INFLUENCE OF PREBIOTICS ON THE ANTIOXIDANT AND THE LIPID PROFILE OF PATIENTS WITH TYPE I DIABETES MELLITUS

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Abstract: Type I diabetes mellitus is an autoimmune disease, in which the immune system attacks the β-cells of the islets of Langerhans in the pancreas, which produce insulin. Some of the main complications of this disease are the micro- and the macrovascular damages with main consequence: cardiovascular diseases, which appear to be the leading cause of mortality in this widespread, socially significant disease. The development of type I diabetes is affected by non-genetic factors such as the development of the optimal microbiome in early life, which programs the immune system. Patients have different intestinal microflora in comparison to healthy individuals as well as alterations in the intestinal permeability, inflammation and insulin resistance. Prebiotics represent a selective fermentative ingredient of food, which allows specific changes in both the composition and in the activity of the intestinal microflora of the person and thus improves his health and well-being. Human milk oligosaccharides, present in breast milk, are modulators of the microbiota and are known for directly regulating the immune response. They are vital for the protection of children at risk of developing type I diabetes by assisting the development of the immune and intestinal microbiota in early life. Soybean oligosaccharides are potential prebiotics, which improve the immune function. After 22 days of administration of 4 g/kg weight soybean oligosaccharides, they significantly affect the proliferation of bifidobacteria and lactic acid bacteria compared to the control group. Probiotic microorganisms show favorable interrelations with their host by influencing the intestinal cell proliferation and differentiation and the immune system, and they counteract pathogenic microorganisms. The supposed direct effects of oligosaccharides on pathogenic flora infections include mimicry of receptors and influence on their virulence. The regulation of virulent genes through the presence of oligosaccharides and polysaccharides in the nutrient medium has been described for a number of pathogenic bacteria. The indirect effects of prebiotics on the immune system can result from the stimulation of the growth of probiotic bacteria and the stimulation of the production of short chain fatty acids. The increase of the number of probiotic bacteria stimulates the immune system and leads to protection against pathogenic invasion. Oxidative stress, which is an important component of a number of diseases, is characterized by an imbalance in the level of oxidants and antioxidants in favor of the oxidants. It can lead to irreversible impairment of lipids, nucleic acids and proteins. It has been proved that the administration of synbiotics has a positive effect on the parameters of the oxidative stress. The elevated level of serum cholesterol is recognized as a risk factor for the development of atherosclerosis, cardiovascular diseases and hypertension. It has been proved that there are significant changes in the lipid profile of patients, treated with galactooligosaccharides. Prebiotics are a cheap and a low risk supplement, which can be used to favorably influence type I diabetes mellitus. They can also improve the glycemic control through changes in the intestinal microflora, the permeability of the intestines and inflammation. The purpose of this review is for the influence of new prebiotics (galactooligosaccharides and xylooligosaccharides) on the lipid and antioxidant profile of patients with type I diabetes mellitus to be studied.
Keywords: type I diabetes mellitus, intestinal microflora, prebiotics, oligosaccharides, microbiota.

1. INTRODUCTION

Type I diabetes mellitus (T1DM), also referred to as diabetes of the young age, is an autoimmune disease, in which the pancreas does not secrete or it secretes an insignificant amount of insulin, due to the destruction of the β-cells by the immune system of the organism. Although the exact reason for its development has not been yet clarified, the disease can be caused by different factors of biological and genetic nature – chemicals, viruses, etc. (Howard, 2018).

Regardless of the active research work on its studying, there still is not a cure for T1DM. Some of the main complications of T1DM are the micro- and the macrovascular damages with main consequence: cardiovascular diseases. According the World Health Organization (WHO) more than 36 million people die of non-infectious diseases worldwide each year. The non-infectious diseases, including cardiovascular diseases, diabetes, respiratory diseases and even cancer, represent 2/3 of the death cases in the world. Nowadays the cardiovascular and the cerebrovascular diseases have become the main reason for death, which makes more than 40 % from the total number of deaths. Here is why studying the risk factors for cardiovascular diseases is of great significance in the clinical medicine and public health (Yang, 2018).

