

# Gut dysbiosis-derived low-grade endotoxemia: A common basis for liver and cardiovascular disease

Francesco Violi<sup>1,2</sup>, Cristina Nocella<sup>1</sup>, Simona Bartimoccia<sup>1</sup>, Valentina Castellani<sup>3</sup>, Roberto Carnevale<sup>4,5</sup>, Pasquale Pignatelli<sup>1,2</sup>, Vittoria Cammisotto<sup>1</sup>

<sup>1</sup>Department of Clinical Internal, Anesthesiology and Cardiovascular Sciences, Sapienza University of Rome, Rome, Italy

<sup>2</sup>Mediterranea Cardiocentro-Napoli, Naples, Italy

<sup>3</sup>Department of General Surgery and Surgical Speciality, Sapienza University of Rome, Rome, Italy

<sup>4</sup>Department of Medical-Surgical Sciences and Biotechnologies, Sapienza University of Rome, Latina, Italy

<sup>5</sup>IRCCS Neuromed, Località Camerelle, Pozzilli, Italy

## Correspondence to:

Prof. Francesco Violi, MD,  
Department of Clinical  
Internal, Anesthesiology and  
Cardiovascular Sciences,  
Sapienza University of Rome,  
Piazzale Aldo Moro, 5,  
00185, Rome, Italy;  
and Mediterranea Cardiocentro-  
Napoli, Via Orazio, 2, 80122  
Naples, Italy,  
phone: +39 0 664 461 933,  
e-mail:  
francesco.violi@uniroma1.it  
Copyright by the Author(s), 2023  
DOI: 10.33963/KPa2023.0115

## Received:

April 19, 2023

## Accepted:

May 14, 2023

## Early publication date:

May 16, 2023

## ABSTRACT

Gut dysbiosis is characterized by bacteria overgrowth that ultimately leads to increased intestinal barrier permeability and translocation of bacteria or bacterial products such as lipopolysaccharide (LPS) in the portal and, eventually, systemic circulation. Intestinal epithelial cells and hepatocytes possess enzymatic armamentarium to counteract the LPS toxic effect, however, impaired degradation results in LPS accumulation in the hepatocytes and endothelial wall. Experimental and clinical studies documented that in patients with liver disease, such as nonalcoholic fatty acid liver disease (NAFLD), low-grade endotoxemia caused by LPS is implicated in liver inflammation and thrombosis via interaction with its Toll-like receptor 4 (TLR4) expressed by hepatocytes and platelets. Furthermore, studies in patients with severe atherosclerosis documented that LPS localizes in atherosclerotic plaque in close association with activated macrophages expressing TLR4 suggesting LPS's role in vascular inflammation, atherosclerotic progression, and thrombosis. Finally, LPS may directly interact with myocardial cells to induce electric and functional changes leading to atrial fibrillation or heart failure. This review will focus on experimental and clinical evidence suggesting that low-grade endotoxemia, as a mechanism, potentially accounts for vascular damage occurring at the level of the hepatic and systemic circulation and myocardial cells.

**Key words:** cardiovascular disease, dysbiosis, endotoxemia, liver, thrombosis

## INTRODUCTION

The gut microbiota comprises trillions of bacteria localized in the intestinal tube with increasing colonization from the stomach to the colon [1]. There is an emerging body of clinical and experimental studies indicating that gut microbiota is implicated in liver and cardiovascular disease. Such a relationship relies on the fact that changes in gut microbiota, so-called dysbiosis, resulting in an imbalance between commensal and pathogenic bacteria, leads to translocation of bacteria or bacterial products into the portal and, eventually, systemic circulation with ensuing damage to the liver and systemic circulation. Gut dysbiosis is an alteration of the gut microbiome characterized by a reduction in microbial diversity,

with a predominance of pathogenic bacteria such as *Bacteroidetes* and *Enterococcaceae* and a reduction in beneficial bacteria such as *Bifidobacterium* and *Firmicutes* [2].

Changes in gut bacteria diversity may represent an important pathogenic factor via translocation of bacterial products such as lipopolysaccharide (LPS)-related endotoxemia into the systemic circulation [3–5].

LPS is a glycolipid component of the bacterial outer membrane of Gram-negative bacteria comprising carbohydrates and lipid A portion and may be detected in the peripheral human circulation with values usually <20 pg/ml [6]. In the blood, LPS is transported by a specific transport 60-kDa acute phase response glycoprotein, the lipopolysaccharide

binding protein (LBP), and cleared from the circulation by plasma lipoprotein subclasses such as HDL, VLDL, and LDL; about 80% of circulating LPS is transported by LDL [6].

An increase in LPS may occur in physiological conditions such as in the post-prandial phase as LPS across the intestinal barrier is embedded in freshly synthesized chylomicrons [7]. Hence, elevated circulating LPS may be detected in the peripheral circulation after a high-fat diet with a deleterious metabolic effect as LPS negatively affect insulin secretion and activity [7]. Pathogenic factors associated with elevated LPS levels include aging, alcohol abuse, metabolic and cardiovascular diseases, acute infections, and systemic inflammation [6–8]. Metabolic diseases such as type 2 diabetes, obesity [9, 10], or acute or chronic cardiovascular disease are associated with elevated circulating LPS levels [11]. Low-grade LPS endotoxemia has also been detected in patients with non-septic pneumonia [12–14], in experimental models of intestinal anoxia [15,16], and in systemic inflammation-associated overproduction of pro-inflammatory cytokines, such as interferon- $\gamma$  and tumor necrosis factor (TNF) [17].

Experimental and clinical studies suggested a potential role for endotoxemia as a mechanism eliciting *in situ* liver inflammation via interaction with its receptor, Toll-like receptor 4 (TLR4) [18–20]. Also, LPS has been reported to prime platelets to respond to the common agonists indicating that LPS behaves as a pro-aggregating molecule interacting with monocytes to promote the expression of Tissue factor (TF), a glycoprotein that converts factor X to Xa [21], and causing endothelial perturbation favoring the release of von Willebrand factor (vWF) and factor VIII (FVIII) [22, 23]. Finally, LPS may directly interact with myocardial cells to elicit electric changes or cardiac dysfunction eventually leading to atrial fibrillation (AF) or heart failure (HF) [24, 25]. Upon interaction with its receptor TLR4, LPS may, therefore, interact with liver, blood, endothelial, and myocardial cells, and potentially it can be a factor causing liver and cardiovascular disease. This review will analyze the experimental and clinical evidence indicating that gut dysbiosis-related low-grade endotoxemia may be implicated in liver damage such as nonalcoholic fatty liver disease (NAFLD) and its sequelae and cardiovascular disease.

### **GUT DYSBIOSIS-RELATED ENDOTOXEMIA: MECHANISM OF DISEASE**

There is emerging evidence that gut dysbiosis-related endotoxemia is detectable in patients with liver disease and/or cardiovascular disease. Small intestine bacterial overgrowth (SIBO) is among the most important mechanisms causing gut dysbiosis and ensuing changes in gut barrier functionality with increased permeability. SIBO may be caused by impaired bile secretion and/or delayed gastrointestinal transition-related mucus layer thinning or downregulation of adhesion proteins [26].

