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REVIEW ARTICLE

Probiotics in prevention and treatment of cardiovascular diseases

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Summary

Increasing knowledge of the gut microbiota and its interference in human homeostasis in recent years has contributed to a better understanding of number of different interactions occurring in the gastrointestinal tract. Disruption of the microbiota is detrimental to health and contributes to the development of numerous diseases and may also be an accelerator of pathophysiological processes such as atherosclerosis. Cardiovascular diseases are the most common cause of death worldwide, so the development of new methods to support the treatment and prevention of these diseases becomes one of the priorities of modern medicine. Probiotics may constitute an important element of support in the treatment and prevention of CVD (cardiovascular diseases). A number of papers support such a statement, however, larger clinical trials are needed. Through a number of mechanisms including mitigating inflammation, sealing the intestinal epithelium, and affecting metabolism, probiotics may have a beneficial effect on general health and slow down the pathogenesis of many diseases, including those affecting the cardiovascular system. This article contains a review of current discoveries on the role of probiotics in the prevention and support of CVD treatment.

Key words: *probiotics, gastrointestinal diseases, microbiota*

Słowa kluczowe: *probiotyki, choroby przewodu pokarmowego, mikrobiota*

INTRODUCTION

The idea of using probiotics to support human health appeared as early as 1974, since then more and more research has been conducted on their beneficial effects on the human body. In parallel with the growing awareness of the enormous role of human microbiome, there is a growing awareness about beneficial role of probiotics in the course of many diseases [1].

Probiotics, as defined in 2001, are “live micro-organisms that, when used in adequate amounts, benefit the health of the recipient” [2]. It was also proven that the gut microbiota plays an important role in maintaining the homeostasis of the body [3]. Use of them is crucial in the support of treatment and prevention of numerous gastroenterological diseases [4]. Nevertheless, there is a sample evidence suggesting great importance of probiotics in CVD – for example, enterolactone produced by bacteria in the gut is associated with lower mortality [5]. Another evidence of the importance of the gut microbiota is that patients with a history of myocardial infarction had a different gut microbiota composition from healthy patients [6]. Some of the metabolites of the gut microbiota are trimethylamine oxide (TMAO) and short chain fatty acids (SCFA) [7]. Dietary intake of compounds such as choline, carnitine or phosphatidylcholine are converted by intestinal bacteria to trimethylamine oxide (TMA) – this is later converted to trimethylamine oxide (TMAO) in the liver and then excreted in urine [8, 9]. TMAO is a predictor of numerous cardiovascular conditions – the higher the level is, the worse it is for the organism [10]. In particular, it plays a role in atherogenesis [7]. Abnormal intestinal microbiota contributes to the formation of larger amounts of TMAO – hence its appropriate qualitative and quantitative composition should be maintained. Probiotics may be a solution to such a problem [11]. On the other hand, short-chain fatty acids (SCFAs), which are the products of fibre metabolism, also have a positive effect on health by accelerating cholesterol metabolism [12, 13]. The effect of probiotics in the context of cardiovascular disease requires further and expanded research – which will facilitate the understanding of the interference of the microbiome in the pathogenesis of these diseases [14]. This paper presents known information on the benefits of probiotic intake in cardiovascular diseases as well as the effects of probiotics on the most relevant modifiable risk factors in the development of CVD.

The most important modifiable risk factors of cardiovascular diseases

Cardiovascular diseases such as atherosclerosis, hypertension, heart failure are the leading cause of death of patients worldwide [15]. Their risk factors are well known – obesity, smoking, hypercholesterolaemia, and diabetes [16]. More and more studies show the positive effect of probiotics on the above-mentioned risk factors which may also indicate their potential in the prevention of these diseases.

Hypercholesterolaemia

Recent studies indicate that hypercholesterolaemia occurs in 70.3% of men and 64.3% of women in Poland [17]. High cholesterol level is one of the most important risk factors for atherosclerosis and plays a key role in the pathomechanism of many cardiovascular diseases. Hence, maintaining normal lipid metabolism including TC (total cholesterol), TG (triglycerides), HDL-C, LDL-C is one of the most important goals in CVD prevention [18]. A 1% reduction in serum cholesterol levels results in a 2–3% reduction in CVD incidence, so it is important to develop the tactics that can lead to decrease in cholesterol levels [19]. Probiotics can lower TC and LDL-C levels. However, they have no clear effect on serum TG and HDL-C levels. Data presented in a 2018 meta-analysis showed that the lowering effect was greater among patients with mild hypercholesterolaemia, compared to patients with moderate hypercholesterolaemia. Significant reductions in TC levels were observed with *Lactobacillus plantarum*, *L. reuteri*, *L. acidophilus*, while reductions in LDL-C levels were most pronounced with *L. plantarum* and a mixture of *Enterococcus faecium* and *L. helveticus*. Probiotics were administered in the form of fermented milk or in the form of probiotic capsules, however, there were no significant changes in results between these two forms [20]. There are several different proven mechanisms of fat lowering by probiotics. One of these is to bind cholesterol on their surface and incorporate it into the cell membrane, thus lowering the amount of cholesterol available for intestinal absorption [21]. Several strains of *Lactobacillus* can produce cholesterol reductase, which catalyses the conversion of cholesterol to coprostanol [22]. *Lactobacillus* bacteria can also produce ferulic acid, which can inhibit enzymes such as HMG-CoA which is involved in cholesterol synthesis [23, 24]. Another mechanism of lowering serum cholesterol levels is the production of bile salt hydrolase, which hydrolyses bile acids and leads to