2. DIABETES AND PATHOLOGY

T1DM induces typical systemic complications (hyperglycemia, polyuria, renal hypertrophy) and is accompanied by a remodeling of the structure of the left camera (cardiomyocytic hypertrophy and collagen content) and contractile dysfunction. The diabetic cardiomyopathy is the main reason for mortality in T1DM (Isfort et al., 2014). A number of data shows that inadequate control over glucose is the main reason for the development of the typical characteristics of the diabetic cardiomyopathy in the early stages of the disease (Tate et al., 2017). The appearance of mitochondrial dysfunction in the cardiomyocytes of the diabetic heart is considered to be a significant factor in the development of the diabetic cardiomyopathy (Isfort et al., 2014). Due to this dysfunction the ongoing of a number of enzyme-catalyzed reactions is damaged. Fundamental importance is given to the raised concentration of Acetyl-CoA, which is due to excess oxidation of fatty acids (Taegtmeyer and Passmore, 1985). The participation of reactive oxygen species (ROS), whose increased amounts are established in the mitochondria of mice with experimental diabetes, is also being discussed (Boudina et al., 2007).

The studying of the morphology and the function of the cardiomyocytes in the early stages of diabetes, using contemporary analytical methods is of importance for assessing the present accompanying pathological alterations and the extent of the risk to the patient.

T1DM is associated with characteristic structural and functional alterations of the liver, which are linked to the changes in the metabolism of glycogen and lipids. Excess glycogen deposition, development of fibrosis, cirrhosis, steatohepatitis and biliary pathology in the liver are conditions, which are reported in 55-80 % of the patients (Levinthal, Tavill, 1999). Microscopic examination of the liver of diabetic rats shows alterations in the liver architecture, cytoplasmic vacuolization of the hepatocytes and signs of necrosis (Nazratun et al., 2017). The blood vessels are dilated with signs of leucocyte aggregation and congestion.

T1DM is also associated with changes in the content of the intestinal microflora. What is more, the amount of bacteria, which are of great significance for the maintenance of the intestinal integrity, is considerably lower in children with diabetes, compared to that in healthy children. Patients with T1DM have different intestinal microflora in comparison to healthy individuals as well as alterations in the intestinal permeability, inflammation and insulin resistance. It has been discovered that the bifidobacteria correlate negatively with the β-cell autoimmunity in Finnish children with diabetes. It is known that Faecalibacterium prausnitzii, a bacterium, which produces butyrate, has some anti-inflammatory effects and is in reduced quantities in children with autoantibodies, related to diabetes. These discoveries could be beneficial for the developing of strategies to control the development of T1DM through modifying the intestinal microflora (Murri et al., 2013).

3. CONCEPT FOR PREBIOTICS

The concept for prebiotics has been introduced in 1995 by Gibson and Roberfroid as an alternative approach to modulate the intestinal microflora. Prebiotics represent a selective fermentative ingredient of food, which allows specific changes in both the activity and the composition of the intestinal microflora of the person and thus improves his well-being and health (Gibson et al., 2004; Roberfroid et al., 2007). They are indigestible and manifest prebiotic effect – they stimulate the development and the metabolism of the useful microorganisms in the large intestine (Ma, 2017). All prebiotics are short-chained oligosaccharides, comprised of 3 to 10 sugar monomers, and have a low degree of polymerization (Gibson et al., 1995). The monosaccharide composition, the glycosidic bond and the degree of polymerization are important for their prebiotic properties. Glucose, galactose, fructose and xylose are the most common monomers of oligosaccharides (Barreteau et al., 2006).

4. PREBIOTICS AND INTESTINAL MICROFLORA

The development of type I diabetes is affected by non-genetic factors such as the development of the optimal microbiome in early life, which programs the immune system. Long breastfeeding is an independent protective factor against the development of T1DM through bioactive components. Human milk oligosaccharides, present in breast milk, are modulators of the microbiota and are known for directly regulating the immune response. They are

vital for the protection of children at risk of developing type I diabetes by assisting the development of the immune and intestinal microbiota in early life. It has been discovered that the administration of 1 % authentic human milk oligosaccharides during early life (only for a six-week period) slows down and inhibits the development of T1DM in non-obese diabetic mice and reduces the development of severe pancreatic insulitis (an autoimmune destruction of the insular apparatus of the islets of Langerhans in type I diabetes) at a later stage. These protective effects are associated with the following: beneficial interactions of the fecal microbiota; anti-inflammatory microbiotic metabolites (for example short-chained fatty acids) in the fecal and the cecum content; induction of anti-diabetogenic cytokines. In addition, in vitro human milk oligosaccharides, combined with short-chained fatty acids, induce the development of tolerogenic dendritic cells (t DC). These cells activate functional regulatory T-cells, which is in support of the protective effects, determined in vivo (Xiao et al., 2018).
Soybean oligosaccharides are potential prebiotics, which improve the immune function. Yan M. et al. (2017) have examined the role of the intragastral administration of soybean oligosaccharides in mice for determining their effects on the autochthonous intestinal microorganisms and the immunological parameters. After 22 days of administration of 4 g/kg weight soybean oligosaccharides, they significantly affect the proliferation of bifidobacteria and lactic acid bacteria compared to the control group (Yan et al., 2017).