Gut dysbiosis may be analyzed by next-generation sequencing approaches that allow identifying specific

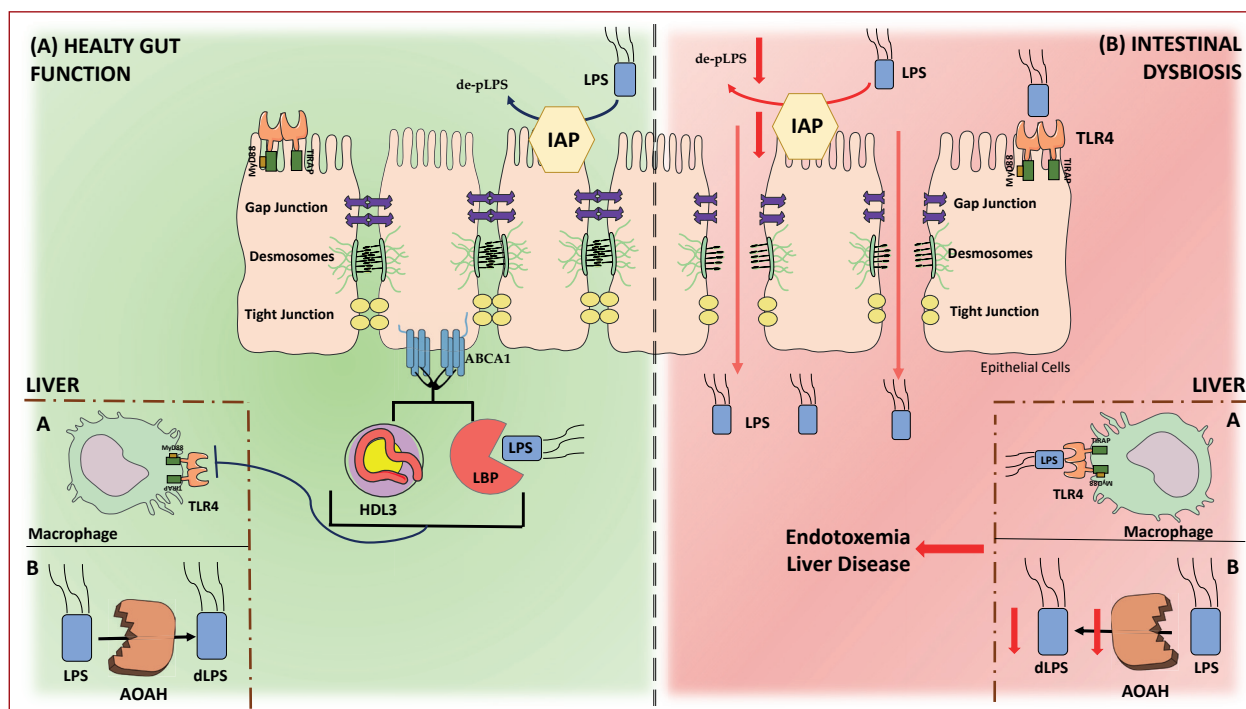
regions of DNA by bacterial 16S ribosomal RNA (16SRNA) and quantifying species of bacteria [27]. Direct sequence of analysis may be also determined by metagenomic shotgun sequencing, which is a more reliable method to quantify gut bacteria [28].

Gut dysbiosis is usually associated with enhanced intestinal permeability; in 35 consecutive biopsy-confirmed NAFLD patients presenting with SIBO, enhanced gut permeability, documented *in vivo* by urinary excretion of  $^{51}\text{Cr}$ -EDTA and reduced expression of tight junctions in duodenal biopsy specimens, was reported [18].

Analysis of gut permeability has been performed in patients at risk or with coronary heart disease by measuring serum levels of zonulin, which is an indirect marker of gut permeability and is released by epithelial cells of the small intestine as a consequence of dysbiosis [29].

LPS detoxification by the human body occurs overall at levels of the intestinal tube and liver. Local defense mechanism includes the intestinal mucus that separates gut microbiota from the intestinal barrier consisting of epithelial cells that are held together by adhesion protein such as tight junction (TJ) proteins, adherence junctions (AJ) proteins (cadherins and catenins), gap junction (connexin) proteins and desmosomes (desmoglein and desmocollins). Just below the epithelial barrier, the gut vascular barrier is also implicated in modulating bacterial translocation into the portal vein [30]. Disruption of the intestinal barrier occurring in metabolic diseases usually results from intestinal dysbiosis and is associated with endotoxemia [31]. This close relationship is supported by an interventional study in animals treated with a large spectrum of antibiotics showing reduced endotoxemia simultaneously with the improvement of gut barrier dysfunctionality [32]. In the case of damage to the intestinal barrier, two sequential mechanisms detoxicating LPS occur at the level of intestinal or liver cells. Indeed, intestinal cells secrete the lipoprotein HDL<sub>3</sub> that exerts anti-inflammatory activity by inactivating LPS [33]. Thus, epithelial cells express the cholesterol transporter ATP-binding cassette transporter 1 (ABCA1), which is essential for the biogenesis of HDL<sub>3</sub>; once secreted, HDL<sub>3</sub> binds LBP so inhibiting LPS recognition by its receptor TLR4 at the level of liver macrophages [33]. A further inactivation of LPS may occur through liver acylglycerol hydrolase, which deacylates critical fatty acid residues for LPS recognition [34] (Figure 1).

Another clearance mechanism for LPS is represented by intestinal alkaline phosphatase (IAP) that removes one of the two phosphate groups of lipid A moiety resulting in LPS degradation to monophosphoryl-LPS [35]; this molecule still binds TLR4 but acts as an antagonist. In animals given a high-fat diet, IAP overexpression resulted in maintaining intestinal mucosa integrity and LPS translocation lowering; a similar detoxification pathway is retained by liver cells, which contributes to lower endotoxemia also via LPS excretion into the bile through scavenger receptors [36]. If these detoxification mechanisms are unable to metabolize



**Figure 1.** Gut dysfunction and endotoxemia in NAFLD. **A.** In healthy individuals, LPS is detoxified by several mechanisms: (1) IAP, an endogenous protein that catalyzes the hydrolysis of one of the 2 phosphate groups from the lipid A moiety of LPS resulting in monophosphoryl-LPS; (2) cholesterol transporter ABCA1 on intestinal epithelial cells generates HDL<sub>3</sub>, which, via LBP, inhibits LPS-TLR4 binding on hepatocytes and intestinal epithelial cells; and (3) extracellular acyloxyacyl hydrolase (AOAH), which removes the two secondary acyl chains to inactivate LPS. **B.** LPS increases gut permeability downregulating adhesion proteins. The impaired gut barrier allows LPS translocation into the portal circulation and can induce liver injury by interacting with its receptor TLR4

Abbreviations: AOA, acyloxyacyl hydrolase; IAP, intestinal alkaline phosphatase; LBP, lipopolysaccharide binding protein; NAFLD, nonalcoholic fatty liver disease; LPS, lipopolysaccharide; TLR4, Toll-like receptor 4

