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Is There a Connection Between Intestinal Barrier Disruption, Dysbiosis, and the Development of Type 2 Diabetes Mellitus? - a literature review

1. Katarzyna Wicha [KW]

1st Military Clinical Hospital with Polyclinic of Independent Public Health Care Unit in Lublin, Aleje Racławickie 23, 20-049 Lublin, Poland

https://orcid.org/0000-0001-8822-2182

kxwicha@gmail.com

2. Monika Brzozowska [MB]

Collegium Medicum, Nicolaus Copernicus University, Bydgoszcz, Poland, Jagiellońska 13/15, 85-067 Bydgoszcz

https://orcid.org/0009-0006-5574-0059

monika.brzozowska99@gmail.com

3. Wiktoria Wardal [WW]

Szpital Pediatryczny w Bielsku-Białej, ul. Sobieskiego 83, 43-300 Bielsko-Biała, Poland

https://orcid.org/0009-0008-6665-2374

wiktoria.wardal97@gmail.com

4. Natalia Furlepa [NF]
Samodzielny Publiczny Zakład Opieki Zdrowotnej w Łukowie: Łuków, Poland, PL
21-400 Łuków, ul. Doktora Andrzeja Rogalińskiego 3
https://orcid.org/0009-0002-8163-2087
nataliafurlepa@gmail.com

5. Robert Rzenno [RR]
Samodzielny Publiczny Zakład Opieki Zdrowotnej w Myślenicach
ul. Szpitalna 2, 32-400 Myślenice, Polska
https://orcid.org/0009-0003-3838-3262
drrobertrzenno@gmail.com

6. Karolina Wojciechowska [KW]
Regionalny Szpital Specjalistyczny im. dr. Władysława Biegańskiego w Grudziądzu
Doktora Ludwika Rydygiera 15/17, 86-300 Grudziądz
https://orcid.org/0009-0004-4535-0327
wojciechowskaxkarolina@gmail.com

7. Marcelina Matuszewska [MM]
Samodzielny Publiczny Szpital Kliniczny im.prof. W. Orłowskiego CMKP
ul. Czerniakowska 231, 00-416 Warszawa
https://orcid.org/0009-0002-2301-669X
marcelina.matuszewska@wp.pl

8. Natalia Sidz [NS]
University Clinical Center in Gdansk, Poland
80-952 Gdansk, Debinki 7
https://orcid.org/0009-0005-0685-4175
sidz.natalia26@gmail.com

9. Magdalena Tomaszewska [MT]
Uniwersytecki Szpital Kliniczny nr. 1 im Norberta Barlickiego w Łodzi
ul. Stefana Kopcińskiego 22, 90-153 Łódź
https://orcid.org/0009-0009-4567-394X
magdalena_tomaszewska@onet.eu

10. Wiktoria Jedlikowska [WJ]
Heliodor Swiecicki Clinical Hospital, Poznań, Poland
https://orcid.org/0009-0002-7874-9911
wiktoria.jedlikowska1998@gmail.com

Abstract

Introduction and purpose: The intestinal barrier and microbiota play an instrumental role in maintaining good health. Its proper function is ensured by many different mechanisms, especially intercellular tight junctions (TJ). Numerous factors such as poor eating habits may lead to dysbiosis, disruption of TJs and subsequently to the development of the leaky gut syndrome.

Objecton: To assess whether there is a connection between intestinal barrier disruption, dysbiosis and higher probability of the development of type 2 diabetes mellitus (T2DM).

Material and method: The review was conducted with the use of databases such as PubMed and Scopus. The used key words were as follows: intestinal barrier, gut microbiome, leaky gut syndrome, diabetes mellitus and hyperglycemia. Only studies which contained relevant information about the influence of an increased intestinal permeability and dysbiosis on diabetes mellitus were enrolled in this research.

Results: DM may lead to increased intestinal permeability due to numerous mechanisms such as GLUT-2-dependent mechanisms, dysfunctions in tight junction, entrance of pathogenic bacteria into the circulation, which consequently may cause a low systemic inflammation and beta cell destruction. There is a distinct possibility that intestinal barrier may be restored with use of butyrate, prebiotics, antibiotics, GLP-2 agonists, probiotics, metformin, colostrum and kombucha. According to studies proper microflora may improve intestinal barrier's function and also glucose management.