5. MECHANISM OF ACTION OF PREBIOTICS

Probiotic microorganisms show favorable interrelations with their host by influencing the intestinal cell proliferation and differentiation and the immune system, and they counteract pathogenic microorganisms. It is well known that the human body has a limited number of enzymes, needed for the breakdown of complex carbohydrates (Roberfroid et al., 2010). Mammals can digest simple sugars (glucose and fructose), they can hydrolyze concrete disaccharides and a very small number of polysaccharides (starch). They cannot digest vegetable fibers – polysaccharides (pectin, xylan and arabinoxylan). A lot of the sugars, which are not degraded by the enzymes of the host, are a good source of carbon atoms and energy for the microflora for example fructooligosaccharides, galactooligosaccharides, glucooligosaccharides, xylooligosaccharides, inulin, starch, arabinoxylan, lactulose and raffinose (Roberfroid et al., 2010). In reality these “indigestible” compounds reach the distal bowel undegraded and here they act as fermenting substrates for the intestinal bacteria, represented by Bifidobacterium, Clostridium, Enterobacterium, etc. These microorganisms can hydrolyze the different carbohydrate poly- and oligomeric substrates and generate monosaccharides.
The supposed direct effects of oligosaccharides on pathogenic flora infections include mimicry of receptors and influence on their virulence. The attachment of receptors to epithelial surfaces is often the first step of the pathogenesis and this phase can be influenced by the presence of oligosaccharides. For example some oligosaccharides from milk products structurally resemble the glycoproteins, through which a lot of pathogens bind to the epithelial cells. In this way they act as receptor analogues and inhibit the infection (Gibson et al., 2004). Some studies show that xylooligosaccharides have a strong anti-adhesive effect against some strains of Listeria monocytogenes (Bovee-Oudenhoven et al., 2003). It is supposed that the anti-adhesive effects can be due to the modulation of the virulent genes of the intestinal pathogen. The regulation of virulent genes through the presence of oligosaccharides and polysaccharides in the nutrient medium has been described for a number of pathogenic bacteria. The prebiotic carbohydrates can function as signal molecules for virulent expression (Medellin-Pen˜a et al., 2007).
The indirect effects of prebiotics on the immune system can result from the stimulation of the growth of probiotic bacteria and the stimulation of the production of short-chain fatty acids (Abrams et al., 2005). The increase of the number of probiotic bacteria stimulates the immune system and leads to protection against pathogenic invasion. Several studies have shown that the administration of lactobacilli and bifidobacteria can inhibit Salmonella infection in mice (Bournet et al., 2012). The increased concentration of short-chain fatty acids (SCFAs) (acetate, propionate, butyrate) during the metabolism of prebiotics is well established and they can affect both the epithelial cells (intestinal gluconeogenesis) and the cells of the immune system (Bournet et al., 2012; De Vadder et al., 2014). It has also been found that short-chain fatty acids bind to specific cell receptors, G-protein coupled receptors (GPCR41 and GPCR43), which play a significant role in the functioning of the intestinal mucosa. What is more they stimulate the immune system and act as energetic regulators (Li et al., 2011).
Except for decreasing the dysbiosis in the intestinal microbial environment, prebiotics also improve the glucose tolerance via mechanisms, which probably include increased production and secretion of glucagon-like peptide-1 (GLP-1). During animal studies, it is found that diabetes is also related to increased intestinal permeability, which allows bacterial lipopolysaccharides (LPS) from gram-negative bacteria to get into the systemic circulation, which leads to metabolic endotoxemia. A secretion of pro-inflammatory cytokines and insulin resistance is triggered. Animal studies show that prebiotic treatment leads to a dose-dependent increase of the bifidobacteria, lowers the

intestinal permeability and the endotoxemia and improves the glucose tolerance. Prebiotics improve the production of GLP-2, which also decreases the intestinal permeability. Prebiotics can therefore improve the glucose homeostasis via two independent mechanisms: (1) regulation of GLP-1 for the improvement of the mass of the β-cells and (2) alteration of the intestinal microflora and the permeability to a less proinflammatory phenotype (Ho et al., 2016).