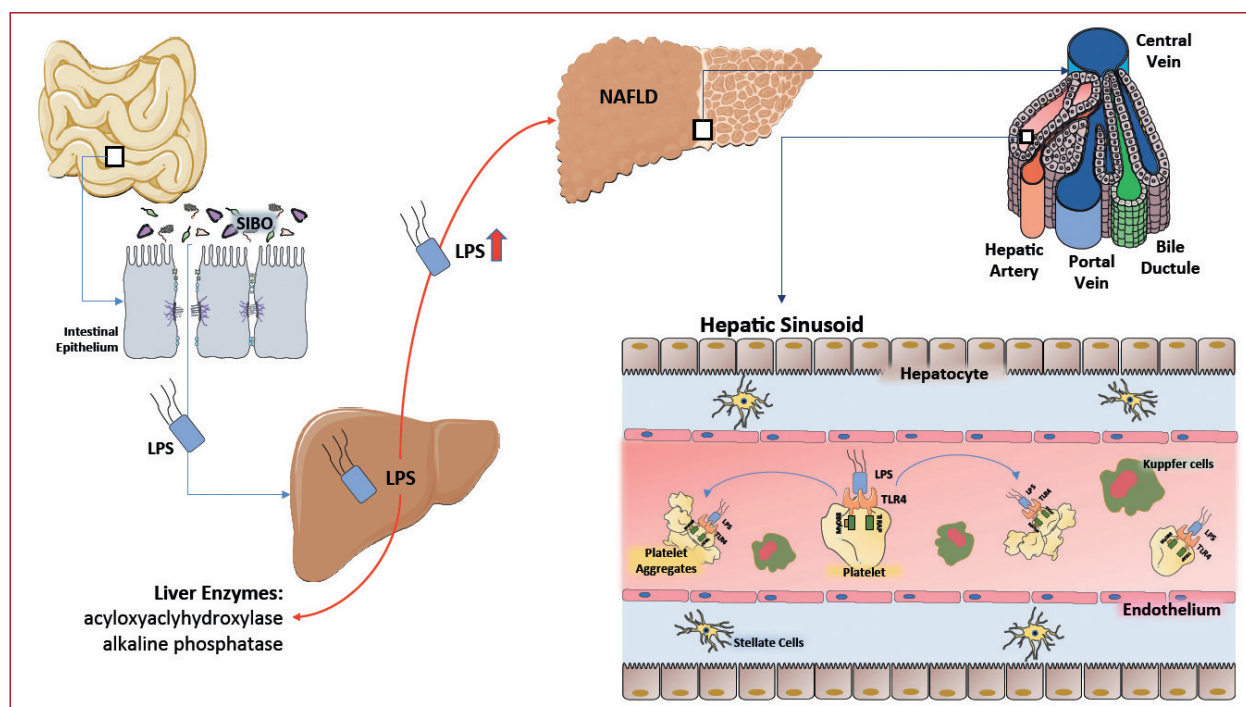
LPS, endotoxemia becomes detectable in the peripheral circulation with potentially deleterious consequences for the human body considering that LPS is a powerful inflammatory molecule (Figure 1). The pro-inflammatory damage by LPS occurs via binding of its lipid moiety, i.e. lipid A to TLR4, which binds LPS via the membrane-bound ligand CD14. LPS binding to TLR4 leads recruitment of the adaptor myeloid differentiation factor 88 (MyD88) to the cytoplasmic domain of TLR4, resulting in activation of transcription factor nuclear factor-kappa B (NF- $\kappa$ B) [37]. TLR4 activation by LPS mediates an inflammatory response that is involved in many chronic inflammatory disorders such as atherosclerosis [38]. Indeed, TLR4 interaction with LPS leads to the downstream stimulation of different signaling pathways including type I interferons (IFNs), activator protein-1 (AP-1), and NF- $\kappa$ B [39] which culminate in the production of large amounts of inflammatory proteins and cytokines, such as TNF $\alpha$ , IL-1 $\beta$ , IL-6, IL-12, secreted by several TLR4 expressing cells such as macrophages, neutrophils, and endothelial cells [40], driving inflammatory responses.

Experimental and clinical studies documented that upon reaching the systemic circulation, i.e. portal and systemic circulation may localize at the levels of specific organs where it may beget detrimental effects. Thus, experimental studies conducted in patients with liver disease showed an LPS increase in the portal circulation, and immune-

-histologic analysis of hepatic specimens taken from patients with NAFLD demonstrated enhanced LPS localization in the liver cells with an up-regulation of TLR4 [20]. A similar study performed in patients with atherosclerosis showed that LPS localizes in the atherosclerotic plaque in close association with activated macrophages overexpressing TLR4, suggesting a potential implication of *in situ* artery inflammation [41]. Together, these data point to gut dysbiosis-related gut barrier dysfunction as the “prime mover” of a sequence of events that lead to potentially detrimental effects of LPS in the liver, systemic circulation, and, eventually, myocardium.

### LOW-GRADE ENDOTOXEMIA AND NAFLD

Systemic levels of LPS have been analyzed in children and adults with NAFLD. Thus, elevated values have been detected in children with biopsy-confirmed NAFLD/NASH showing that low-grade endotoxemia is an early phenomenon of the disease [42]. Similar findings have been reported in adults with NAFLD showing a significant association between circulating LPS and the severity of liver steatosis [43] and between serum LBP and liver steatosis [44]. The relationship between LPS and liver inflammation has been experimentally investigated in mice on methionine, and choline-deficient diet-induced NASH, in which administration of rifaximin, a non-absorbable antibiotic, reduced gut



**Figure 2.** Low-grade endotoxemia and liver damage. Small intestinal bacterial overgrowth (SIBO) contributes to increased gut barrier permeability, low-grade endotoxemia, and eventually liver damage. After lipopolysaccharide (LPS) translocation into the portal circulation, LPS is metabolized by liver cell enzymes, such as acyloxyacyl hydroxylase and alkaline phosphatase. If LPS is not fully metabolized, it accumulates within hepatocytes with potentially deleterious effects in terms of inflammation and eventually hepatic fibrosis. Furthermore, LPS, through the binding of TLR4 on platelets into sinusoids, results in platelet-related micro-thrombosis with ensuing liver damage.

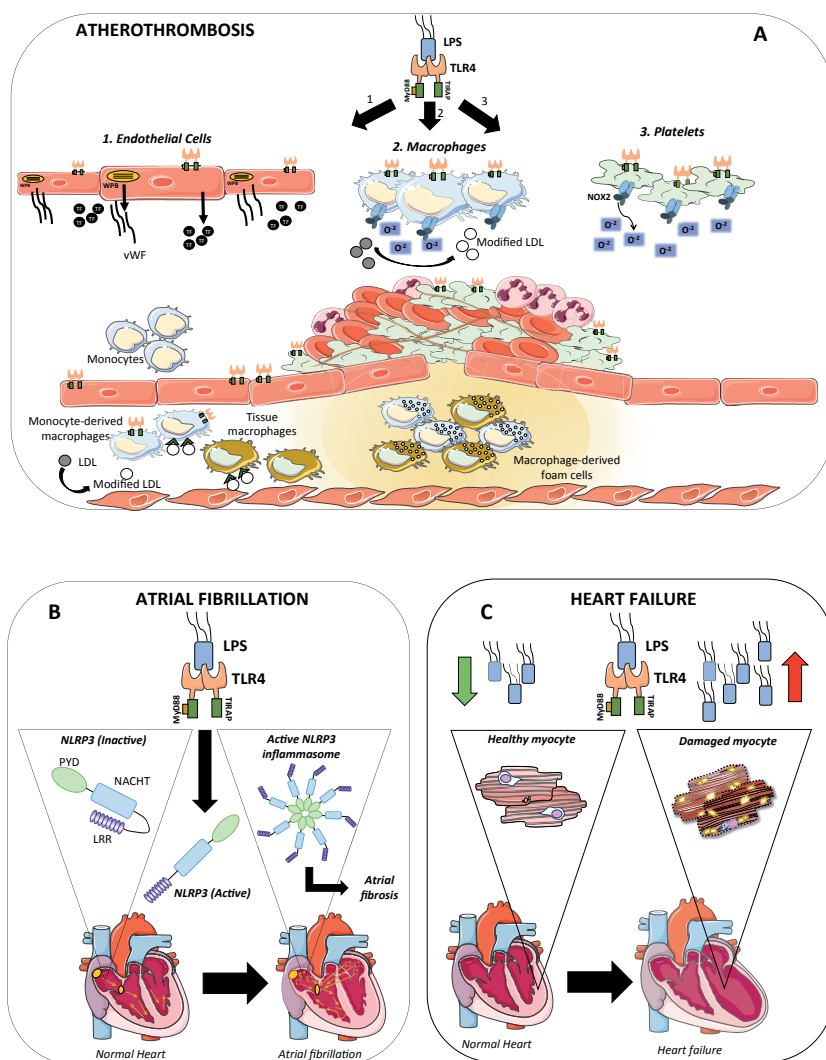
Abbreviations: see Figure 1

dysbiosis, endotoxemia, liver inflammation, and eventually NASH [45]. LPS-TLR4 is likely to play a key role in this process as supported by experiments in TLR4 knock-out mice displaying resistance to experimentally-induced NAFLD [46]. Studies in humans corroborated this hypothesis as documented by immune-histochemistry analysis of liver specimens taken from NAFLD-NASH patients reporting greater LPS localization in patients compared to controls as well as macrophage and platelet TLR4 overexpression that significantly correlated with serum LPS. Reduced liver inflammation detected in experimentally-induced NASH in animals treated with a TLR4 inhibitor corroborated the role of the LPS-TLR4 axis in favoring NASH [20]. In this context, the role of platelets has attracted attention as platelets express TLR4; thus, *in vitro* experiments showed a functional interplay between LPS and platelet activation via TLR4 [47] and studies in 24 consecutive nonobese and nondiabetic biopsy-confirmed NAFLD/NASH patients found a higher number of platelets and platelet aggregates in the sinusoids of NASH patients compared to controls [48].