Conclusion: Taking into consideration all facts mentioned above, the authors drew a conclusion that there is a strong connection between intestinal barrier disruption, state of a microbiome and the development of T2DM.

Keywords

intestinal barrier, gut microbiome, leaky gut syndrome, diabetes mellitus, hyperglycemia

1. Introduction and purpose

This study was conducted in order to assess whether there is a connection between an occurrence of an intestinal barrier disruption, dysbiosis and higher probability of DM 2 development.

Leaky gut syndrome

The intestinal barrier plays various roles in the human body out of which the most important are probably digesting ingested food and absorption of nutrients. The epithelium constitutes not only a physical barrier but also biochemical, thus it prevents the penetration of pathogens, toxins, and allergens from the lumen to the mucosal tissues [1]. The intestinal barrier dysfunctions may negatively affect organs and processes occurring in the human body. The main issue is caused by increased penetration of proinflammatory agents, which includes lipopolysaccharide (LPS) to the bloodstream and then all sorts of tissues. It leads to a low-grade systemic inflammation which consequently increases the risk of a development of numerous gastrointestinal diseases such as inflammatory bowel disease (IBD), celiac disease and irritable bowel syndrome (IBS) [2]. Moreover, there are other conditions such as diabetes, obesity, autoimmune chronic kidney disease which are also frequently observed [3]. The proper function of the intestinal barrier depends on numerous factors such as adhesive mucous gel layer, immunoglobulin A, antibacterial peptides and intercellular tight junctions (TJ). There is a distinct possibility that TJ may be the major determinant of the intestinal physical barrier [4]. One of the reasons behind TJ dysfunction is an unhealthy diet that is rich in saturated fats, simple carbohydrates and many other components considered commonly detrimental. The weakness of TJ is probably the main reason for a translocation of LPS from the intestines to the bloodstream [5,6]. Moreover, the increased intestinal permeability is frequently observed when the organism is under some kind of stress such as a long endurance exercises, non-steroidal anti inflammatory drugs intake or even during a pregnancy. In these states the normal function of the intestinal barrier may be restored by introducing the right diet. On the contrary, in conditions caused by organic diseases probably the proper diet won't

bring back the correct barrier function. However, it is still worth implementing. What is interesting is that the leaky gut syndrome may be both contributing to a disease or be a result of the disease itself [7]. This theory was researched by the scientist that conducted a study which indicated that stress may be an additional factor of the intestinal barrier dysfunction. Thus, it seems to be instrumental to reduce our daily stress level as low as possible in order to decrease the risk of autoimmune diseases [8].

Microbiome

There are about 10^{13} different types of microorganisms in human intestinal mucosa. Firmicutes and Bacteroidetes constitute approximately 90% of the gut microbiome, with Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia constituting the other major phyla of gut bacteria [9]. The microbiota play an instrumental role in maintaining good health, it helps with digestion and produce short-chain fatty acid. Besides that, microflora also activates the immune system, improves an intestinal passage, is responsible for absorption of nutrients and prevents toxins and bacteria from the absorption into circulation. [10] Moreover, an intestinal microflora exhibits many physiological functions, such as forming the intestinal epithelium, ensuring an intestinal integrity maintenance, the production of vitamins, and protection against pathogens. Dysbiosis is a state when the proper composition or the number of microorganisms is altered. It leads to impaired homeostasis and consequently conditions such as diabetes, obesity and allergies. Several types of disruptions to the gut microbiota have been identified: SIBO (Small Intestinal Bacterial Overgrowth), LIBO (Large Intestinal Bacterial Overgrowth), SIFO (Small Intestinal Fungal Overgrowth), and IMO (Intestinal Methanogen Overgrowth) The most common symptoms of dysbiosis go as follows: abdominal pain, bloating, gas, diarrhoea and constipation. As a result conditions such as malabsorption, nutrient deficiencies, anaemia and hypoproteinemia [11] The homeostasis is ensured by not only proper microflora but also by intestinal epithelial cells and the host immune system. This functional unit strictly depends on the integrity of the gut epithelium, which is made not only by TJ but also by desmosomes and adheren junctions, which form a physical barrier and connect adjacent epithelial cells, together with the lamina propria [12] Unfortunately, numerous factor, including bad eating habit or pharmacotherapy, may lead to dysbiosis and subsequently to inhibition of the expression of proteins responsible for maintaining the integrity of intestinal tight junctions. Finally there is a good chance of the development of the leaky gut syndrome [5].

