Research Progress on the Correlation between Human Intestinal Microbiota and Diabetic Retinopathy

Wenjun Jiang[1], Ya Li[2,*]

[1]Shaanxi University of Traditional Chinese Medicine, Xi'an, China
[2]Clinical Laboratory Center of Xi'an People's Hospital (Xi'an Fourth Hospital), Xi'an, China
*Corresponding author

Abstract: Diabetic retinopathy is the most common type of specific complication of diabetes and is the leading cause of blindness in adults. Compared with normal people, the inflammatory bacteria in the intestinal tract of diabetic retinopathy patients decreased, while the pro-inflammatory bacteria increased, leading to the increase of inflammatory factors in the body, leading to the aggravation of the condition of diabetic retinopathy patients. This provides a new research direction for the treatment of diabetic retinopathy by changing the structure and quantity of human intestinal microflora. In this review, we will summarize the research progress of intestinal microbiota and diabetic retinopathy, and discuss the action mechanism, treatment prospects and prospects of intestinal microbiota in diabetic retinopathy, so as to contribute to the development of new and targeted treatment methods in this field.

1. Introduction

Diabetes mellitus (DM) is one of the most common chronic diseases worldwide. With the continuous improvement of people's living standards, the number of DM patients is gradually increasing. By 2019, according to the data provided by the International Diabetes Federation, the number of diagnosed DM patients worldwide has reached 463 million, and it is estimated that by 2030, the number of patients will reach about 578 million, and in 2045 will rise to 700 million, among which the Chinese adult DM patients up to 116.4 million, ranking the first in the world [1]. Diabetic retinopathy (DR) is one of the most common microvascular complications of DM, which is the ocular manifestation of end-organ damage in DM. About one third of DM patients suffer from DR, and one tenth of them have lesions that damage vision [2]. In recent years, a large number of studies have shown that there is a close relationship between gut microbiota (GM) and DR. In this review, we discuss the research progress of DR and GM and the mechanism between them, in order to provide new and targeted treatment ideas for clinical treatment of DR.

2. Overview and research progress of DR

DR is a common microvascular complication of DM, mainly manifested as visual impairment, blurred vision and even blindness. If patients do not receive regular treatment in time, they will

increase the risk of blindness and affect their normal life, so timely and effective prevention of DR is very important. DR can be divided into proliferative DR (PDR) and non-proliferative DR (NPDR) according to fundus changes. NPDR is in the early stage of the disease and confined to the retina. Clinical manifestations include microhemangioma, hemorrhage, hard and soft exudates, retinal artery and vein lesions. PDR lesions with at least partial extension beyond the inner limiting membrane and the appearance of new blood vessels are markers of this type. Early DR can not damage the central vision, patients often have no conscious symptoms. At this point, without timely and correct clinical intervention, DR may further develop, eventually leading to irreversible visual damage and even blindness. The increasing number of cases of blindness due to DR has had a significant economic impact on individuals and their families, health systems and national economies.

DR is a disease with complex pathogenesis and a variety of factors. Long-term chronic hyperglycemia is the basis of its pathogenesis, because it is believed to cause a series of biochemical and physiological changes, eventually leading to microvascular damage and retinal dysfunction, but the exact factors have not been fully elucidated. With the rapid development of medicine, the study of DR has been continuously deepened, and the pathogenesis of DR has been systematically studied, mainly including the following: Vascular endothelial growth factor (VEGF) VEGF up-regulation[3], inflammatory response [4], abnormal polyol metabolic pathway [5], oxidative stress[5], abnormal aggregation of advanced glycosylation end products [6], abnormal protein kinase C signaling pathway[7], and other unknown pathogenic factors. These mechanisms are interrelated, thus aggravating the prognosis of DR.