Also, our group showed that in biopsy-confirmed patients, a higher number of platelets were detected in the liver sinusoids of patients with liver steatosis and NASH and highly expressed TLR4; a significant correlation was detected between LPS and platelet TLR4 suggesting LPS can be a pivotal trigger of platelet TLR4 overexpression [20] (Figure 2). Finally, in high-fat diet-treated mice, the role of platelets and TLR4 in the pathogenesis

of NAFLD/NASH animals was supported by administering a TLR4 inhibitor, which resulted in lowered liver inflammation [20]. Together, these data suggest that NAFLD-NASH LPS may trigger TLR4-mediated platelet activation resulting in platelet-related micro-thrombosis with ensuing liver damage (Figure 2). In accordance with this, a significant reduction of NAFLD has been detected in animals treated with antiplatelet drugs such as aspirin [49] or clopidogrel [50].

*In vivo* and *in vitro* studies have been conducted to support the hypothesis that LPS behaves as a pro-aggregating molecule. An interventional study in humans consisting of intravenous injection of LPS (20 IU/kg i.v.) documented acute activation of platelets just after one hour of infusion with a return to baseline values after 24 hours. Platelet-monocyte aggregates, TF binding on monocytes, and surface expression of platelet CD40L significantly increased after LPS administration [51]. Also, experiments *in vitro* documented that LPS per se, at levels detectable in human circulation, is unable to promote aggregation but amplifies platelet response to common agonists, such as collagen and ADP, via over-production of eicosanoids that are implicated in platelet aggregation such as  $\text{TxA}_2$  and 8-iso-PGF $_{2\alpha}$ -III as well as oxidant species such as  $\text{H}_2\text{O}_2$  [52]. Such an effect was inhibited in the presence of an inhibitor of TLR4 suggesting that LPS-TLR4 interaction was a prerequisite for eicosanoids and oxidant species overproduction [52].



**Figure 3.** Low-grade endotoxemia and cardiovascular disease. **A.** LPS as a trigger of thrombosis. LPS enhances thrombus growth by binding to Toll-like receptor 4 (TLR4) at several cell lines: (1) LPS can favor a prothrombotic milieu by eliciting endothelial secretion of von Willebrand factor (vWF) and Factor VIII (FVIII) via formation and secretion of Weibel-Palade bodies (WPb); (2) LPS promotes inflammation within the arterial wall by activating macrophages overexpressing TLR4; (3) LPS activates platelet via Nox2-mediated oxidative stress. **B.** LPS in atrial fibrillation (AF): increased levels of circulating LPS up-regulate the expression of NOD-like receptor protein (NLRP)-3 inflammasome in the atria, resulting in atrial structural remodeling favoring fibrosis and eventually promoting AF development. **C.** LPS in heart failure (HF): elevated blood LPS levels may contribute to structural and functional changes in the myocytes, reducing myocardial function or eliciting atrial fibrosis that contributes to worsening HF

Abbreviations: see [Figure 1](#)

The elevated levels of endotoxemia in NAFLD patients may be a tool to interpret the reported association between NAFLD and cardiovascular disease. In a cohort of 898 patients with and without NAFLD followed up for 41 months, we found, in fact, that the risk of cardiovascular events were higher in NAFLD versus non-NAFLD patients. Such a difference persisted after adjusting for confounding factors and was similarly detectable if patients were divided according to the FIB-4 score to classify liver fibrosis [53]. In an even higher cohort including 14 819 patients treated with lipid-lowering drugs, NAFLD classified by the fibrosis score allowed identifying patients at higher risk of cardiovascular events [54]. These studies, however, did not analyze if the relationship between NAFLD and cardiovascular diseases may depend upon elevated LPS levels, thereby further studies are necessary to assess if endotoxemia may account for increased risk of cardiovascular events in NAFLD.

### LOW-GRADE ENDOTOXEMIA AND CARDIOVASCULAR DISEASE

Low-grade endotoxemia has been detected in patients at risk of cardiovascular disease, in those with acute and chronic cardiovascular disease, and in patients with AF or HF.

The relationship between endothelial damage and endotoxemia has been investigated by Loffredo et al. [55] who reported elevated LPS levels in patients with microvascular angina, which correlated inversely with serum nitric oxide and directly with serum endothelin 1. Similarly, enhanced LPS levels have been detected in patients with stable angina and myocardial infarction with a gradient increase from stable to unstable disease. Notably, LPS localized in coronary thrombi overexpressing leucocyte TLR4 suggests LPS can be a trigger of thrombosis [11].

This hypothesis has been substantiated in an experimental study in animals that were injected with a quantity of LPS mimicking the concentration detected in human thrombi. The study showed that LPS enhanced thrombus growth via interaction with TLR4 just as a concomitant infusion of a TLR4 inhibitor blunted thrombus growth coincidentally with inhibition of platelet activation [11]. Another mechanism potentially contributing to thrombosis by LPS has been evidenced by *in vitro* experiments documenting that LPS can favor a prothrombotic milieu by eliciting endothelial secretion of FVIII and vWF [23] ([Figure 3](#)). Regarding thrombosis, the LPS-TLR4 axis acts at several cellular levels such as endothelial cells, platelets, and white

cells. Thus, experimental studies demonstrated that LPS elicits FVIII and vWF secretion by endothelial cells, up-regulates monocyte TF, and amplifies the platelet response to common agonists. In addition, clinical studies showed an inverse relationship between flow-mediated dilatation (FMD) and endotoxemia, which suggests that LPS may also induce changes in endothelial cell redox status via production of reactive oxygen species (ROS) that are known to neutralize nitric oxide thus reducing the endothelial vasodilating property [56].

Considering the impact of LPS on clotting activation, it cannot be excluded that endotoxemia may also be associated with venous thrombosis. There is evidence, for instance, that gut dysbiosis-associated inflammatory bowel disease is associated with venous thromboembolism, but the role of LPS needs further investigation [57]. Conversely, in patients with advanced liver disease, who are characterized by an enhanced risk of portal vein thrombosis [58–60], elevated levels of LPS have been detected in the portal circulation with a significant association with endothelial damage, hypercoagulation, and platelet activation [3, 61, 62].

In addition to this prothrombotic property, LPS may damage the arterial wall so predisposing to atherosclerotic progression. Thus, in patients undergoing endarterectomy, immuno-histochemical analysis of atherosclerotic plaque revealed that LPS localizes within the arterial wall in close association with activated macrophages overexpressing TLR4, suggesting a potential role of LPS as a promoter of inflammation *in situ* (Figure 3). Also, a previous study analyzing the relationship between endotoxemia and atherosclerotic burden demonstrated that during a 5-year follow-up, subjects with LPS >50 pg/ml at baseline had a threefold increased risk of incident carotid artery atherosclerosis compared with subjects with blood LPS levels <50 pg/ml [63].

AF is another setting characterized by low-grade endotoxemia, which may be a risk factor for arrhythmia as well as incident cardiovascular disease. Thus, an experimental model of AF demonstrated that gut dysbiosis may promote AF in old rats, an effect that could be counteracted in old rats receiving fecal transplantation from young animals [64]. Overexpression of TLR4 and activation of the NLRP3 inflammasome in the atria were key factors driving atrial fibrosis and increased susceptibility to AF [64] (Figure 3). In addition, an observational study conducted in AF patients showed that LPS may be a risk factor for poor vascular outcomes in AF patients as shown by a higher incidence of major adverse cardiovascular events during a 3-year follow-up in patients with blood LPS levels >100 pg/ml. It was also interesting that AF patients following a Mediterranean diet, which is known to protect from gut barrier dysfunction, had lower blood LPS and reduced risk of poor outcomes [65].

