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KALP BAĞIRSAK EKSENİ

ÖZET. Bağırsak-kalp ekseninde birçok etkileşim rol oynamaktadır. Bunlara bağırsak epitelyal disfonksiyonu, disbiyoz, bütirat üreten bakteriler, safra asitleri ve bağırsak mikroplarından türetilen metabolitler dahildir. Kalp yetmezliği (KY) olan hastalarda perfüzyonun azalması, konjesyonun artması ve sempatik aracılı vazokonstriksiyona bağlı olarak bağırsakta mikrodolaşım bozuklukları sonucu mukozal emilim bozukluğu, bağırsak duvarı ödemi ve bariyer disfonksiyonu gelişir. Toksik, patojenik, immünojenik ve inflamatuar faktörler, bağırsaktaki sıkı bağlantıların hasar görmesi sonucu bağırsak geçirgenliğinin artmasıyla mukozadan geçerek sistemik dolaşıma ulaşarak lokal-sistemik inflamasyona neden olur. KY'de sıklıkla görülen bağırsak florasını değiştirerek dysbiosis'e neden olan birçok faktör, bakteriyel aşırı çoğalmaya, bakteriyel translokasyona ve lipopolisakkarit (LPS), trimetilamin N-oksit (TMAO), p-kresilsülfat (PCS) ve indoksil sülfat (IS) gibi birçok toksik maddenin oluşumuna yol açar. Bağırsak geçirgenliğinin artmasına bağlı olarak bu toksik maddeler sistemik dolaşıma ulaşır; Tromboz, trombosit invazyonu, köpük hücre oluşumu ve inflamasyon süreçlerinde rol oynayarak ateroskleroz riskini artırır. Gastrointestinal sistem üzerinde birçok etkisi olan kısa zincirli yağ asitlerinden biri olan bütirat seviyelerinin azalması, bağırsak bariyer bütünlüğünü korumak dahil; köpük hücre oluşumunu teşvik eder, disbiyozu şiddetlendirir ve endotoksinlerin genel dolaşıma ulaşmasına neden olarak bağırsak bariyer fonksiyonunun bozulmasında rol oynar. Bu derleme ile bağırsak-kalp eksenindeki fizyopatolojik süreçler hakkında güncel literatür ışığında bilgi verilmesi amaçlanmıştır.

Anahtar Kelimeler: Bağırsak geçirgenliği, Disbiyoz, IS, SCFA, TMAO.

GUT-HEART AXIS

ABSTRACT. Many interactions play a role in the gut-heart axis. These include intestinal epithelial dysfunction, dysbiosis, butyrate-producing bacteria, bile acids, and intestinal microbe-derived metabolites. In patients with heart failure (HF), mucosal malabsorption, intestinal wall edema and barrier dysfunction develop as a result of microcirculation disorders in the gut due to decreased perfusion, increased congestion and sympathetically mediated vasoconstriction. Toxic, pathogenic, immunogenic and inflammatory factors, through the increase in intestinal permeability as a result of damaged tight junctions in the intestine, pass through the mucosa and reach the systemic circulation, causing local-systemic inflammation. Many factors that cause dysbiosis by changing the intestinal flora, which are frequently seen in HF, lead to bacterial overgrowth, bacterial translocation and formation of many toxic substances, including lipopolysaccharide (LPS), trimethylamine N-oxide (TMAO), p-cresylsulfate (PCS) and indoxyl sulfate (IS). Depending on the increase in intestinal permeability, these toxic substances reach the systemic circulation; it increases the risk of atherosclerosis by playing a role in thrombosis, platelet invasion, foam cell formation and inflammation processes. Decreased levels of butyrate, one of the short-chain fatty acids that have many effects on the gastrointestinal tract, including maintaining intestinal barrier integrity; It promotes foam cell formation, exacerbates dysbiosis, and plays a role in the disruption of intestinal barrier function, causing endotoxins to reach the general circulation. With this review, it is aimed to inform about the physiopathological processes in the gut-heart axis, in the light of the current literature.

