MADEJ, Aleksandra, SENAT, Hanna, GRABOWSKA, Patrycja, BOLLA, Patrycja, SENAT, Aleksandra, MARCZYŃSKA, Zuzanna, NIEMCZYK, Anna and DOROCHOWICZ, Mateusz. The role of the gut microbiota in the pathogenesis and therapy of type 2 diabetes mellitus. Journal of Education, Health and Sport. 2024;55:38-51. eISSN 2391-8306.
https://dx.doi.org/10.12775/JEHS.2024.55.003
https://apcz.umk.pl/JEHS/article/view/47867
https://zenodo.org/records/10552237

The journal has had 40 points in Ministry of Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne z 2019 - aktualny rok 40 punktów. Załącznik do komunikatu Ministra Edukacji i Nauki z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 07.01.2024. Revised: 07.01.2024. Accepted: 21.01.2024. Published: 22.01.2024.

The role of the gut microbiota in the pathogenesis and therapy of type 2 diabetes mellitus

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ABSTRACT:

INTRODUCTION: Diabetes mellitus type II (DM2) is one of the most frequently diagnosed diseases worldwide with a constantly increasing prevalence. It represents an important clinical challenge. The studies are concentrating on improving our knowledge of both pathogenesis and therapeutic opportunities.
The influence of intestinal flora on many health conditions is being investigated. It was found that the gut microbiota of the healthy and diabetic individuals are different. This provides a highly important focus for the consideration of whether and how, based on the content of the intestinal flora, the development and treatment of this disease and its complications can be affected.
PURPOSE: The aim of the study is to present the current state of knowledge about the The role of the gut microbiota in the pathogenesis and therapy of type 2 diabetes.

MATERIALS AND METHOD: The available literature in PubMed was reviewed to write the article, using the keywords ,,gut microbiota diabetes", ,,diabetes

mellitus", ,,intestinal microbiome diabetes", ,,dysbiosis diabetes" and ,,gut microbiota diabetes".

CONCLUSION: The intestinal microbiome is a diverse community of microorganisms that inhabit the gut and has been shown to be essential for the health of the body. Modifications in the diversity and frequency of microorganisms residing in the gut, and the accumulation of metabolites they generate, have been correlated with DM2. The study of intestinal microflora could lead to the discovery of new methods of diagnosis and therapies of DM2 and its complications, such as diabetic kidney disease, neuropathy, retinopathy and cardiovascular disease. In conclusion, further studies are needed to understand the role of the gut microbiome in the pathogenesis and therapy of DM2.

Keywords: type 2 diabetes mellitus, gut microbiota, diabetes mellitus, intestinal dysbiosis, probiotics, intestinal microbiome, diabetic kidney disease

1. Introduction:

Diabetes mellitus type II (DM2) is a metabolic disease that evolved into a significant worldwide health epidemic. It is predicted that by 2035, the number of diabetes cases worldwide will increase to 592 million. The progression of diabetes is characterized by the evolution of its long-term consequences, which not only affect the health, but also the quality of life of the patients (1,2).

DM2 is a disease resulting from chronic high levels of glucose in the blood as a condition of the inability of beta cells in the pancreas to adequately produce insulin or the ineffective usage of insulin by cells in the body (3,4).

DM2 is related to multiple complications which include cardiovascular disease (CVD), chronic renal failure, neuropathy, and diabetic skin lesions, which lead to higher morbidity, blindness, renal failure and an overall lower quality of life (4,5). Data from the past years have shown that the incidence of heart failure in people with diabetes is extremely high and that CVD is the major cause of death in people with DM2 . (6) (7)

The microbiota is a diverse ecosystem of microorganisms that reside in various parts of the human organism, including the gastrointestinal tract (GT), skin, and the respiratory system (RS) (8). The gut hosts the majority of these microorganisms.

The two bacterial species, Firmicutes and Bacteroidetes, are the most common microorganisms in the GT (9). While most studies have concentrated on the bacterial community, evidence is increasing that non-bacterial microbiota may also have a role in both healthy and pathological conditions. The microbiota has been shown to be responsible for regulating gut and body hormone function, modifying and eliminating certain toxins or drugs, modulating bone density, and enhancing gut barrier integrity (10).

The healthy intestinal microbiota generates a variety of beneficial substances, such as short-chain fatty acids (SCFA), vitamins, anti-inflammatory, and antioxidant substances, as well as toxic substances (neurotoxins, carcinogens, and immunotoxins). All of these substances are able to pass into the blood circulation, regulate gene activity, and influence immune and metabolic activities. Consequently, a balanced gut microbiota is important for proper functioning of the body (11,12).