Finally, there is consistent evidence that endotoxemia and HF are closely associated (Figure 3). Thus, an experimental study with low LPS doses demonstrated that

endotoxemia may reduce myocardium function or elicit atrial fibrosis, which potentially contributes to triggering AF, which frequently complicates and worsens HF [64]. Clinical studies involved essentially of cross-sectional studies, which reported enhanced circulating levels of LPS in HF patients compared to control groups. Thus, LPS blood levels were more elevated in patients with severe HF and during an acute edematous exacerbation, with a significant reduction after clinical compensation [66], which supports the hypothesis that bowel congestion is a prerequisite for gut barrier dysfunctionality and ensuing LPS translocation into the systemic circulation. However, while there is an agreement that endotoxemia could contribute to systemic inflammation occurring in HF, the impact of endotoxemia on clinical outcomes is still unclear.

### THERAPEUTIC PERSPECTIVES

The data so far reported suggest that once crossing the intestinal epithelial wall, LPS may exert a pro-inflammatory and pro-thrombotic effect at two different levels, i.e. the liver as the first level and the systemic circulation thereafter. At the level of the liver, LPS may accumulate as a consequence of impaired degradation so favoring platelet-dependent thrombosis, steatosis, and inflammation. Impaired liver degradation is also responsible for releasing enhanced LPS levels into the systemic circulation, which may be deleterious not only at the level of the arterial wall but also may directly interact with myocardial cells. Thus, the LPS-TLR4 axis may represent a unique mechanism causing local and systemic inflammation and thrombosis.

This hypothesis, however, must be substantiated by interventional trials aimed at reducing systemic LPS and eventually, the vascular disease occurring in the liver and systemic circulatory compartments. At least 3 therapeutic approaches could be considered for lowering LPS, i.e. (1) reducing dysbiosis; (2) improving gut permeability; and (3) LPS detoxifying. Concerning the first point, non-absorbable antibiotics such as rifaximin are an interesting option as they reduce LPS by increasing the beneficial flora and exert anti-inflammatory activity by lowering TNF- $\alpha$  or leucocyte TLR4 [67]. The second option includes the use of microbiota metabolites with a protective role for the gut barrier, such as short-chain fatty acid (SCFA) including propionate, butyrate, and acetate, which can up-regulate epithelial adhesive protein [68]. Alternative approaches to improve gut permeability include probiotics, which are live bacteria, or prebiotics, which are plant-derived fibers, with a high intake of fish oils to increase the n-3/n-6 polyunsaturated fatty acids (PUFA) ratio, or drugs such as statins, or glucagon-like peptides that may have a beneficial effect on gut barrier dysfunction by modulating gut dysbiosis or up-regulating the intestinal adhesive proteins [69–72]. LPS detoxification is the third possibility to reduce the negative effects of endotoxemia. Enhancing physiological properties to degrade LPS upregulating the secretion of HDL<sub>3</sub> or IAP may represent an innovative approach to lower

endotoxemia and its local and systemic deleterious effects; this therapeutic option may be considered in the future.

## CONCLUSIONS

In conclusion, experimental and clinical studies provide evidence of gut dysbiosis-related endotoxemia as a novel mechanism potentially favoring the occurrence of inflammation and thrombosis in the liver and systemic circulation and damaging myocardial cells potentially favoring AF and HF occurrence. A cause-effect relationship *in vivo*, however, is still lacking, and further studies are necessary to assess if lowering endotoxemia actually cures liver and cardiovascular diseases.

## Article information

**Conflict of interest:** None declared.

**Funding:** None.

**Open access:** This article is available in open access under Creative Commons Attribution-Non-Commercial-No Derivatives 4.0 International (CC BY-NC-ND 4.0) license, which allows downloading and sharing articles with others as long as they credit the authors and the publisher, but without permission to change them in any way or use them commercially. For commercial use, please contact the journal office at [kardiologiapolska@ptkardio.pl](mailto:kardiologiapolska@ptkardio.pl).