Keywords: Dysbiosis, IS, Intestinal permeability, SCFA, TMAO

INTRODUCTION

The gastrointestinal tract (GIT) is colonized by many various of microorganisms. This community of microorganisms is called the intestinal microbiota and its homeostasis is important because it plays a key role in physiological-pathological conditions (Mondo et al., 2019). The duties of the gut microbiota include digestion of indigestible nutrients, vitamin-hormone synthesis, immunomodulation, and prevention of colonization by opportunistic pathogens (Lerner et al., 2021). The main function of the intestinal barrier mechanism, which can be defined as selective, is to prevent the absorption of toxins while ensuring the absorption of nutrients (Bischoff et al., 2014). Many harmful substances that affect the pathophysiological processes by reaching the systemic circulation are produced by the intestinal microbiota, but these substances cannot enter the circulation unless the intestinal barrier function is impaired (Bischoff et al., 2014). Gut microbiota catabolically participates in the digestion process via saccharolytic and proteolytic pathways and provides the production of short-chain fatty acids (SCFA). SCFA's have multiple effects on the GIT and play a role in modulating cardiovascular risk factors (Edwards et al., 2017). This review focuses on factors involved in the gut-heart axis, including intestinal epithelial dysfunction, dysbiosis, butyrate-producing bacteria, bile acids, and metabolites derived from gut microbes.

INTESTINAL EPITHELIAL DYSFUNCTION IN HEART DISEASES

In heart failure (HF), microcirculation disorders occur in the intestine due to decreased perfusion, increased congestion and sympathetic vasoconstriction; functional damage to intestinal epithelium may happen as a result of ischemia (Rogler and Rosano, 2014; Kamo et al., 2017a). Mucosal malabsorption, intestinal barrier disorder and edema in the intestinal wall may occur due to decreased perfusion and impaired microcirculation in the intestine (Sandek et al., 2007). In the study of Sandek et al. (2007) in dogs with HF, an increase in ileum and colon wall thickness was determined due to edema in the intestinal wall. In another study (Arutyunov et al., 2008), they determined collagen deposition in the small intestine mucosa in HF patients.

Low blood oxygen pressure causes GIT dysmotility, intestinal acidosis, and barrier dysfunction (Fruhwald et al., 2007). Decreased GI motility may exacerbate the neuroendocrine compensatory mechanism of HF, as well as changes in gut flora and function (Ralls et al., 2014). Taking into account elevated intestinal permeability as a result of dysfunction in the intestinal barrier; induction of the immune system by toxic, pathogenic, immunogenic and inflammatory agents results in chronic inflammation (Lerner et al., 2021). Chronic inflammation also plays a role in the pathogenesis of cardiovascular diseases (CVD) (Dregan et al., 2014). In HF patients, the increase in intestinal permeability determined by the sugar cellobiose test was associated with right atrial pressure and C-Reactive Protein (CRP) values (Sandek et al., 2007; Pasini et al., 2016). It has been reported that endotoxins induce cytokine production by their effects on mononuclear cells in HF patients (Anker et al., 1997). Researches reviously indicated elevated cytokines of inflammatoric origin (Tumor Necrosis Factor α (TNF-α), ST2, interleukin-6, CRP and galectin-3) in HF patients, associating them with poor prognosis (Hori and Yamaguchi, 2013; Mann, 2015). These inflammatory cytokines play a role in the pathogenesis of HF by inducing cardiomyocyte apoptosis, hypertrophy and fibrosis (Mann, 2015). They also cause an increase in inflammatory reactions by disrupting the intestinal barrier function (Sandek et al., 2007). The higher level of endotoxin levels in hepatic venous blood compared to left ventriculus at decompensation stage denoted that endotoxins enter the central circulation from the intestine (Peschel et al., 2003).

GUT MICROBIOTA IN HEART DISEASES

There are many factors that can cause dysbiosis in patients with HF, such as insufficient oxygen supply due to decreased intestinal perfusion and consequently increased colonization of pathogenic anaerobic bacteria, sudden changes in fluid balance, GI dysmotility and nutrient deprivation (Sandek et al., 2014; Salzano et al., 2020a). All these factors cause bacterial overgrowth and bacterial translocation (Salzano et al., 2020a). Wang et al. (2012), have shown that the colon microbiota is altered after intestinal ischemia-reperfusion in rats. In the study by Dinakaran et al. (2014), examining the microbiome in people with HF; after the determination of higher bacterial DNA and different microbiota composition in HF patients, elimination of gram-negative bacilli with polymyxin B

resulted in a decrease in fecal endotoxin levels and an improvement in endothelial functions.