Pathomechanism of the DM development

There are 2 different types of diabetes which is insulin- dependent type 1 diabetes mellitus caused by pancreatic beta cells destruction and type 2 diabetes mellitus which mainly occurs due to the insulin resistance and mainly violation of insulin secretion [13]. The genetic predispositions play the major role in the development of diabetes mellitus type 2. Yet, there are also other risk factors such as an unhealthy diet, a sedentary lifestyle or lack of physical activity. Numerous cases of this disease could have been avoided if the proper change would have been implemented on time. All people at risk of DM are recommended to modify their lifestyle, improve their eating habits, be physically active and abstain from alcohol and cigarettes. In the majority of the patients with DM at least one severe complication will occur during their life due to the disease. These conditions are potentially life and health threats and frequently require immediate treatment. The best example may be cardiovascular diseases characterized by a high mortality rate such as a heart attack or stroke [14]. It is proved that patients with DM (no matter which type) are more prone to develop the increased intestinal permeability than healthy people. Nevertheless, it is still a matter of debate whether diabetes is the reason behind the increased intestinal permeability or in reverse, the intestinal permeability leads to DM development. The scientists also consider if the increase in gut permeability is an epiphenomenon, an early manifestation of disease, or a critical step in disease pathogenesis [2].

2. Description of the state of knowledge

Leaky gut syndrome and diabetes mellitus

Hyperglycemia is regarded as one of the factors which may lead to an increased intestinal permeability. The reason behind that is the occurrence of numerous different mechanisms. Nevertheless, it is believed that GLUT-2 dependent mechanisms and dysfunctions of TJs cohesion play an instrumental role in the intestinal barrier's disruptions [15]. Precise mechanism that combines both diabetes mellitus and the microbiom's disruption is still not fully understood. However, recent findings indicate a number of plausible mechanisms that could account for an increased exposure of luminal contents to immunoreactive host cells contributing to insulin deficiency or resistance. This increased exposure to luminal antigens can possibly result in an autoimmune destruction of pancreatic beta cells as has been proposed

in type 1 diabetes, or in an increased peripheral insulin resistance and subsequently type 2 diabetes. Thus, a restoration of the proper intestinal barrier may be helpful in preventing and managing diabetes mellitus. There was a conducted study in which scientists achieved success restoring intestinal barrier with use of butyrate, prebiotics, antibiotics and GLP-2 agonists [16] Another considered mechanism is based on the entry of pathogenic bacteria into the bloodstream which further are the possible reason of low inflammation and beta cell destruction through molecular mimicry and autoimmunity [17]. As previously mentioned, low-grade inflammation is often directly caused by increased intestinal permeability. Usually there is an increased level of LPS and interleukin 6. In one of the conducted trials 93 Gambian women were divided into groups as follow: lean (BMI): 18.5-22.9 kg m(-2)), obese non-diabetic (BMI: 30.0 kg m(-2)) and obese diabetic (BMI: 30.0 kg m(-2) and attending a diabetic clinic). Scientists measured the level of LPS, endotoxin-core IgM and IgG antibodies (EndoCAb) as measures of endotoxin exposure and interleukin-6 as a marker of inflammation. It was observed that the level of Interleukin-6 was independently and positively associated with both obesity and diabetes LPS levels were highest in the obese-diabetic group compared with the other two groups. This directly indicates that gut-derived inflammatory products are associated with obesity and diabetes [18]. Increased intestinal permeability threatens not only to increase the risk of autoimmune diseases' development but also it is thought to be the reason behind worsening conditions in critically ill patients with pre-existing hyperglycemia. In one of recently conducted studies, there was observed a relationship between intestinal barrier biomarkers such as LPS, D-lactate, glycated hemoglobin A1c (HbA1c), fasting blood glucose (FBG), and prognosis of critically ill patients. D-lactate and LPS, which is increased in the leaky gut syndrome, were associated with sequential organ failure assessment (SOFA) score and 90-day mortality. LPS was an independent risk factor of 90-day mortality [19]. Thus, improvement of intestinal barrier function is hugely important even in elderly, chronically and critically ill patients. Moreover, there was another research on this matter carried out with diabetic mice. The animals were given insulin receptor antagonists (S961) for one week. After 7 days from the last dose the mice underwent some tests. There was a significant deterioration of intestinal barrier's function due to its increased permeability and impairment of cell-cell junction integrity. In addition the mice rapidly developed severe gut dysbiosis characterized for instance by an increased number of pro-inflammatory Proteobacteria. It is worth mentioning that cessation of applying S961 promotes restored the proper intestinal barrier. The outcomes of this study indicate that insulin signaling is an indispensable gatekeeper of intestinal barrier integrity,