## REFERENCES

- Wang B, Yao M, Lv L, et al. The human microbiota in health and disease. *Engineering*. 2017; 3(1): 71–82, doi: [10.1016/j.eng.2017.01.008](https://doi.org/10.1016/j.eng.2017.01.008).
- O'Toole PW, Jeffery IB. Gut microbiota and aging. *Science*. 2015; 350(6265): 1214–1215, doi: [10.1126/science.aac8469](https://doi.org/10.1126/science.aac8469), indexed in Pubmed: [26785481](https://pubmed.ncbi.nlm.nih.gov/26785481/).
- Violi F, Ferro D, Basili S, et al. Ongoing prothrombotic state in the portal circulation of cirrhotic patients. *Thromb Haemost*. 2018; 77(01):044–047, doi: [10.1055/s-0038-1655904](https://doi.org/10.1055/s-0038-1655904).
- Violi F, Ferro D, Basili S, et al. Association between low-grade disseminated intravascular coagulation and endotoxemia in patients with liver cirrhosis. *Gastroenterology*. 1995; 109(2): 531–539, doi: [10.1016/0016-5085\(95\)90342-9](https://doi.org/10.1016/0016-5085(95)90342-9), indexed in Pubmed: [7615203](https://pubmed.ncbi.nlm.nih.gov/7615203/).
- Prytz H, Holst-Christensen J, Korner B, et al. Portal venous and systemic endotoxaemia in patients without liver disease and systemic endotoxaemia in patients with cirrhosis. *Scand J Gastroenterol*. 1976; 11(8): 857–863, indexed in Pubmed: [794999](https://pubmed.ncbi.nlm.nih.gov/794999/).
- Violi F, Cammisotto V, Bartimoccia S, et al. Gut-derived low-grade endotoxaemia, atherothrombosis and cardiovascular disease. *Nat Rev Cardiol*. 2023; 20(1): 24–37, doi: [10.1038/s41569-022-00737-2](https://doi.org/10.1038/s41569-022-00737-2), indexed in Pubmed: [35840742](https://pubmed.ncbi.nlm.nih.gov/35840742/).
- Erridge C, Attina T, Spickett CM, et al. A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. *Am J Clin Nutr*. 2007; 86(5): 1286–1292, doi: [10.1093/ajcn/86.5.1286](https://doi.org/10.1093/ajcn/86.5.1286), indexed in Pubmed: [17991637](https://pubmed.ncbi.nlm.nih.gov/17991637/).
- Wood Heckman LK, DeBoer MD, Fasano A. Zonulin as a potential putative biomarker of risk for shared type 1 diabetes and celiac disease autoimmunity. *Diabetes Metab Res Rev*. 2020; 36(5): e3309, doi: [10.1002/dmrr.3309](https://doi.org/10.1002/dmrr.3309), indexed in Pubmed: [32162764](https://pubmed.ncbi.nlm.nih.gov/32162764/).
- Li X, Atkinson MA. The role for gut permeability in the pathogenesis of type 1 diabetes – A solid or leaky concept? *Pediatr Diabetes*. 2015; 16(7): 485–492, doi: [10.1111/pedi.12305](https://doi.org/10.1111/pedi.12305), indexed in Pubmed: [26269193](https://pubmed.ncbi.nlm.nih.gov/26269193/).
- Jayashree B, Bibin YS, Prabhu D, et al. Increased circulatory levels of lipopolysaccharide (LPS) and zonulin signify novel biomarkers of proinflammation in patients with type 2 diabetes. *Mol Cell Biochem*. 2014; 388(1-2): 203–210, doi: [10.1007/s11010-013-1911-4](https://doi.org/10.1007/s11010-013-1911-4), indexed in Pubmed: [24347174](https://pubmed.ncbi.nlm.nih.gov/24347174/).
- Carnevale R, Sciarretta S, Valenti V, et al. Low-grade endotoxaemia enhances artery thrombus growth via Toll-like receptor 4: implication for myocardial infarction. *Eur Heart J*. 2020; 41(33): 3156–3165, doi: [10.1093/eurheartj/ehz893](https://doi.org/10.1093/eurheartj/ehz893), indexed in Pubmed: [31898723](https://pubmed.ncbi.nlm.nih.gov/31898723/).
- Oliva A, Cammisotto V, Cangemi R, et al. Low-Grade Endotoxemia and Thrombosis in COVID-19. *Clin Transl Gastroenterol*. 2021; 12(6): e00348, doi: [10.14309/ctg.0000000000000348](https://doi.org/10.14309/ctg.0000000000000348), indexed in Pubmed: [34092777](https://pubmed.ncbi.nlm.nih.gov/34092777/).
- Cangemi R, Pignatelli P, Carnevale R, et al. Low-grade endotoxemia, gut permeability and platelet activation in community-acquired pneumonia. *J Infect*. 2016; 73(2): 107–114, doi: [10.1016/j.jinf.2016.05.013](https://doi.org/10.1016/j.jinf.2016.05.013), indexed in Pubmed: [27288596](https://pubmed.ncbi.nlm.nih.gov/27288596/).
- Hanada S, Pirzadeh M, Carver KY, et al. Respiratory Viral Infection-Induced Microbiome Alterations and Secondary Bacterial Pneumonia. *Front Immunol*. 2018; 9: 2640, doi: [10.3389/fimmu.2018.02640](https://doi.org/10.3389/fimmu.2018.02640), indexed in Pubmed: [30505304](https://pubmed.ncbi.nlm.nih.gov/30505304/).
- Ghosh S, Whitley CS, Haribabu B, et al. Regulation of intestinal barrier function by microbial metabolites. *Cell Mol Gastroenterol Hepatol*. 2021; 11(5): 1463–1482, doi: [10.1016/j.jcmgh.2021.02.007](https://doi.org/10.1016/j.jcmgh.2021.02.007), indexed in Pubmed: [33610769](https://pubmed.ncbi.nlm.nih.gov/33610769/).
- Zhou X, Li J, Guo J, et al. Gut-dependent microbial translocation induces inflammation and cardiovascular events after ST-elevation myocardial infarction. *Microbiome*. 2018; 6(1): 66, doi: [10.1186/s40168-018-0441-4](https://doi.org/10.1186/s40168-018-0441-4), indexed in Pubmed: [29615110](https://pubmed.ncbi.nlm.nih.gov/29615110/).
- Sakai J, Cammarota E, Wright JA, et al. Lipopolysaccharide-induced NF-κB nuclear translocation is primarily dependent on MyD88, but TNFα expression requires TRIF and MyD88. *Sci Rep*. 2017; 7(1): 1428, doi: [10.1038/s41598-017-01600-y](https://doi.org/10.1038/s41598-017-01600-y), indexed in Pubmed: [28469251](https://pubmed.ncbi.nlm.nih.gov/28469251/).
- Miele L, Valenza V, La Torre G, et al. Increased intestinal permeability and tight junction alterations in nonalcoholic fatty liver disease. *Hepatology*. 2009; 49(6): 1877–1887, doi: [10.1002/hep.22848](https://doi.org/10.1002/hep.22848), indexed in Pubmed: [19291785](https://pubmed.ncbi.nlm.nih.gov/19291785/).
- Pang J, Xu W, Zhang X, et al. Significant positive association of endotoxemia with histological severity in 237 patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther*. 2017; 46(2): 175–182, doi: [10.1111/apt.14119](https://doi.org/10.1111/apt.14119), indexed in Pubmed: [28464257](https://pubmed.ncbi.nlm.nih.gov/28464257/).
- Carpino G, Del Ben M, Pastori D, et al. Increased Liver Localization of Lipopolysaccharides in Human and Experimental NAFLD. *Hepatology*. 2020; 72(2): 470–485, doi: [10.1002/hep.31056](https://doi.org/10.1002/hep.31056), indexed in Pubmed: [31808577](https://pubmed.ncbi.nlm.nih.gov/31808577/).
- Camerer E, Huang W, Coughlin SR. Tissue factor- and factor X-dependent activation of protease-activated receptor 2 by factor VIIa. *Proc Natl Acad Sci U S A*. 2000; 97(10): 5255–5260, doi: [10.1073/pnas.97.10.5255](https://doi.org/10.1073/pnas.97.10.5255), indexed in Pubmed: [10805786](https://pubmed.ncbi.nlm.nih.gov/10805786/).
- Saliola M, Lorenzet R, Ferro D, et al. Enhanced expression of monocyte tissue factor in patients with liver cirrhosis. *Gut*. 1998; 43(3): 428–432, doi: [10.1136/gut.43.3.428](https://doi.org/10.1136/gut.43.3.428), indexed in Pubmed: [9863491](https://pubmed.ncbi.nlm.nih.gov/9863491/).
- Carnevale R, Raparelli V, Nocella C, et al. Gut-derived endotoxin stimulates factor VIII secretion from endothelial cells. Implications for hypercoagulability in cirrhosis. *J Hepatol*. 2017; 67(5): 950–956, doi: [10.1016/j.jhep.2017.07.002](https://doi.org/10.1016/j.jhep.2017.07.002), indexed in Pubmed: [28716745](https://pubmed.ncbi.nlm.nih.gov/28716745/).
- Yang D, Dai X, Xing Y, et al. Intrinsic cardiac adrenergic cells contribute to LPS-induced myocardial dysfunction. *Commun Biol*. 2022; 5(1): 96, doi: [10.1038/s42003-022-03007-6](https://doi.org/10.1038/s42003-022-03007-6), indexed in Pubmed: [35079095](https://pubmed.ncbi.nlm.nih.gov/35079095/).
- Peschel T, Schönauer M, Thiele H, et al. Invasive assessment of bacterial endotoxin and inflammatory cytokines in patients with acute heart failure. *Eur J Heart Fail*. 2003; 5(5): 609–614, doi: [10.1016/s1388-9842\(03\)00104-1](https://doi.org/10.1016/s1388-9842(03)00104-1), indexed in Pubmed: [14607199](https://pubmed.ncbi.nlm.nih.gov/14607199/).
- Nishimura N, Kaji K, Kitagawa K, et al. Intestinal permeability is a mechanical rheostat in the pathogenesis of liver cirrhosis. *Int J Mol Sci*. 2021; 22(13), doi: [10.3390/ijms22136921](https://doi.org/10.3390/ijms22136921), indexed in Pubmed: [34203178](https://pubmed.ncbi.nlm.nih.gov/34203178/).
- Caporaso JG, Lauber CL, Walters WA, et al. Global patterns of 16S rRNA diversity at a depth of millions of sequences per sample. *Proc Natl Acad Sci U S A*. 2011; 108 Suppl 1(Suppl 1): 4516–4522, doi: [10.1073/pnas.1000080107](https://doi.org/10.1073/pnas.1000080107), indexed in Pubmed: [20534432](https://pubmed.ncbi.nlm.nih.gov/20534432/).
- Koh AY. Potential for monitoring gut microbiota for diagnosing infections and graft-versus-host disease in cancer and stem cell transplant patients. *Clin Chem*. 2017; 63(11): 1685–1694, doi: [10.1373/clinchem.2016.259499](https://doi.org/10.1373/clinchem.2016.259499), indexed in Pubmed: [28720679](https://pubmed.ncbi.nlm.nih.gov/28720679/).
- Fasano A. Intestinal permeability and its regulation by zonulin: diagnostic and therapeutic implications. *Clin Gastroenterol Hepatol*. 2012; 10(10): 1096–1100, doi: [10.1016/j.cgh.2012.08.012](https://doi.org/10.1016/j.cgh.2012.08.012), indexed in Pubmed: [22902773](https://pubmed.ncbi.nlm.nih.gov/22902773/).
- Spadoni I, Zagato E, Bertocchi A, et al. A gut-vascular barrier controls the systemic dissemination of bacteria. *Science*. 2015; 350(6262): 830–834, doi: [10.1126/science.aad0135](https://doi.org/10.1126/science.aad0135), indexed in Pubmed: [26564856](https://pubmed.ncbi.nlm.nih.gov/26564856/).