Dogs with congestive heart failure (CHF) had higher rates of adhesive bacterial species (eg, *Bacteroides, Prevotella, Eubacterium, Fusobacterium*) on the mucosa compared to healthy controls (Sandek et al., 2007). Adhesive bacteria cause chronic inflammation by attaching to the intestinal epithelium without invasion/translocation, inducing cytokine release and increasing intestinal permeability (Alverdy et al., 1994) or mixing of microbial products into the systemic circulation (Conraads et al., 2004). Seo et al. (2020) reported that *Enterobacteriacea* and *Escherichia coli* increased and dysbiosis developed in their pilot study in dogs with CHF. Regarding trials comparing patients with coronary heart disease (cHd) with those without, cHd cases presented a diminished relative abundance of *Bacteroidetes phylum* and an elevated ratio of *Firmicutes* (Cui et al., 2017); it has been reported that the levels of several *Streptococcus* species and genus of *Enterobacteriaceae* family are increased (Jie et al., 2017). It has been shown that the abundance of many pathogenic bacteria (including *Campylobacter spp, Shigella spp, Salmonella spp, Yersinia Enterolytica* and *Candida spp.*) is increased (Pasini et al., 2016) while the abundance of *Eubacterium rectale* and *Dorea longicatena* (SCFA producers) decreased (Kamo et al., 2017b) in HF patients. More atherosclerotic plaque detection in mice fed germ-free conditions and a low-cholesterol diet than the control group (Stepankova et al., 2010); as supported by some researchers (Chistiakov et al., 2015; Battson et al., 2018), it proves that intestinal microbiota has an atherosclerosis preventive effect by affecting lipid metabolism.

Bacteria can transmit genes that can enable other bacteria to acquire antibiotic resistance or suppress the immune system. This is called luminal gene transfer (Deshmukh et al., 2011). Cardiogenic dysbiosis may be formed as a result of the transfer of foreign cardiogenic genes, which increase due to changing environmental factors, by luminal gene transfer and may play a role in the pathogenesis of heart diseases (Reif and Lerner, 2004; Lerner et al., 2021):

Butyrate Producing Bacteria

Indigestible fibers in food are converted by some anaerobic bacteria in the microbiota into SCFs (acetate, propionate, butyrate), which have many effects on the GI tract including maintaining intestinal barrier integrity (Morrison and Preston, 2016; Edwards et al., 2017). SCFAs also modulate CVD risk factors by lowering blood pressure, antienflamatuar effect and regulating glucose-lipid metabolism (Edwards et al., 2017). Butyrate, which is the main energy source of the colon mucosa, regulates the expression of various genes (related to microbial balance, intestinal barrier function, inflammation, phagocytosis, differentiation, efferocytosis), inhibits intestinal permeability by upregulating tight junctions in the intestine so limits the access of endotoxins to the systemic circulation (Fluitman et al., 2018; Bastin and Andreelli, 2020). The reduction of butyrate production due to the decrease in dietary fiber causes CVD by playing a role in foam cell formation. In addition, the decrease in butyrate level causes dysbiosis and deterioration in intestinal barrier function; Increasingly pathogenic bacteria and their metabolites reach the systemic circulation, results in local-systemic inflammation, foam cell formation, platelet aggregation and so atherosclerosis (Chen et al., 2020; Trøseid et al., 2020).

Jie et al. (2017) report a reduced amount of *Roseburia intestinalis* and *Faecalibacterium prausnitzii* (butyrate producers) in CVD patients. *Roseburia intestinalis* improves intestinal barrier function, reduces systemic inflammation, circulating lipopolysaccharide (LPS) levels, and macrophage migration to plaques (Jie et al., 2017). *Roseburia intestinalis* and *Akkermansia muciniphila* have been shown to inhibit the development of atherosclerotic plaques in mice (Li et al., 2016; Jie et al., 2017). It has been reported that the abundance of *Faecalibacterium prausnitzii*, which has high anti-inflammatory activity, decreases in patients with high cholesterol values (Khan et al., 2018). In addition to producing butyrate, *Clostridium butyricum* increases the abundance and diversity of other butyrate-producing bacteria (Weng et al., 2015; Jia et al., 2017).