their faster elimination in the faeces [25, 26]. Probiotic supplementation also leads to increased levels of short-chain fatty acids, which reduces cholesterol synthesis and accelerates cholesterol metabolism [27]. Protocatechuic acid produced by bacteria in the gut promotes reverse cholesterol transport [28].

Obesity

Obesity is a multifactorial, inherited and chronic disease in which an excessive accumulation of lipids in the patient's adipose tissue occurs. The diagnosis of obesity depends on the body mass index (BMI). Obesity is defined as BMI equal to or greater than 30 kg/m². Genetic susceptibility, epigenetics, metagenomics, and environmental factors are involved in its pathomechanism. Obesity affects many aspects of health: it negatively impacts physical, mental and social health [29–31]. Recently, it is said to exist an obesity epidemic. It affects over 2 billion people. Since 1975, the number of people suffering from obesity has almost tripled. The prevalence of obesity continues to rise [32, 33]. It has been proposed that altering the gut microbiota through oral administration of probiotics can induce weight loss and reduce weight gain, however, this mechanism is not fully understood [34]. In contrast, other studies have shown that probiotics can promote both weight gain and weight loss [35, 36]. In a 2020 meta-analysis of studies on the role of synbiotics (a combination of a probiotic and a prebiotic) in the treatment of obesity it was found that that: synbiotics can increase weight loss, change BMI, and can improve fat mass reduction [37]. Obesity is a very important risk factor for the development of dyslipidaemia, insulin resistance, hypertension and is an accelerator of atherosclerosis. Summarising, obesity contributes to more rapid development of cardiovascular disease both in adults and children [38, 39]. The increase in the risk of the abovementioned diseases is based on the fact that obesity is a chronic inflammatory state in which an increase in the amount of adipose tissue and decrease in synthesis of adiponectin, which has an anti-inflammatory effect, play a role. This leads to a loss of balance between inflammatory and anti-inflammatory factors and thus to the development of complex metabolic complications of obesity, including endothelial dysfunction and increased insulin resistance [40].

Diabetes

According to the International Diabetes Federation (IDF), 463 million people will be diabetics in 2019.

Diabetes is a chronic disease caused by inefficient use of insulin produced or insufficient production of insulin. Insufficient insulin levels and insulin resistance lead to hyperglycaemia. High glucose levels can lead to many complications such as diabetic kidney disease and comorbidities such as cardiovascular disease [41]. Through increased insulin resistance and metabolic changes in the body, diabetes significantly accelerates the processes of atherogenesis, thus better control of this disease will contribute to slowing down the process of atherosclerosis development and thus delay the development of heart failure. In addition, endothelial dysfunction occurs in diabetes as a result of oxidative stress resulting from higher glycaemic levels. Not only do glycaemic levels fluctuate in diabetes, but this entity also contributes to excessive platelet activity as well as myocardial fibrosis. These processes result in the development of heart failure, lead to myocardial infarctions and diabetic cardiomyopathy [42]. Probiotics may have beneficial effects on hyperglycaemia, insulin resistance, and oxidative stress. The 2020 meta-analysis showed that probiotic supplementation can improve glucose metabolism and affect body weight [43]. However, the mechanism of the beneficial effect of probiotics on hyperglycaemia is not fully understood. One hypothesis is that probiotics improve glucose levels in diabetic patients by inhibiting oxidative stress [44]. They may also increase gastrointestinal absorption of antioxidants [45]. Yao *et al.* showed that administration with probiotics could improve the clinical prognosis of type 2 diabetes. They significantly lowered glucose levels and alleviated insulin resistance. Lipid profile and oxidative and antioxidant stress biomarkers were also moderately improved [44]. On the other hand, *Bifidobacterium bifidum* with *L. acidophilus* and fructooligosaccharides in the form of a synbiotic cocktail reduced fasting blood glucose in elderly subjects with type 2 diabetes [46]. It is worth noting that insulin resistance is a risk factor for cardiovascular morbidity, hence, increasing insulin sensitivity can be considered as a therapeutic target [47]. Specially prepared bread containing *L. sporogenes* and inulin may reduce serum insulin levels in diabetic patients [48]. Insulin sensitivity index can also be increased by oral administration of probiotics [49].