The intestinal microbiota has an important role in DM2 through influences on both their composition and their function. A reduction in the number of butyrate-producing bacteria, like Faecalibacterium and Roseburia, as well as a decrease in butyrate are frequently found in DM2. In addition to being a potential diagnostic marker, the intestinal flora may be a promising treatment option for patients with diabetes mellitus. The healthy gut microbiota includes six groups of bacteria, all of them anaerobic: Firmicutes (Lactobacillus, Enterococcus, Clostridium), Bacteroidetes, Proteobacteria (Enterobacteria), Actinobacteria (Bifidobacterium), Fusobacteria, and Verrucomicrobia. These first four groups represent 98% of the entire GT. Recently, there has been an increasing number of publications suggesting that the gut microbiome may be involved in the pathogenesis of several human diseases, particularly DM2 (13,14,15,16).

2. The purpose of the study

The aim of the study is to present the current state of knowledge about the role of the gut microbiota in the pathogenesis and therapy of type 2 diabetes mellitus.

3. Materials and method

The available articles were reviewed for their clinical relevance to the role of gut microbiota in patients with type 2 diabetes mellitus. The eligible English-language publications retrieved from the PubMed database were reviewed by using key words in different combinations: ,,gut microbiota diabetes," ,,diabetes mellitus," ,,gut microbiome diabetes," ,,dysbiosis diabetes," and ,,gut microbiota diabetes".

4. Description of knowledge

4.1. Role of gut microbiota in type 2 diabetes pathophysiology

The great majority of trials have found relationships between particular types of bacteria and the illness or its symptoms. Frequently described results included the following species: Bifidobacterium, Bacteroides, Faecalibacterium, Akkermansia, and Roseburia with negative correlation to DM2 and Ruminococcus, Fusobacterium, and Blautia with positive (17).

Gut microbiota is an essential component in the onset and progression of DM2. The dysbiosis of the intestinal microbiome in diabetic patients results in the disruption of the balance of the bacterial community. The reduction of the useful flora or the increase of the pathogenic flora may lead to long-lasting mild inflammatory conditions in GT. Studies have discovered that the decrease of probiotics like intestinal Lactobacillus and Bifidobacterium was strongly associated with disturbed glycemic tolerance, which may influence the uptake of glucose and energy, and simultaneously enhance the formation and accumulation of lipids, and be involved in the pathogenesis of DM2. Nevertheless, the exact role of the gut microbiome in the onset and evolution of DM2 is unknown (18).

The treatment effectiveness and the possible negative reactions after the intake of antidiabetics are affected by the intestinal microbiota. The occurrence of specific species or types may indicate the likelihood of a positive reaction. Medications that are taken in the oral form migrate through the gut and interact with the resident microbiota. Research is underway to determine if and how specific types may be relevant to an overall response to antidiabetic medications (19).

4.2. Gut microbiota-target therapies in patients with DM2

There are evidences that the intestinal microbiota has an important impact on the pathophysiology of several metabolic diseases, including defense against inflammation caused by pathogenic bacteria, maintaining the integrity of the intestinal barrier, and developing immunogenic tolerance, thus avoiding and reducing the progression of DM2 (14). Therapies that target the intestinal microbiome have been used, including a high-fiber diet, probiotic or prebiotic supplementation, fecal microbiota transplantation, bariatric surgery and diabetic medications that modify the intestinal microbiome, for example metformin and SGLT-2 (20).

Prior studies have shown that probiotic supplements can reduce insulin resistance and influence glucose metabolism in diabetes mellitus. Many studies have also indicated that probiotic or prebiotic supplementation may decrease uremic toxin and blood glucose levels and reduce oxidative stress and inflammation (13).

Concretely, green tea, caffeine, and omega-3 polyunsaturated fatty acids are beneficial for restoring the changed gut microbiota composition. (21)

Studies have shown that the composition of the microflora affects specific complications of diabetes, such as diabetic kidney disease, cardiovascular disease, diabetic retinopathy and diabetic neuropathy. In many of these conditions, interference with the composition of the gut flora has been shown to have a major impact on the ability to control these conditions.(13) .

Diabetic Kidney Disease

Approximately 40% of people with uncontrolled DM2 develop diabetic kidney disease (DKD). However, multiple research studies have recently demonstrated that dysbiosis of the intestinal flora may be involved in the pathogenesis of chronic kidney disease. According to Li et al, when diabetic rats were fed a high-fiber diet and diabetic control rats were fed a standard diet or a no-fiber diet, the first group was found to be significantly less prone to developing diabetic kidney disease, which is characterized by albuminuria, hypertrophy of the glomeruli, injury to podocytes, and formation of fibrotic interstitial tissue. Dietary fiber may beneficially alter the gut microbiota and enhance microbial dysbiosis. For instance, dietary fiber increased the colonization of Prevotella and Bifidobacterium (22,23,24,25).