acting as a safeguard against microbial imbalance and acute infections by enteropathogens [20].

Microbiome and diabetes mellitus

Outcomes from various studies indicate that the reason behind an intestinal barrier dysfunction may be dysbiosis characterized as a loss of beneficial bacterial species and increase of the harmful ones. Research prove that there is a significant change in the gut microbial composition between healthy people and animals and those who are struggling with T2D [21]. One of the studies was conducted in order to assess the state of the intestinal microbiome of mice which spontaneously developed T2D. Scientists primarily discovered underrepresentation of the major butyrate producer, Faecalibacterium prausnitzi [22]. What is worth noticing is that F. prausnitzii is also nearly absent from Crohn's disease-associated gut microbiota [23]. These microorganisms play a major role in producing microbial anti-inflammatory molecule, which consolidates TJ integrity, Treatment of db/db mice with the F. prausnitzii-derived anti-inflammatory molecule improved intestinal permeability. [24].Outcomes outlined by a recently conducted study indicate the negative correlation of the HbA1c level with abundance of bacterias such as Prevotella, Faecalibacterium, and Ruminococcaceae. There was also a positive correlation with abundance of Dorea formicigenerans, Bacteroidetes, Lactobacillales, and Bacteriodes. Bacteroides were negatively correlated with FBG. Moreover, there was a positive correlation between inflammatory parameters and gut dysbiosis in patients with T1D.It means that diabetics are more prone to develop leaky gut syndrome. Restoring the proper microbiome may improve not only the intestinal barrier's function but also glucose management and consequently lower risk of diabetes complications [25].

The abundance of clostridium citroniae C. bolteae, Tyzzerella nexilis, and Ruminococcus gnavus is also positively correlated with t2dm's development. These species may be the reason for the occurrence of numerous metabolic diseases such as obesity and lead to increased levels of inflammatory cytokines secretions [26].. The major site of production of those cytokines is probably adipose tissue, which is frequently overgrowth in obeseT2DM people. The inflammatory response contributes to T2DM occurrence by causing IR [27.