3. Overview and research progress of GM

3.1. The basic concept of GM and the latest research progress

GM is a general term for a large number of microorganisms that depend on the human gut. It is an important component of the body and plays a huge role in maintaining the regulation of normal substance metabolism. The human gut is colonized by more than 1,500 different microbiota. Under normal physiological conditions, GM mainly contains Bacteroides and Firmicutes, and a small amount of actinomycetes and Proteobacteria as the main stable components. Body can in a short period of time after tectonic changes in diet and eating habits to change the composition of intestinal flora, but GM will in turn affect the host nutrition metabolism, growth promoting and immune regulation, eliminate pathogenic microorganism, etc., through its biological activity of a variety of metabolites to host life activities play a role, is closely related to a host of health and disease [8].

Research on the relationship between GM and host diseases has received widespread attention from all walks of life. It has been confirmed that GM dysregulation is related to a variety of diseases. These include inflammatory diseases (obesity, inflammatory bowel diseases), autoimmune diseases (rheumatoid arthritis, muscular dystrophy, diabetes), various cancers and mental disorders (Alzheimer's, anxiety and autism), among others. Therefore, GM has the potential to treat obesity, diabetes, central nervous system diseases and other diseases [9].

Beli et al. found that the ratio of intestinal firmicutes to Bacteroides in intermittent fasting mice increased, and the level of taurourin deoxycholic acid also increased significantly [10]. Tetz et al. demonstrated for the first time that amyloid-producing Escherichia coli, their bacteriophages, and bacteria-derived amyloid proteins may be involved in the activation of prediabetic pathways in children at risk of T1DM[11]. Zhao et al. showed in their early studies that in susceptible children with T1DM, intestinal microbial modification precedes autoimmunity[12].

3.2. Research progress on the mechanism of GM in DR

At present, a large number of studies have shown that there are various pathogenesis of DR, among which the effect of GM on DR has received more and more attention and reports. In recent years, various studies have found the relationship between microorganisms and eye diseases, and some scholars have proposed the concept of gut-retina axis [13], believing that GM can affect the functions of various retinal cells through its metabolites. Intestinal microbiome changes Lipopolysaccharides (LPS), short-chain Fatty Acids (SCFAs) and Bile Acids (SCFAs) in blood circulation. BAs, trimethylamine-oxide (TMAO) and tryptophan metabolism, which are involved in the regulation of host metabolism, intestinal integrity and the occurrence and development of DR[14,15]. GM diversity contributes to the production of essential vitamins, polysaccharides, amino acids, the growth of regulatory T cells, and the metabolism of many substances including foreign substances or toxins [16, 17].

3.2.1. GM affects DR by regulating BAs metabolism

BAs are components of bile, endogenous steroid molecules synthesized from cholesterol, which play an important role in fat and carbohydrate metabolism. Primary bile acids interact with FXR as ligands for Farnesoid X receptor (FXR), which changes glucose metabolism. Secondary bile acids bind to Takeda G protein-coupled receptor 5 (TGR5), which promotes glucose homeostasis, preventing retinal neuropathy and inflammation [18]. Zhu et al. [19] found that the weakening of bile acid signaling pathway could not alleviate the pathological process of DR, while upregulated or activated TGR5 could delay the progression of DR by inhibiting RhoA/ROCK signaling. Because of their ability to mediate energy metabolism by binding to and activating nuclear transcription factors such as FXR in the gut and liver, manipulation of bile acids by modulating GM helps control blood glucose and prevent metabolic memory in subjects with early-onset T2DM [20]. Patients with uncontrolled T2DM have elevated bile acids, elevated deoxycholic acid levels, and decreased goose deoxycholic acid levels [21].

3.2.2. GM population affects DR by regulating LPS metabolism

LPS is an important component of the outer wall structure of Gram-negative bacteria cell wall. LPS is a macromolecular substance formed by lipids and polysaccharides. The increase of Gram-negative bacteria in DM patients is associated with a corresponding increase of LPS. LPS not only inhibits innate immune signaling and endotoxin tolerance, causes metabolic endotoxemia, disrupts the sequence of tight junction proteins, and increases intestinal permeability, but also is related to the pathogenesis of DM [22]. Increased circulating LPS concentration in the blood activates NF-κB through TLR-4-MyD88, then the expression of IL-6 and TNF-α is also increased, and increased Helicobacter pylori can also cause the expression of IL-6 and TNF-α, IL-6 can also form the injury of vascular endothelial cells. The destruction of vascular endothelial cells will affect vascular tension and change hemodynamics, thereby activating platelets and blood coagulation system, increasing the permeability of blood vessels, and eventually leading to the occlusion of microvessels and the formation of neovascularization, resulting in the occurrence of diabetic microangiopathy [23].