31. Stolfi C, Maresca C, Monteleone G, et al. Implication of Intestinal Barrier Dysfunction in Gut Dysbiosis and Diseases. *Biomedicines*. 2022; 10(2), doi: [10.3390/biomedicines10020289](https://doi.org/10.3390/biomedicines10020289), indexed in Pubmed: 35203499.
32. González-González M, Díaz-Zepeda C, Eyzaguirre-Velásquez J, et al. Investigating Gut Permeability in Animal Models of Disease. *Front Physiol*. 2018; 9: 1962, doi: [10.3389/fphys.2018.01962](https://doi.org/10.3389/fphys.2018.01962), indexed in Pubmed: 30697168.
33. Bezhaeva T, Karper J, Quax PHA, et al. The Intriguing Role of TLR Accessory Molecules in Cardiovascular Health and Disease. *Front Cardiovasc Med*. 2022; 9: 820962, doi: [10.3389/fcvm.2022.820962](https://doi.org/10.3389/fcvm.2022.820962), indexed in Pubmed: 35237675.
34. Munford RS, Hunter JP. Acyloxyacyl hydrolase, a leukocyte enzyme that deacylates bacterial lipopolysaccharides, has phospholipase, lysophospholipase, diacylglycerolipase, and acyltransferase activities in vitro. *J Biol Chem*. 1992; 267(14): 10116–10121, indexed in Pubmed: 1577781.
35. Bentala H, Verweij WR, Huizinga-Van der Vlag A, et al. Removal of phosphate from lipid A as a strategy to detoxify lipopolysaccharide. *Shock*. 2002; 18(6): 561–566, doi: [10.1097/00024382-200212000-00013](https://doi.org/10.1097/00024382-200212000-00013), indexed in Pubmed: 12462566.
36. Bates JM, Akerlund J, Mittge E, et al. Intestinal alkaline phosphatase detoxifies lipopolysaccharide and prevents inflammation in zebrafish in response to the gut microbiota. *Cell Host Microbe*. 2007; 2(6): 371–382, doi: [10.1016/j.chom.2007.10.010](https://doi.org/10.1016/j.chom.2007.10.010), indexed in Pubmed: 18078689.
37. Liu T, Zhang L, Joo D, et al. NF- $\kappa$ B signaling in inflammation. *Signal Transduct Target Ther*. 2017; 2: 17023–17023, doi: [10.1038/sigtrans.2017.23](https://doi.org/10.1038/sigtrans.2017.23), indexed in Pubmed: 29158945.
38. Heine H, Zamyatina A. Therapeutic targeting of TLR4 for inflammation, infection, and cancer: a perspective for disaccharide lipid mimetics. *Pharmaceuticals (Basel)*. 2022; 16(1), doi: [10.3390/ph16010023](https://doi.org/10.3390/ph16010023), indexed in Pubmed: 36678520.
39. Ureña-Peralta JR, Pérez-Moraga R, García-García F, et al. Lack of TLR4 modifies the miRNAs profile and attenuates inflammatory signaling pathways. *PLoS One*. 2020; 15(8): e0237066, doi: [10.1371/journal.pone.0237066](https://doi.org/10.1371/journal.pone.0237066), indexed in Pubmed: 32780740.
40. Vijay K. Toll-like receptors in immunity and inflammatory diseases: Past, present, and future. *Int Immunopharmacol*. 2018; 59: 391–412, doi: [10.1016/j.intimp.2018.03.002](https://doi.org/10.1016/j.intimp.2018.03.002), indexed in Pubmed: 29730580.
41. Carnevale R, Nocella C, Petrozza V, et al. Localization of lipopolysaccharide from *Escherichia Coli* into human atherosclerotic plaque. *Sci Rep*. 2018; 8(1): 3598, doi: [10.1038/s41598-018-22076-4](https://doi.org/10.1038/s41598-018-22076-4), indexed in Pubmed: 29483584.
42. Loffredo L, Zicari AM, Perri L, et al. Does Nox2 Overactivate in Children with Nonalcoholic Fatty Liver Disease? *Antioxid Redox Signal*. 2019; 30(10): 1325–1330, doi: [10.1089/ars.2018.7596](https://doi.org/10.1089/ars.2018.7596), indexed in Pubmed: 30019598.
43. Nier A, Huber Y, Labenz C, et al. Adipokines and endotoxemia correlate with hepatic steatosis in non-alcoholic fatty liver disease (NAFLD). *Nutrients*. 2020; 12(3), doi: [10.3390/nu12030699](https://doi.org/10.3390/nu12030699), indexed in Pubmed: 32151020.
44. Kitabatake H, Tanaka N, Fujimori N, et al. Association between endotoxemia and histological features of nonalcoholic fatty liver disease. *World J Gastroenterol*. 2017; 23(4): 712–722, doi: [10.3748/wjg.v23.i4.712](https://doi.org/10.3748/wjg.v23.i4.712), indexed in Pubmed: 28216979.
45. Jian J, Nie MT, Xiang B, et al. Rifaximin ameliorates non-alcoholic steatohepatitis in mice through regulating gut microbiome-related bile acids. *Front Pharmacol*. 2022; 13: 841132, doi: [10.3389/fphar.2022.841132](https://doi.org/10.3389/fphar.2022.841132), indexed in Pubmed: 35450049.
46. An L, Wirth U, Koch D, et al. The role of gut-derived lipopolysaccharides and the intestinal barrier in fatty liver diseases. *J Gastrointest Surg*. 2022; 26(3): 671–683, doi: [10.1007/s11605-021-05188-7](https://doi.org/10.1007/s11605-021-05188-7), indexed in Pubmed: 34734369.
47. Andonegui G, Kerfoot SM, McNagny K, et al. Platelets express functional Toll-like receptor-4. *Blood*. 2005; 106(7): 2417–2423, doi: [10.1182/blood-2005-03-0916](https://doi.org/10.1182/blood-2005-03-0916), indexed in Pubmed: 15961512.
48. Miele L, Alberelli MA, Martini M, et al. Nonalcoholic fatty liver disease (NAFLD) severity is associated to a nonhemostatic contribution and proinflammatory phenotype of platelets. *Transl Res*. 2021; 231: 24–38, doi: [10.1016/j.trsl.2020.11.003](https://doi.org/10.1016/j.trsl.2020.11.003), indexed in Pubmed: 33171266.
49. Patrono C, García Rodríguez LA, Landolfi R, et al. Low-dose aspirin for the prevention of atherothrombosis. *N Engl J Med*. 2005; 353(22): 2373–2383, doi: [10.1056/NEJMra052717](https://doi.org/10.1056/NEJMra052717), indexed in Pubmed: 16319386.
50. Herbert JM, Savi P, Savi P, et al. P2y(12), a new platelet ADP receptor, target of clopidogrel. *Biochem Biophys Res Commun*. 2001; 283(2): 379–383, doi: [10.1006/bbrc.2001.4816](https://doi.org/10.1006/bbrc.2001.4816), indexed in Pubmed: 11327712.
51. Kältsch T, Elmas E, Nguyen XD, et al. Endotoxin-induced effects on platelets and monocytes in an in vivo model of inflammation. *Basic Res Cardiol*. 2007; 102(5): 460–466, doi: [10.1007/s00395-007-0667-y](https://doi.org/10.1007/s00395-007-0667-y), indexed in Pubmed: 17624488.
52. Nocella C, Carnevale R, Bartimoccia S, et al. Lipopolysaccharide as trigger of platelet aggregation via eicosanoid over-production. *Thromb Haemost*. 2017; 117(8): 1558–1570, doi: [10.1160/TH16-11-0857](https://doi.org/10.1160/TH16-11-0857), indexed in Pubmed: 28492699.
53. Baratta F, Pastori D, Angelico F, et al. Nonalcoholic fatty liver disease and fibrosis associated with increased risk of cardiovascular events in a prospective study. *Clin Gastroenterol Hepatol*. 2020; 18(10): 2324–2331.e4, doi: [10.1016/j.cgh.2019.12.026](https://doi.org/10.1016/j.cgh.2019.12.026), indexed in Pubmed: 31887443.
54. Simon TG, Corey KE, Cannon CP, et al. The nonalcoholic fatty liver disease (NAFLD) fibrosis score, cardiovascular risk stratification and a strategy for secondary prevention with ezetimibe. *Int J Cardiol*. 2018; 270: 245–252, doi: [10.1016/j.ijcard.2018.05.087](https://doi.org/10.1016/j.ijcard.2018.05.087), indexed in Pubmed: 29903515.
55. Loffredo L, Ivanov V, Ciobanu N, et al. Low-grade endotoxemia and NOX2 in patients with coronary microvascular angina. *Kardiol Pol*. 2022; 80(9): 911–918, doi: [10.33963/KP.a2022.0130](https://doi.org/10.33963/KP.a2022.0130), indexed in Pubmed: 35579023.
56. Chen Q, Wang Q, Zhu J, et al. Reactive oxygen species: key regulators in vascular health and diseases. *Br J Pharmacol*. 2018; 175(8): 1279–1292, doi: [10.1111/bph.13828](https://doi.org/10.1111/bph.13828), indexed in Pubmed: 28430357.
57. Hasan RA, Koh AY, Zia A. The gut microbiome and thromboembolism. *Thromb Res*. 2020; 189: 77–87, doi: [10.1016/j.thromres.2020.03.003](https://doi.org/10.1016/j.thromres.2020.03.003), indexed in Pubmed: 32192995.
58. Violi F, Corazza GR, Caldwell SH, et al. Portal vein thrombosis relevance on liver cirrhosis: Italian Venous Thrombotic Events Registry. *Intern Emerg Med*. 2016; 11(8): 1059–1066, doi: [10.1007/s11739-016-1416-8](https://doi.org/10.1007/s11739-016-1416-8), indexed in Pubmed: 27026379.
59. Fimognari FL, De Santis A, Piccheri C, et al. Evaluation of D-dimer and factor VIII in cirrhotic patients with asymptomatic portal venous thrombosis. *J Lab Clin Med*. 2005; 146(4): 238–243, doi: [10.1016/j.lab.2005.06.003](https://doi.org/10.1016/j.lab.2005.06.003), indexed in Pubmed: 16194685.
60. Violi F, Corazza GR, Caldwell SH, et al. Incidence and Recurrence of Portal Vein Thrombosis in Cirrhotic Patients. *Thromb Haemost*. 2019; 119(3): 496–499, doi: [10.1055/s-0038-1676981](https://doi.org/10.1055/s-0038-1676981), indexed in Pubmed: 30616246.
61. Queck A, Carnevale R, Uschner FE, et al. Role of portal venous platelet activation in patients with decompensated cirrhosis and TIPS. *Gut*. 2020; 69(8): 1535–1536, doi: [10.1136/gutjnl-2019-319044](https://doi.org/10.1136/gutjnl-2019-319044), indexed in Pubmed: 31270166.
62. Praktinjo M, Trebicka J, Carnevale R, et al. Von Willebrand and Factor VIII Portosystemic Circulation Gradient in Cirrhosis: Implications for Portal Vein Thrombosis. *Clin Transl Gastroenterol*. 2020; 11(2): e00123, doi: [10.14309/ctg.000000000000123](https://doi.org/10.14309/ctg.000000000000123), indexed in Pubmed: 32032127.
63. Wiedermann CJ, Kiechl S, Dunzendorfer S, et al. Association of endotoxemia with carotid atherosclerosis and cardiovascular disease: prospective results from the Bruneck Study. *J Am Coll Cardiol*. 1999; 34(7): 1975–1981, doi: [10.1016/s0735-1097\(99\)00448-9](https://doi.org/10.1016/s0735-1097(99)00448-9), indexed in Pubmed: 10588212.
64. Zhang Y, Zhang S, Li B, et al. Gut microbiota dysbiosis promotes age-related atrial fibrillation by lipopolysaccharide and glucose-induced activation of NLRP3-inflammasome. *Cardiovasc Res*. 2022; 118(3): 785–797, doi: [10.1093/cvr/cvab114](https://doi.org/10.1093/cvr/cvab114), indexed in Pubmed: 33757127.
65. Pastori D, Carnevale R, Nocella C, et al. Gut-Derived Serum Lipopolysaccharide is Associated With Enhanced Risk of Major Adverse Cardiovascular Events in Atrial Fibrillation: Effect of Adherence to Mediterranean Diet. *J Am Heart Assoc*. 2017; 6(6), doi: [10.1161/JAHA.117.005784](https://doi.org/10.1161/JAHA.117.005784), indexed in Pubmed: 28584074.
66. Sandek A, Bjarnason I, Volk HD, et al. Studies on bacterial endotoxin and intestinal absorption function in patients with chronic heart failure. *Int J Cardiol*. 2012; 157(1): 80–85, doi: [10.1016/j.ijcard.2010.12.016](https://doi.org/10.1016/j.ijcard.2010.12.016), indexed in Pubmed: 21190739.
67. Kaji K, Saikawa S, Takaya H, et al. Rifaximin alleviates endotoxemia with decreased serum levels of soluble CD163 and mannose receptor and partial modification of gut microbiota in cirrhotic patients. *Antibiotics (Basel)*. 2020; 9(4), doi: [10.3390/antibiotics9040145](https://doi.org/10.3390/antibiotics9040145), indexed in Pubmed: 32235367.