The Western diet

Typical Western diet is widely regarded as detrimental to our health. It contains high amounts of soil, trans fats, simple carbohydrates and moreover, most of the products are full with harmful flavour enhancers. This kind of diet leads directly to development of numerous types of health conditions. Conducted studies proved that a high-fat diet is one of the reasons for intestinal barrier's disruption due to increasing its permeability and causing gut dysbiosis [28]. On the molecular level this diet may weaken the adherence of TJ proteins in the gastrointestinal tract. As a result, leaky gut syndrome and penetration of toxic metabolites into circulation may occur. It leads to low grade systemic inflammation and secondary to metabolic disorders. Moreover endotoxemia affects the composition of the gut microbiome and decreases the production of metabolites like short- chain fatty acids, which have strongly beneficial properties, and subsequently the disorder is getting worse. [28,29] Particularly harmful is the penetration of LPS, which is derived from gram-negative bacteria, into the bloodstream and next to tissues and organs. It has been associated not only with above mentioned intestinal conditions, but also it may cause numerous diseases such as as autoimmune disorders, neurological, metabolic diseases like diabetes and cardiovascular disease [30]. Fats are not the only threats to the intestinal barrier, yet also carbohydrates have been associated with high risk of causing intestinal disruption. Outcomes of the recent study indicate that both hyperglycemia and excessive sugar intake may cause profound gut microbiota dysbiosis, which results in a disturbance in mucosal immunity that enhances infection susceptibility [31]. There is a wide variety of artificial food compounds that are used to enhance the products' taste. One of those is a glucose-fructose syrup which currently is commonly added to all kinds of products, it can be found for instance in drinks, alcohol drinks, juices, yoghurts, dairy products, ice creams, sweets etc. It seems to be unavoidable in our diet. Unfortunately a recent study, conducted with humans, showed that fructose is probably detrimental to the gastrointestinal system. In the trial, intake of this substance significantly elevated plasma bacterial endotoxin levels, likely resulting from decreased levels of intestinal tight junction , proteins (zonula occludens 1, occludin, claudin-1, and claudin-4). Fructose intake causes protein nitration of intestinal TJ and AJ proteins, resulting in increased gut leakiness and endotoxemia [32.

Beneficial products

The gut microflora is particularly sensitive to the type of consumed food. Thus, it gives a possibility to support it by the use of proper diet, diet supplements and avoiding harmful products and medications. In one of a recent conducted studies the scientists took a closer look at metformin, which is commonly used in diabetes and prediabetes conditions. However, its precise mechanism hasn't not been discovered yet. The already known mechanisms go as follows: reducing hepatic glucose production, acting on the gut to increase glucose utilisation, increase GLP-1 and alter the microbiome. At the molecular level, metformin inhibits the mitochondrial respiratory chain in the liver, leading to activation of AMPK, enhancing insulin sensitivity [33. The scientist proved that metformin may increase the level of the beneficial short chain fatty acids, diminish the permeability of an intestinal barrier and also positively affect the organism's immune response. The positive effect of the metformin might be multiplied by use of the high fiber diet based on plant products. Unfortunately, numerous patients might not be able to take this drug due to its high activity in the gastrointestinal tract, which may cause unpleasant symptoms such as nausea or bloating [34]. In order to precisely assess how metformin affects the intestinal microbiome, the scientists conducted a study with mice sick with T2DM. For a month mice ,dependent on the assigned group,were given metformin or placebo. Transfer of fecal samples (obtained before and 4 months after treatment) from metformin-treated donors to germ-free mice showed that glucose tolerance was improved in mice that received metformin-altered microbiota [35].

A research into diabetics's microflora outlined the diminished number of the types of bacteria which are the main producers of a short chain fatty acid- butyrate. Butyrate has many beneficial properties such as promoting the integrity of the gastrointestinal barrier and its deficiency may cause an increased risk of intestinal permeability. According to studies prebiotics and non-digestible carbohydrates can be helpful in coping with this matter. These substances are fermented by the colonic microbiota which lead to the production of a range of metabolites including SCFAs [36]. In animal investigations bacteria such as Bacteroidesuniformis and Bacteroides acidifaciens were also found to reduce insulin resistance and prevent obesity in diabetic mice. Due to that fact another trial with was conducted to assess the influence of probiotics intake on carbohydrate metabolic parameters. 25 out of the 50 enrolled patients were given for 8 weeks Lactobacillus sporogenes GBI-30 (probiotic), maltodextrin and fructooligosaccharide (prebiotic) and the rest of them were given 2g placebo. Blood samples had been collected before the beginning of the trial and after

its completion. In the study group, after the intervention, there was observed a significant decrease in the mean serum levels of HbA1c, marginally significant decrease in FBG, and mean serum levels of insulin and TAC were significantly increased [37]. These outcomes are confirmed by another study conducted as follows. Mice that were regularly given probiotics improved their lipid and glucose profile and also improved the function of their intestinal barrier. Moreover, there was observed the increased expression of claudin-1 and mucnin-2 and diminished number of E. Coli and LPS. It was also proved that probiotics may enhance the insulin secretion by stimulating the secretion of the GLP-1 hormone. Probiotics also act protectively on pancreatic beta cells and prevent them from apoptosis. [38]. Probiotics lower the oxidation stress and due to that may support the treatment of diabetes. Those that include Bacteroides and Lactobacillus, are being considered potential agents for the treatment of diabetes because of their role in increasing insulin sensitivity, lowering total cholesterol, and reducing body weight [39].