3.2.3. GM affects DR by regulating TMAO metabolism

The trimethylamine formed after GM metabolizes choline is transported to the liver, where flavin monooxygenase 3 oxidizes it to become TMAO. Studies have shown that bacteria such as Firmicutes, Proteobacteria, Clostridium aspartate, Clostridium harhardii, Sporobacteria, Escherichia,

Proteobacteria Pennii, Providenciella, Edwardiella tardigiflorum, and Vibrio desulphurum are TMAO generators [24]. TMAO has the properties of accelerating atherosclerosis, exacerbating vascular inflammatory response, activating NLRP3 inflammasome, inducing reactive oxygen species generation, and attenuating cholesterol reversal [25]. Some studies have suggested that the activation of NLRP3 inflammasome is related to the pathogenesis of PDR [26].

3.2.4. GM affects DR by regulating SCFAs metabolism

Dietary fiber and other carbohydrates or amino acids in food are degraded and metabolized by colonic bacteria into monosaccharides and oligosaccharides, and finally fermented into SCFAs and gases (H_2, CH_4 and CO_2). SCFAs are fatty acids with carbon atoms less than 6. The most common SCFAs in the intestine are mainly composed of acetic acid, propionic acid and butyric acid. These material support cytokines, chemokines, protect peptide and release, and the generation of phagocytes SCFAs is not only the key medium in the process of mitochondrial energy metabolism, also have to adjust the action of the human body glucose and fat metabolism, endocrine system, nervous system, to produce a variety of biological effects, such as cardiovascular diseases mediated immune response and adjust the level of inflammation, and so on. There are two main mechanisms of action of SCFAs. One is that fermentation-generated SCFAs stimulate the secretion of glucagon-like peptide-1, glucagon-like peptide-2 and intestinal castide-peptide by binding to G protein-coupled receptors. The former two increase the expression of adiponectin and insulin, thereby expanding the proliferation of insulin-sensitive pancreatic S cells, intestinal peptide has the effect of reducing appetite, increasing satiety and lowering blood sugar.

The other is the regulation of gene expression as an inhibitor of histone deacetylase (HDACs). Tight junction protein-2 is considered as a "leakage protein" in the tight junction protein family. Butyrate activates activator 3 and inhibits HDACs. The expression of CLDN-2 is inhibited in an IL-10-dependent manner to enhance the epithelial barrier function and promote the recovery of intestinal mucosal barrier function. Moreover, the binding of butyrate and G-protein-coupled receptors can inhibit intestinal inflammation, aggravate the differentiation of regulatory T cells and generated T cells, and maintain the stability of immune homeostasis.

3.2.5. GM affects DR by regulating the metabolism of indole propionate and branched-chain amino acids

GM degrades approximately 10 grams of protein per day to produce metabolites such as amines, indole, and phenols. 3-Indole propionic acid (IPA) is an endogenous substance produced by GM using tryptophan in the intestine. IPA is absorbed by intestinal epithelial cells and then transported to the blood circulation. IPA is helpful for glucose metabolism as well as antioxidant and anti-inflammatory. Therefore, IPA in the blood may be a potential biomarker of diabetes because it is associated with the development of T2DM and it can play a normal role by maintaining β-cells.

3.2.6. GM affects DR by regulating H2S metabolism

Some metabolites produced by GM degradation of proteins or sugars, such as H_2S, are related to the regulation of host metabolism and intestinal integrity. GM alleviates and inhibits diabetes and its complications through metabolites. H_2S can regulate insulin sensitivity, lipolysis, and the production of inflammatory factors, promote hepatic gluconeogenesis and glycogenolysis, and inhibit glucose utilization and glycogen reserve. An in vitro study has shown that excess H_2S levels inhibit pancreatic cell function and therefore have a pro-diabetic effect. The potential role of H_2S in the development of T2DM is far from established, and further studies are needed to elucidate the exact mechanism of involvement of this GM.