6. PREBIOTICS AND OXIDATIVE STRESS

Oxidative stress is considered to be an important component of different diseases. It is characterized by an imbalance in the level of oxidants and antioxidants in favor of the oxidants and this leads to impaired physiological function. Oxidative stress can also lead to irreversible chemical modifications of nucleic acids, lipids and proteins (carbamylation). Enzymes such as xanthine oxidase, NADPH oxidase and nitric oxide synthase can produce reactive oxygen and nitrogen species (ROS and RNS).

Lipid peroxidation is a process, in which oxidants attack lipids, containing a double bond, especially polyunsaturated fatty acids. The malondialdehyde (MDA), the hexanal and the 4-hydroxynonenal are amongst the many different aldehydes, which can be formed as by-products during lipid peroxidation. MDA has been broadly used for a long time as a convenient biomarker in the tracking of lipid peroxidation of omega-6 and omega-3 fatty acids because of its easy reaction with thiobarbituric acid (TBA) (Ayala et al.,2014).

Paulina Kleniewska and Rafał Pawliczak have proven that the administration of synbiotics lowers the serum levels of MDA and has a positive effect on the parameters of the oxidative stress (Kleniewska, Pawliczak, 2017).

7. PREBIOTICS AND LIPID PROFILE

The elevated level of serum cholesterol is recognized as a risk factor for the development of atherosclerosis, hypertension and cardiovascular diseases. It is supposed that by the year 2030 the cardiovascular diseases will become the main reason for death and will affect approximately 23, 6 million people worldwide. It is also considered that even 1 % lowering of the serum cholesterol can decrease the risk of coronary heart disease with 2-3 %. The risk of myocardial infarction is three times higher in patients with hypercholesterolemia compared to patients with a normal blood lipid profile (Hashmi et al., 2016).

Hashmi et al. have proven that there is a significant alteration in the lipid profile of rats, trated with galactooligosaccharides. They have reported a decrease in the serum levels of the total cholesterol, triglycerides, LDL cholesterol, VLDL cholesterol and an increase in the HDL cholesterol, as well as a reduction of the body weight of the rats.

The paraoxonases (PON) are a family of enzymes, which have wide specificity. Three members of the family have been found until this moment – PON1, PON2 and PON3. The synthesis of PON1 occurs in the liver, from where it is secreted into the bloodstream, where it is almost fully connected to HDL through the N-terminal hydrophobic signal peptide. The association with HDL is needed for the stability of the enzyme and the modeling of its activity. PON1 plays an important physiological role in the metabolism of lipids and the prevention of atherosclerosis via the protection of HDL and LDL against oxidation and lowering the risk of atherosclerotic damages. The serum concentration of PON1 correlates with the level of HDL and the concentration of apoA1 and thus the sufficient production of PON is related to a decreased risk of cardiovascular diseases. The lowering of the serum activity of PON is accompanied by an increase in oxidative stress and elevated risk not only of cardiovascular diseases and metabolic disorders, but also of a number of gynecological and tumor diseases. The physiologic role of the paraoxonase is connected to its ability to inhibit the oxidation of LDL and to stimulate the cholesterol removal from macrophages (Borovkova et al., 2017).

8. CONCLUSIONS

The consumption of prebiotics can modulate the intestinal microbiota, influencing the bacterial composition, the metabolic profile and human health. The intestinal microbes are key factors, included in the regulation of the energetic homeostasis, the lipid and the glucose metabolism. Therefore the modulations of the intestinal microbiota, caused by selectively fermenting oligosaccharides or brobiotic bacteria are of interest.

Oligosaccharides are relatively new, functional supplements, which are low in calories and they stimulate the growth of the beneficial microflora in the large intestine and favorably influence T1DM.

Further studies are needed for the efficiency of the use of prebiotics as an addition to the treatment of T1DM for improving the glycemic control and the prevention of complications, as the chronic hyperglycemia is the main reason for endothelial disfunction and for increased risk of cardiovascular diseases (Russell et al., 2016).

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