Polyphenols are a group of phytochemicals with potential health-promoting effects. They are classified as flavonoid (flavonols, flavanols, flavones, flavanones, isoflavones, and anthocyanins) and non-flavonoid molecules (phenolic acids, hydroxycinnamic acids, lignans, stilbenes, and tannins) [40]. They can be found in a large variety of food products and some studies proved their multiple beneficial properties such as: antioxidant and anti- cancer activity, anti-diabetic, cardio protective, neuro protective and anti-aging effects [41]. There was research conducted in order to assess whether the polyphenols rich diet may improve an intestinal barrier function. 66 individuals aged over 60 had been enrolled to study which lasted for 8 weeks. The Zonulin levels, an IP surrogate marker involved in tight junction modulation, had been checked on the beginning and completion of the trial. Patients had increased their polyphenol intake up to 1391 mg/day. After 8 weeks the zonulin significantly decreased which meant the improvement in intestinal permeability. Moreover, this therapy also resulted in lower blood pressure and increased fibre- fermenting and butyrate-producing bacteria [42]. Another scientist focused their studies on one specific polyphenol rich substance which was the resveratrol. It can be found in various food products such as dark chocolate, grapes, red wine and nuts. The research was conducted with mice which had been given supplementation with resveratrol for a few weeks. After that, mice underwent intraperitoneal glucose tolerance testing. The outcomes showed that the mice that were given resveratrol improved their lipid and glucose profils, glucose tolerance and the intestinal barrier function due to an increased number of Bilophia and Ruminococcus and reducing the

proportion of Firmicutes and the Firmicutes-to-Bacteroidetes ratio [43]. Kombucha is a fermented tea rich in polyphenols and organic acids and it probably can be beneficial to people struggling with diabetes mellitus type 2. However, the precise mechanism of this phenomenon hasn't been discovered yet. The research conducted on mice with previously induced diabetes shows the increased number of bacterias that produce SCFs and diminished number of gram negative bacterias after 4 weeks of an intake of a kombucha. Despite that, the damage of an intestinal barrier was repaired, displacement of LPS was reduced and thereby the decrease of inflammatory and insulin resistance. The increased level of SCFAs led to improvement of pancreatic beta cells by increasing the secretion of GLP1/PYY. [44]. Curcumin exhibits many health-promoting properties such as positive affection on carbohydrates metabolism. The outcomes of study conducted on rats show significant improvement of an intestinal barrier after 10 weeks of supplementation with 200mg/kg of curcumin a day. Moreover, there was also a lowered level of glucose and diminished the insulin resistance. The authors suggest that curcumin may prevent the intestinal mucosal barrier [45]. Lately many people started to supplement colostrum due to its restorative properties and possible effect of strengthening the immunity. A recent systematic review indicates that colostrum may be highly beneficial for athletes suffering due to the leaky gut syndrome, since it improves the gut permeability [46]. Nevertheless, there are also products that are detrimental and may exhibit harmful properties to our intestines. These are compounds such as zonulin, lactulose/mannitol, sucralose, sucrose, lactulose/L-rhamnose, and sucralose/erythritol, which might be the reason for increased intestinal permeability [25]. When it comes to a healthy lifestyle, diet is not the only thing that matters. The main focus of a recently conducted trial was to assess whether physical activity may affect gut microbiota of people struggling with diabetes mellitus type 2. 30 enrolled individuals underwent some tests before the experiment and after its completion, which was 6 months. During this time they were doing endurance, resistance and flexibility training. Diabetes caused significant overgrowth of mycetes and increased intestinal permeability with low- grade systemic inflammation and chronic exercises reduced all of these phenomenons [47].