4. Research progress of therapeutic regimens developed by using the mechanism of GM action on DR

4.1. Take probiotics or prebiotics

Added probiotics and prebiotics proper supplementation of probiotics and prebiotics can interfere with function and composition of the intestinal microbial flora, selective stimulation of one or more beneficial bacteria breeding so as to activate the immune system, control inflammation, promote the production of short chain fatty acids, improve blood glucose and insulin resistance, a beneficial impact on the host. Common probiotics include Lactobacillus, bifidobacterium, Lactococcus, Streptococcus and Enterococcus [27].

4.2. Take antioxidants and their supplements

According to oxidative stress and other pathways in the pathogenesis of DR, intake of vitamin-rich foods, such as fruits and vegetables and supplements, is also related to the reduction of the risk of chronic diseases or DR itself [28], and they also produce some hypoglycemic effects through their bioactive compounds (such as flavonoids, alkaloids and anthocyanins) [29]. The latter is found in wild blueberries, bilberries, cranberries, elderberry, raspberry seeds and strawberries and has potent antioxidant activity.

4.3. Laser or surgical treatment

Timely laser treatment is very effective for visual protection of proliferative retinopathy and macular edema, but its ability to reverse visual loss is poor. Advanced DR may occasionally require vitrectomy. Newer therapies, such as intraocular steroid injections and anti-VEGF drugs, are less damaging to the retina than older therapies and may be useful in patients who respond poorly to conventional therapies.

4.4. Treatment by bile acid pathway

Bile acid chelators have recently been introduced as a treatment option for patients with diabetes inadequately controlled by normal antidiabetic therapy. In addition, the administration of the semi-synthetic bile acid derivative obcholic acid, a high-affinity ligand of FXR, has yielded clear results in diabetic subjects. The use of TGR5 agonists and FXR agonists via GM modulation is a potential treatment for type 2 diabetes. The introduction of taurodeoxycholate into the blood circulation can activate TGR5. Intermittent feeding can prevent DR by increasing the level of taurodeoxycholate, and TGR5 may become a new therapeutic target for DR [30].

4.5. Drug therapy

Some drugs can also improve glucose metabolism and lipid metabolism by regulating intestinal microbiota, shortening the residence time of metabolites in the intestine and reducing the production of toxins. For example, metformin is the first choice for doctors in the treatment of type 2 diabetes, because in addition to its effect on blood glucose control in DM patients, it has been recently discovered that it also has the effect of protecting microvascular and macrovascular complications in DM patients. The effect of metformin in GM is mainly manifested as increasing the production of SCFAs, regulating the metabolism of bile acids and promoting the secretion of intestinal hormones. Metformin also significantly reduced the ox-LDL-induced increase in NLRP3 protein

expression and NLRP3 inflammasome activation in macrophages [31].

5. Summarization and prospect

The pathogenesis of GM and its metabolites in DM and its related retinopathy has not been fully explained, and the relevant basic and clinical studies need to be further carried out. This paper summarizes the latest research progress of GM and DR In human body, and focuses on the influence of GM and its metabolites on DR From many aspects. It is found that the research of GM related to DR Has great application value and research prospect.

References

[1] P. Saeedi, I. Petersohn, P. Salpea, B. Malanda, S. Karuranga, N. Unwin, S. Colagiuri, L. Guariguata, A.A. Motala, K. Ogurtsova, J.E. Shaw, D. Bright, R. Williams, Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9(th) edition, Diabetes Res Clin Pract, 157 (2019) 107843.

[2] M.L. Rodríguez, S. Pérez, S. Mena-Mollá, M.C. Desco, L. Ortega Á, Oxidative Stress and Microvascular Alterations in Diabetic Retinopathy: Future Therapies, Oxid Med Cell Longev, 2019 (2019) 4940825.