Diabetic retinopathy

Diabetic retinopathy represents the most frequent and harmful microvascular condition associated with diabetes mellitus. It has emerged as a leading cause of vision loss and disability in the adult population. Numerous studies have reported an association between dysbiosis of the gut microbiome and eye biofilm and a variety of diseases of the ocular system. Specifically, a decrease in the proportion of Bacteroidetes and Actinobacteria has been observed in patients with diabetic retinopathy compared to control individuals. Changing the gut microbiota profile through probiotic supplementation has shown positive effects in preclinical studies of diabetic retinopathy. An abnormality in the intestinal microbial composition may induce or accelerate diabetic retinopathy, while the presence of useful bacteria like Lactobacillus may decrease the likelihood and reduce its progression. Inflammation is a central mechanism involved in the development of diabetic retinopathy, so consequently, focus on anti-inflammatory strategies as a first-line therapy for diabetic retinopathy is needed. For instance, Coriobacteriaceae may modulate glucose balance in the body by influencing energy metabolism in the hepatic system and preventing hyperglycemia. Ruminococcaceae and Firmicutes may enhance the role of ClpB-like in the reduction of adipose tissue (26,27,28).

Diabetic neuropathy

Diabetic neuropathy has been associated with alterations in the gut microbiota diversity and increased presence of microbial dysbiosis. A comparative study of the intestinal flora of patients with diabetic neuropathy, diabetes without diabetic neuropathy and healthy persons revealed an enhancement of Firmicutes and Actinobacteria and a reduction of Bacteroidetes in diabetic nephropathy patients in comparison to patients with diabetes without diabetic neuropathy and healthy persons. In addition, a reduction in Bacteroides and Faecalibacterium and an increased frequency of Escherichia-Shigella, Lachnoclostridium, Blautia, Megasphaera and Rumincoccus were found. It is suggested that these alterations in the intestinal microbiome are a consequence of insulin resistance. Supplementation with Bifidobacteria and Lactobacillus or fecal transplantation may help in the therapy of DM2. The precise role of the intestinal microbiome in the

development and pathogenesis of diabetic neuropathy remains to be investigated (29,30,31).

Cardiovascular complications

A nutritional intervention approach has been shown to be an important mechanism for decreasing cardiovascular disease risk. Diets high in fiber, probiotics and prebiotics increase the number of useful organisms and decrease the number of known opportunistic pathogenic microorganisms, which result in reduced blood pressure and inhibited cardiac enlargement and cardiac fibrosis. (32,33)

The intestinal microbiome dysbiosis also influences the occurrence of hypercholesterolemia by affecting the hepatic metabolism of cholesterol and by modifying bile acids. Research has increasingly suggested that the microbiome of the intestine may play a role in the development of CVD by generating metabolic products including bile acids, coprostanol, short-chain fatty acids, and total metabolites of fatty acids.(13,34,35)

Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a potential treatment that aims to replace intestinal pathogens by transferring fecal material from healthy individuals into the GT of patients. FMT has been shown to be beneficial in the management of Clostridioides difficile infections, where fecal transplantation has been shown to achieve an 80% cure rate. The use of FMT is presently limited because of the inherent dangers, including the potential transmission of infectious agents or toxins that may lead to new gastrointestinal disorders. Additional studies are required to determine whether FMT can be applied to other aspects of cardiometabolic disease. Rather than fecal samples, the transfer of just a specific panel of bacteria could provide a reasonable option to FMT (36,37,38).

Conclusion

Preclinical and clinical studies have shown that the use of nutrition, prebiotics, probiotics and fecal microbiota transplantation represent possible measures to optimize the gut microbiota and decrease the risk of DM2. The purpose of this paper is to review the recent research on the gut microbiota and possible impact

on type 2 diabetes mellitus. More and more studies have supported that the gut microbiota has an important impact on the pathogenesis and the therapy of this disease. Modifications in the diversity and frequency of microorganisms residing in the gut, and the accumulation of metabolites they generate, have been correlated with DM2. The study of intestinal microflora could lead to the discovery of new treatments. It is also worthwhile to explore new approaches for therapeutic intervention that target the intestinal flora in DM2. In conclusion, further studies are needed to understand the role of the gut microbiome in the pathogenesis and therapy of DM2. Novel therapeutics aimed at altering the gut flora in DM2 are promising (39,40).

Declarations

Funding

This research did not receive any specific grant from funding agencies.

Author contributions

Conceptualization, A.M., H.S. ; Methodology, P.G. and A.M. ; Validation, P.B. and A.S. ; Formal Analysis, Z.M, M.D.; Investigation, A.N. and A.M; Resources, A.M. ; Data Curation, H.S. and A.M. ; Writing – Original, A.M. ; Writing – Review & Editing, A.M. and A.S. ; Visualization, P.B. and P.G. ; Supervision, A.S.; Project Administration, A.N., M.D.

Conflicts of interest

The authors have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

Institutional Review Board Statement

Not applicable.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data availability

The data have not been made public, but are kept with the authors, if necessary.

Ethics approval

Written informed consent for publication was obtained from the patient. We complied with the policy of the journal on ethical consent.

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