improved. Therefore, HOMAIR is higher than the baseline level of patients in the baseline P group. [29] Besides, changes in intestinal flora can reduce the adverse reactions of hypoglycemic drugs [54]

In summary, different treatment responses are related to the ability of the microbial communities in the two microbiomes to metabolize BA. More importantly, this result suggests that stratifying patients based on baseline gut microbiota composition could provide options for drug treatment strategies and predict anti-diabetics tools for metabolic benefits.

5. Conclusion exhibition and outlook

Acarbose inhibits host digestion. It increases the flux of starch to the lower digestive system, leading to changes in the intestinal microbiota and its fermentation products, and effectively reducing postprandial blood sugar in patients with T2DM. Moreover, acarbose completely acts on the gastrointestinal tract and has the characteristics of affecting insulin secretion and improving IR [24]. The administration of acarbose on patients with hyperlipidemia or T2D has further shown to increase lactobacilli and bifidobacteria [35] [28] [32], as well as other SCFA-producing bacteria such as Faecalibacterium and Prevotella [28]. The increment improves the health of the host.[30]. Based on numerous physiologically beneficial effects of SCFA, in the future, acarbose have high possibility to be used as a flora regulator with little side effects under certain circumstances to change the flora products, improve human SCFA and achieve various aspects of health requirements. Exploiting the influence of acarbose on the flora could indirectly treat many other diseases. For example, for those that are greatly

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affected by the fermentation products of the flora such as short chain fatty acids, and attach importance to the development of its health effects [45]. Studies have shown that acarbose can increase the healthy lifespan of mice, and there are also good reasons to clinically evaluate this small molecule as one of the most effective protective drugs for the elderly so far. Acarbose therapy has been evaluated in many animal models for the prevention or treatment of a variety of other diseases, such as cardiovascular disease [55] [56] [57] and cognition [58]. In addition, acarbose has a beneficial effect on overweight by lowering blood pressure and triglycerides and down regulating biomarkers of low-grade inflammation (Hanefeld et al., 2004) [59].

In terms of precise medication, T2D patients are classified according to the type of intestinal flora before treatment, and those with intestinal type driven by Bacteroides (cluster B) will directly use acarbose treatment. Other drugs and treatment options are available for intestinal patients driven by Prevotella (cluster P)[29]; there have been some articles discussing the biological factors and processes of intestinal microbial regulation, as well as the potential use of symbiotic bacteria as therapeutic agents to treat diseases. Supplementing specific probiotics can further improve the hypoglycemic effect of antidiabetic drugs [37]. Intestinal type can also be adjusted by taking frozen vaccines or changing diet to form a flora environment that promotes the efficacy of acarbose. Based on the influence of acarbose on the intestinal tract, many other diseases that can be treated for it is also able to be classified and treated through this idea.

Acarbose is considered a safe treatment because of its local effects on intestinal enzymes and minimal absorption in the blood, but it is often under prescribed because the treatment needs to be dosed with each meal and take into account the digestion of starch. In addition, although it may cause gastrointestinal discomfort and shunt to the colon, these side effects are usually short-lived and can be avoided by starting with a low dose of acarbose and gradually increasing over time [60]

As we learn more about how human diseases are affected by the intestinal bacterial community and by-products, the influence of acarbose on the intestinal flora, and the influence of different flora on the efficacy of drugs. Assessing how to use the interaction between acarbose and the flora to treat and prevent [57] diseases will become increasingly important.

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