[3] Y. Li, J.M. Busoy, B.A.A. Zaman, Q.S.W. Tan, G.S.W. Tan, V.A. Barathi, N. Cheung, J.J. Wei, W. Hunziker, W. Hong, T.Y. Wong, C.M.G. Cheung, A novel model of persistent retinal neovascularization for the development of sustained anti-VEGF therapies, Exp Eye Res, 174 (2018) 98-106.

[4] W. Wang, A.C.Y. Lo, Diabetic Retinopathy: Pathophysiology and Treatments, Int J Mol Sci, 19 (2018).

[5] Q. Kang, C. Yang, Oxidative stress and diabetic retinopathy: Molecular mechanisms, pathogenetic role and therapeutic implications, Redox Biol, 37 (2020) 101799.

[6] J. Xu, L.J. Chen, J. Yu, H.J. Wang, F. Zhang, Q. Liu, J. Wu, Involvement of Advanced Glycation End Products in the Pathogenesis of Diabetic Retinopathy, Cell Physiol Biochem, 48 (2018) 705-717.

[7] N. Mahajan, P. Arora, R. Sandhir, Perturbed Biochemical Pathways and Associated Oxidative Stress Lead to Vascular Dysfunctions in Diabetic Retinopathy, Oxid Med Cell Longev, 2019 (2019) 8458472.

[8] Leonor, García-Bayona, Laurie, Comstock, Bacterial antagonism in host-associated microbial communities, Science, (2018).

[9] B. Dalile, L.V. Oudenhove, B. Vervliet, K. Verbeke, The role of short-chain fatty acids in microbiota–gut–brain communication, Nature Reviews Gastroenterology &#38 Hepatology, 16 (2019) 1.

[10] E. Beli, Y. Yan, L. Moldovan, C.P. Vieira, R. Gao, Y. Duan, R. Prasad, A. Bhatwadekar, F.A. White, S. Townsend, Restructuring of the Gut Microbiome by Intermittent Fasting Prevents Retinopathy and Prolongs Survival in db/db Mice, Diabetes, (2018) db180158.

[11] E. Coli, T. Phages, G. Tetz, S.M. Brown, Y. Hao, V. Tetz, type 1 diabetes: an association between autoimmunity the dynamics of gut amyloid- 1 producing, (2019).

[12] G. Zhao, T. Vatanen, L. Droit, A. Park, A.D. Kostic, T.W. Poon, H. Vlamakis, H. Siljander, T. Härkönen, A.M. Hämäläinen, A. Peet, V. Tillmann, J. Ilonen, D. Wang, M. Knip, R.J. Xavier, H.W. Virgin, Intestinal virome changes precede autoimmunity in type I diabetes-susceptible children, Proc Natl Acad Sci U S A, 114 (2017) E6166-e6175.

[13] S. Rowan, S. Jiang, T. Korem, J. Szymanski, A. Taylor, Involvement of a gut–retina axis in protection against dietary glycemia-induced age-related macular degeneration, Proceedings of the National Academy of Sciences, 114 (2017) 201702302.

[14] T. Zhu, M.O. Goodarzi, Metabolites Linking the Gut Microbiome with Risk for Type 2 Diabetes, Curr Nutr Rep, 9 (2020) 83-93.

[15] A.K. Sikalidis, A. Maykish, The Gut Microbiome and Type 2 Diabetes Mellitus: Discussing a Complex Relationship, Biomedicines, 8 (2020).

[16] G. Clarke, K.V. Sandhu, B.T. Griffin, T.G. Dinan, J.F. Cryan, N.P. Hyland, Gut Reactions: Breaking Down Xenobiotic-Microbiome Interactions, Pharmacol Rev, 71 (2019) 198-224.

[17] D. Takahashi, N. Hoshina, Y. Kabumoto, Y. Maeda, A. Suzuki, H. Tanabe, J. Isobe, T. Yamada, K. Muroi, Y. Yanagisawa, A. Nakamura, Y. Fujimura, A. Saeki, M. Ueda, R. Matsumoto, H. Asaoka, J.M. Clarke, Y. Harada, E. Umemoto, N. Komatsu, T. Okada, H. Takayanagi, K. Takeda, M. Tomura, K. Hase, Microbiota-derived butyrate limits the autoimmune response by promoting the differentiation of follicular regulatory T cells, EBioMedicine, 58 (2020) 102913.