Bile Acids

Bile acids are signal molecules with regulatory effects. These effects are related to energy, glucose, lipid metabolism and other physiological processes (Watanabe et al., 2006; Staels and Fonseca, 2009). Due to the bile acid receptor expression in cardiomyocyte, bile acids influence cardiovascular system, as well as the interaction between bile acid metabolites and the intestinal microbiome, which

plays a role in the formation of heart diseases (Khurana et al., 2011; Forkosh and Ilan, 2019). Primary bile acids are converted to secondary bile acids by intestinal bacteria before they are absorbed from the gut and enter the enterohepatic circulation (Chiang, 2009). This bile acid conversion plays a role in the interaction of the intestinal microbiome with the cardiovascular system, through its agonistic effect on bile acid receptors (such as the farnesoid X receptor) (Chiang, 2009). Mayerhofer et al. (2017) reported that the secondary bile acid: primary bile acid ratio is increased in patients with HF and this is associated with a poor prognosis. Administration of ursodeoxycholic acid in patients with HF has demonstrated improvement in peripheral blood flow and improvement in liver functions (Von Haehling et al., 2012).

GUT MICROBE-DERIVED METABOLITES IN HEART DISEASES

Metabolites produced by intestinal bacteria have been shown to play a role in the development of various diseases (Schroeder and Bäckhed, 2016). As a result of an imbalance in the intestinal microbiota resulting in dysbiosis, many harmful substances such as Phenylacetylglutamine (PAGln), LPS, Trimethylamine N-Oxide (TMAO), p-cresylsulfate (PCS) and indoxyl sulfate (IS) are released and the intestinal barrier is damaged due to the decrease of SCFAs (Cosola et al., 2018; Nemet et al., 2020). Due to the increased permeability of the damaged intestinal barrier, these toxic substances reach the systemic circulation and play a role in the pathogenesis of CVD by causing platelet invasion, thrombosis, foam cell formation, inflammatory response and oxidative stress (Chen et al., 2020).

PAGln

Phenylalanine is a PAGln precursor and is largely absorbed from the small intestine after ingestion with food. The unabsorbed part is converted to phenylpyruvic acid and then to phenylacetic acid by the microbiota in the large intestine, absorbed in the portal system and metabolized to PAGln in the liver. PAGln causes thrombocytosis and thrombosis through G-protein coupled receptors (α2A, α2B and β2-adrenergic receptors) (Nemet et al., 2020). Chen et al. (2020), report that PAGln correlates positively with CVD and poor prognosis. Chen et al. report that PAGln is positively correlated with CVD and poor prognosis, therefore it may be a biomarker for CVD.

LPS

LPS is a molecule composed of lipids and polysaccharides found in the cell wall of gram-negative bacteria. When there is an increase in permeability due to damage to the intestinal wall, LPS reaches the systemic circulation and induces inflammatory reactions by acting on cardiomyocytes, cardiac fibroblasts, macrophages and monocytes through Toll like receptor (TLR)-4 recognition receptors (Sandek et al., 2007; Deitch, 2002; Lu et al., 2008; Frangogiannis, 2014).

A high level of LPS in plasma has been detected in patients with CHF, indicating that severe venous occlusion is an important factor for bacterial overgrowth and increased intestinal permeability during the edematous decompensation process (Niebauer et al., 1999; Marshall and Levy, 2011). As a result of a study evaluating LPS levels in 516 people (age: 50-79), it was determined that the risk of atherosclerosis increased 3 times in those with LPS levels above the 90th percentile (Fokosh and Ilan, 2019). High serum LPS levels as a result of dysbiosis are associated with metabolic syndrome obesity, coronary heart disease (CHD) and diabetes (Kallio et al., 2015; Chen et al., 2020).

Uremic Toxins

Indoxyl sulfate and p-cresyl sulfate, which are formed as a result of fermentation of dietary tryptophan and tyrosine by intestinal bacteria, are defined as uremic toxins (Lekawanvijit, 2015). A comparative evaluation of germ-free and conventional mouse plasmas exibited that the gut microbiota has a significant impact on uremic toxins and other metabolites (Wikoff et al., 2009). Among the uremic toxins, indoxyl sulfate, as evidenced by its causation of cardiac hypertrophy and renal damage in rodents; It causes cardiac and renal prohypertrophic-profibrotic effect (Lekawanvijit, 2015). In addition to reporting that indoxyl level correlates negatively with prognosis in those with chronic renal disease (Barreto et al., 2009), there is also a study that high indoxyl sulfate levels in healthy mice cause LV hypertrophy without affecting renal function (Yang et al., 2015).