68. Vinolo MAR, Rodrigues HG, Nachbar RT, et al. Regulation of inflammation by short chain fatty acids. *Nutrients*. 2011; 3(10): 858–876, doi: [10.3390/nu3100858](https://doi.org/10.3390/nu3100858), indexed in Pubmed: [22254083](https://pubmed.ncbi.nlm.nih.gov/22254083/).
69. Xu M, Luo LL, Du MY, et al. Simvastatin improves outcomes of endotoxin-induced coagulopathy by regulating intestinal microenvironment. *Curr Med Sci*. 2022; 42(1): 26–38, doi: [10.1007/s11596-022-2526-3](https://doi.org/10.1007/s11596-022-2526-3), indexed in Pubmed: [35041135](https://pubmed.ncbi.nlm.nih.gov/35041135/).
70. Cani PD, Possemiers S, Van de Wiele T, et al. Changes in gut microbiota control inflammation in obese mice through a mechanism involving GLP-2-driven improvement of gut permeability. *Gut*. 2009; 58(8): 1091–1103, doi: [10.1136/gut.2008.165886](https://doi.org/10.1136/gut.2008.165886), indexed in Pubmed: [19240062](https://pubmed.ncbi.nlm.nih.gov/19240062/).
71. Welnicki M, Gorczyca-Głowacka I, Mamcarz A, et al. The use of GLP-1 analogues in the treatment of diabetes in patients with cardiovascular diseases. The expert opinion of the Working Group of Cardiovascular Pharmacotherapy of the Polish Cardiac Society. *Kardiol Pol*. 2022; 80(12): 1286–1289, doi: [10.33963/KP.a2022.0282](https://doi.org/10.33963/KP.a2022.0282), indexed in Pubmed: [36601885](https://pubmed.ncbi.nlm.nih.gov/36601885/).
72. Siniarski A, Gajos G. Polyunsaturated fatty acids in cardiovascular diseases: uncertainty prevails. *Pol Arch Intern Med*. 2021; 131(7-8): 716–723, doi: [10.20452/pamw.16066](https://doi.org/10.20452/pamw.16066), indexed in Pubmed: [34463083](https://pubmed.ncbi.nlm.nih.gov/34463083/).