[18] A. Wahlström, S.I. Sayin, H.U. Marschall, F. Bäckhed, Intestinal Crosstalk between Bile Acids and Microbiota and Its Impact on Host Metabolism, Cell Metab, 24 (2016) 41-50.

[19] L. Zhu, W. Wang, T. Xie, J. Zou, T.i. Wei, TGR5 receptor activation attenuates diabetic retinopathy through suppression of RhoA/ROCK signaling, The FASEB Journal, 34 (2020).

[20] C. Rajani, W. Jia, Bile acids and their effects on diabetes, Front Med, 12 (2018) 608-623.

[21] H. Liu, C. Hu, X. Zhang, W. Jia, Role of gut microbiota, bile acids and their cross-talk in the effects of bariatric surgery on obesity and type 2 diabetes, J Diabetes Investig, 9 (2018) 13-20.

[22] T. Vatanen, A.D. Kostic, E. d'Hennezel, H. Siljander, E.A. Franzosa, M. Yassour, R. Kolde, H. Vlamakis, T.D. Arthur, A.M. Hämäläinen, A. Peet, V. Tillmann, R. Uibo, S. Mokurov, N. Dorshakova, J. Ilonen, S.M. Virtanen, S.J. Szabo, J.A. Porter, H. Lähdesmäki, C. Huttenhower, D. Gevers, T.W. Cullen, M. Knip, R.J. Xavier, Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans, Cell, 165 (2016) 842-853.

[23] K.M. Sayed, A.A. Mahmoud, Heat shock protein-70 and hypoxia inducible factor-1α in type 2 diabetes mellitus patients complicated with retinopathy, Acta Ophthalmol, 94 (2016) e361-366.

[24] J. Qi, T. You, J. Li, T. Pan, L. Xiang, Y. Han, L. Zhu, Circulating trimethylamine N-oxide and the risk of cardiovascular diseases: a systematic review and meta-analysis of 11 prospective cohort studies, J Cell Mol Med, 22 (2018) 185-194.

[25] A. Nowiński, M. Ufnal, Trimethylamine N-oxide: A harmful, protective or diagnostic marker in lifestyle diseases?, Nutrition, 46 (2018) 7-12.

[26] S. Loukovaara, N. Piippo, K. Kinnunen, M. Hytti, K. Kaarniranta, A. Kauppinen, NLRP3 inflammasome activation is associated with proliferative diabetic retinopathy, Acta Ophthalmol, 95 (2017) 803-808.

[27] P. Markowiak, K. Śliżewska, Effects of Probiotics, Prebiotics, and Synbiotics on Human Health, Nutrients, 9 (2017).

[28] A.E. Millen, M.W. Sahli, J. Nie, M.J. LaMonte, P.L. Lutsey, B.E. Klein, J.A. Mares, K.J. Meyers, C.A. Andrews, R. Klein, Adequate vitamin D status is associated with the reduced odds of prevalent diabetic retinopathy in African Americans and Caucasians, Cardiovasc Diabetol, 15 (2016) 128.

[29] M.N. Beidokhti, A.K. Jäger, Review of antidiabetic fruits, vegetables, beverages, oils and spices commonly consumed in the diet, J Ethnopharmacol, 201 (2017) 26-41.

[30] M. Haluzík, M. Mráz, Intermittent Fasting and Prevention of Diabetic Retinopathy: Where Do We Go From Here?, Diabetes, 67 (2018) 1745-1747.

[31] L. Zhang, L. Lu, X. Zhong, Y. Yue, Y. Hong, Y. Li, Y. Li, Metformin reduced NLRP3 inflammasome activity in Ox-LDL stimulated macrophages through adenosine monophosphate activated protein kinase and protein phosphatase 2A, Eur J Pharmacol, 852 (2019) 99-106.