TMAO

Trimethylamine (TMA) precursors (such as choline, betaine, L-carnitine) found in western diet (red meat, fish, eggs, dairy products, sugar, saturated fats) is

converted to TMA by microbial enzymes called carnitine monooxygenase (cntA/B), yeaW/X, choline-TMA (cut C/D), TMAO reductase and betaine reductase (Pascal et al., 1984; Andreesen, 1994; Cracium et al., 2014; Koeth et al., 2014; Zhu et al., 2014; Salzano et al., 2020a). TMA, which enters the circulation from the intestine, is oxidized to TMAO in the liver by FMO1 and especially FMO3, which belongs to the family of hepatic flavin monooxidases (Bennett et al., 2013).

According to literature data, *Gammaproteobacteria* (*E. coli, Klebsiella pneumoniae, Shigella, Citrobacter spp*. and *Providencia* spp.), *Actinobacteria, Firmicutes* (*Sporosarcina spp.*), *Betaproteobacteria (Achromobacter spp.*), *Proteus mirabilis, Proteus penneri* and *Proteus mirabilis* are TMA producing bacteria (Romano et al., 2015; Wang et al., 2015; Zeisel and Warrier, 2017; Janerio et al., 2018). In addition, Bäckhed (2013) reports that TMA level is positively correlated with *Clostridiaceae, Peptostreptococcaceae, Clostridium* abundance and negatively correlated with *Lachnospira* abundance. Nutrition with a Western diet increases the TMAO levels and increases the risk of CVH by changing the composition of the microbiota with the decrease in the abundance of *Bifidobacteria*, *Bacteroides* and the increase in the levels of *Proteobacteria*, *Firmicutes* (Koeth et al., 2013; Boutagy et al., 2015; Chen et al., 2017). According to another study, TMAO level is associated with the abundance of *Shigella* and *Escherichia* (Hayashi et al., 2018).

TMAO is thought to play a role in the pathogenesis of CVD by increasing myocardial fibrosis, stimulating cytokines, causing cardiac microvascular dysfunction and neurohormonal imbalances (Nagatomo and Tang, 2015). Depending on the similar prognostic value of TMAO in ischemic and non-ischemic patients, it has been reported that TMAO has a direct harmful effect on the heart, independent of its atherogenic effect (Tang et al., 2014; Nagatomo and Tang, 2015). By affecting intracellular calcium utilization and cardiomyocyte contraction, TMAO causes mitochondrial dysfunction and consequently a decrease in energy production (Savi et al., 2018).

While TMAO increases forward cholesterol transport, it inhibits macrophage reverse cholesterol transport, causing foam cell formation in the endothelial wall, resulting in plaque formation and inflammation. (Wang et al., 2011; Tang et al., 2014). In plaque or arterial areas with low laminar flow, LDL accumulates and oxidizes, then macrophages are attracted to this area and collect lipoproteins, resulting in inflammatory foam cells that release chemotactic cytokines and generate a monocyte response (Charo and Taub, 2011; Bentzon et al., 2014). In addition, foam cells secrete vascular permeability molecules that can cause plaque rupture and thus thrombosis and ischemia (Bentzon et al., 2014).

Studies in patients undergoing acute HF, acute myocardial infarction, and coronary angiography have associated high TMAO levels with hospitalization, myocardial infarction, stroke, and death (Tang et al., 2013; Suzuki et al., 2016; Suzuki et al., 2017). In the study of Organ et al. (2016), mice fed with TMAO or choline and compared with control groups; They identified LV enlargement, aortic stenosis, pulmonary edema, cardiac fibrosis, elevated brain natriuretic peptide (BNP) levels, and exacerbated cardiac remodeling. Tang et al. (2015) report that an increase in TMAO level is associated with LV diastolic dysfunction, but not with systolic dysfunction. They found that in 972 patients with HF, patients with high TMAO levels were highly elderly, decreased heart rate, hemoglobin levels, blood pressure, kidney function, and LV ejection fraction, as well as increased NT proBNP and potassium levels (Suzuki et al., 2016). It has been demonstrated that TMAO is a stronger indicator because NT-proBNP loses its significance when adjusted for CRP (Schuett et al., 2017). In addition, it has been reported that it is more beneficial to consider TMAO and BNP together in the risk stratification of patients with HF with preserved ejection fraction, whose BNP is less elevated (Salzano et al., 2020b). In animals with myocardial infarction, by targeting the intestinal microbiota; It was observed that TMAO levels and myocardial hypertrophy decreased also HF regressed (Martin et al., 2008).

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