3. Summary

Undoubtedly, there is a significant association between gut microbiome, intestinal barrier and metabolic disorders including diabetes mellitus. However, it still hasn't been assessed which of these disorders is a trigger factor and appears as the first disturbance. This matter seems tough to assess due to the possibility of a mutual influence of diabetes mellitus and intestinal

barrier dysfunction. According to a recent study the gut microbiome may modulate human metabolic pathways, thus its alterations lead to increased risk of developing diabetes mellitus. Some of the reasons behind this phenomenon are a lower production of short chain fatty acids due to shortage of beneficial bacterias and translocation of bacterial-derived toxins into the bloodstream. These toxins might lead to several conditions such as insulin resistance, vascular injury or podocyte damage. [48]. Findings of another research which aimed to assess whether there is an influence on mices' offsprings intestinal barrier caused by maternal intermittent fasting. The researchers came to the conclusion that maternal intermittent fasting deteriorates glucose and lipid metabolism in offspring. It is probably due to reduction in beneficial bacteria such as Lactobacillus intestinalis that may contribute to the metabolic consequence of prolonged maternal intermittent fasting on the offspring [49].The abundance of L. intesingalis has been also proved to be negatively correlated with obesity [50]. When it comes to the exact type of bacterias which are associated with a higher rate of diabetes development, it is necessary to name the main triggers. In one of the conducted studies T1D was negatively correlated with abundance of Prevotella, Faecalibacterium, and Ruminococcaceae and positively correlated with abundance of Dorea formicigenerans, Bacteroidetes, Lactobacillales, and Bacteriodes. Bifidobacteria was negatively correlated with fasting blood glucose. What is worth emphasising is occurance of a positive correlation between inflammatory parameters and gut dysbiosis in patients struggling with T1DM, thus this group is at higher risk of experiencing leaky gut syndrome, bacterial transformation and low grade systemic inflammation [51]. According to a recent study some of the innate chemokine signals such as eosinophils, immunoglobulin A (IgA), T helper (Th) 17 cells and their cytokines may be associated with obesity and dysregulated glucose homeostasis. In this research Intestinal epithelial cells emerged as critical modulators of obesity and glucose homeostasis through their effect on lipopolysaccharide (LPS) signaling and decontamination. Furthermore, IECs create a link between microbial metabolites and whole-body metabolic function. These discovers are highly promising due to the future possibility of providing treatments and prevention strategies for obesity and T2D [52].

Taking into consideration all the facts mentioned above, the authors drew a conclusion that there is a strong connection between intestinal barrier disruption, microbiome and the development of type 2 diabetes mellitus.An altered microbiome may negatively affect the intestinal barrier, which increases risk of T2DM through numerous mechanism. Nevertheless, there are many ways to help restore proper microflora and the intestinal barrier. These include

changes in lifestyle and eating habits, as well as the introduction of certain types of medications and supplements, which might be beneficial in restoring the proper microflora and intestinal barrier.

Disclosure

Authors contribution

Conceptualization: Katarzyna Wicha,

Methodology: Katarzyna Wicha, Monika Brzozowska,

Software: Monika Brzozowska, Natalia Furlepa,

Check: Robert Rzenno, Karolina Wojciechowska, Magdalena Tomaszewska,

Formal analysis: Monika Brzozowska, Marcelina Matuszewska, Magdalena Tomaszewska,

Investigation: Katarzyna Wicha, Karolina Wojciechowska, Natalia Sidz,

Resources: Natalia Furlepa, Marcelina Matuszewska, Wiktoria Jedlikowska

Data curation: Robert Rzenno, Marcelina Matuszewska, Wiktoria Jedlikowska

Writing-rough preparation: Katarzyna Wicha, Karolina Wojciechowska,

Writing-review and editing: Katarzyna Wicha, Magdalena Tomaszewska,

Visualization: Natalia Furlepa, Robert Rzenno, Natalia Sidz,

Supervision: Monika Brzozowska, Natalia Sidz, Wiktoria Jedlikowska

Project administration: Monika Brzozowska, Natalia Furlepa, Magdalena Tomaszewska

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