Cardiovascular disease and probiotics

Atherosclerosis

Atherosclerosis is a global health problem. Its pathomechanism is complex. The most important factors

affecting its development are vascular inflammation, oxidative stress and elevated cholesterol levels [50]. The combination of these factors leads to thickening of the intima, accumulation of foam cells and formation of atherosclerotic plaque, which may enlarge and lead to vessel obstruction resulting in e.g., stroke or myocardial infarction [51]. Of the aforementioned, endothelial damage caused by oxidative stress is the most important risk factor [52]. Probiotics can enhance antioxidant mechanisms – they perform this by increasing glutathione peroxidase levels, thus lowering oxidative stress [53]. The immune system also plays a key role in atherosclerotic plaque formation by inducing inflammation. Studies have shown that certain strains of probiotics, by acting as an immunomodulatory agent, can potentially reduce the number of pro-inflammatory immune cells and cytokines responsible for the inflammatory response [54].

Hypertension

About 972 million people suffer from hypertension. As a risk factor, hypertension is associated with many diseases such as chronic kidney disease, stroke and cardiovascular disease [55]. Hypertension, like atherosclerosis, has a multifactorial pathomechanism. It has been demonstrated that the gut microbiota can influence hypertension through multiple mechanisms: affecting inflammatory factors, the brain-gut-kidney axis [56], or affecting TMAO levels [57], and through other metabolites produced by the gut microbiota [58]. A meta-analysis by Chi *et al.* presented data supporting the blood pressure lowering effect of probiotics, especially in diabetic subjects [59]. Another study also demonstrated positive effects on hypertension through different mechanisms [60]. Probiotics hydrolyse casein and lactoprotein, producing peptides that inhibit angiotensin-converting enzyme, which lower blood pressure [61]. Furthermore, animal studies have shown that probiotics have positive effects on heart muscle cells – reducing their apoptosis. They may also attenuate ventricular remodelling in spontaneously hypertensive rats [62].

Heart failure

Heart failure (HF) is a consequence of many cardiovascular diseases. It is a progressive and chronic disease caused by remodelling of the heart structure and loss of adequate cardiac function [63]. The gut microbiota is altered in patients with chronic heart

failure – they have been reported to have decreased amount *Faecalibacterium prausnitzii* and increased amount *Ruminococcus gnavus* [64]. Imbalances in the gut microbiome and impaired intestinal barrier function can lead to cardiac dysfunction. First, patients with heart failure show a significant reduction in bacteria that produce short-chain fatty acids (SCFAs) [65]. *E. rectale* and *F. prausnitzii* produce butyrate [66]. Butyrate regulates epithelial barrier integrity, provides an energy source for intestinal epithelial cells, and suppresses intestinal and extraintestinal inflammation [67-69]. Second, production of harmful metabolites such as lipopolysaccharide and TMAO is higher in patients with chronic heart failure [64]. The increase in TMAO, which is a metabolite derived from the gut microbiota, is particularly significant. Patients with heart failure have higher plasma levels of TMAO, and its levels are also associated with higher mortality [70]. This lipopolysaccharide may increase inflammation and thus promote the development of heart failure [71]. Endotoxemia results from dysbiosis and leads to systemic inflammation that may contribute to the progression of heart failure [72]. The use of probiotics may decrease intestinal permeability and thus reduce systemic inflammation [73]. It has been shown that probiotics can influence the cardiac remodelling process [74]. Probiotic therapy with *Lactobacillus plantarum* 299v improved ventricular function and cardiac remodelling after left anterior descending artery ligation and reduced blood leptin levels [75]. Another study showed that the use of *Saccharomyces boulardii* can improve left atrial diameter and left ventricular ejection fraction in patients with CHF [76]. Probiotics have great potential to improve the quality of life of patients with heart failure. However, there is a great need for more clinical trials to clarify the use of probiotics in patients with heart failure.

Myocardial infarction

Animal studies by Lam *et al.* have shown that the use of probiotics can reduce the area of myocardial infarction [75]. *Lactobacillus plantarum* 299v can reduce leptin production – leading to greater resistance to cardiac ischaemia [77]. An animal study report by Gan *et al.* showed that probiotics can affect heart failure after myocardial infarction by reducing myocardial hypertrophy. Supplementation delayed the progression of heart failure after coronary occlusion. In addition, probiotic therapy can modulate the leptin: adiponectin ratio and reduce amino acids, nucleosides and sugar in tissues – which are factors

produced by coronary artery occlusion in rats [74]. Nonetheless, it is still unknown if probiotics might help patients after myocardial infarction and thus clinical studies would shed more light on this topic.

CONCLUSIONS

In last few decades there has been a tremendous development in the knowledge concerning the human microbiome. Bacteria turn out to be a very important element in maintaining homeostasis of the human body. Probiotics aiming to improve – both quantitatively and qualitatively – the composition of the intestinal microbiota are also in the focus of interest of the medical world. Compounds synthesized by bacteria may have a negative effect on the body, e.g., TMAO, or a positive one, e.g., SCFA. Interfering in the pathogenesis of many diseases such as diabetes, atherosclerosis, or obesity – microorganisms in our intestines can accelerate or slow down the development of many cardiovascular diseases. Existing research results put the effect of probiotics in a positive light, but the amount of data currently available does not allow definite conclusions. Further research is necessary to develop more effective methods of prevention and treatment of cardiovascular disease using probiotics.

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