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STATE-OF-THE-ART REVIEW

Endotoxemia and Platelets

2 Players of Intrahepatic Microthrombosis in NAFLD

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HIGHLIGHTS

- **NAFLD is characterized by gut dysbiosis-related LPS translocation into portal circulation with ensuing LPS localization in the hepatocytes that overexpress TLR4, the LPS receptor.**
- **This review discusses the experimental and clinical evidence on the interplay between LPS and platelet activation as mechanism potentially eliciting intrahepatic microthrombosis and eventually NAFLD focusing on the role of the LPS-TLR4 axis as the mechanism inducing platelet activation and liver inflammation.**
- **Further study will be required to assess if reducing LPS translocation by lowering gut dysbiosis or detoxifying LPS may result in lowering intrahepatic microthrombosis and eventually NAFLD.**

SUMMARY

Gut dysbiosis-related intestinal barrier dysfunction with increased translocation of bacterial products such as lipopolysaccharide (LPS) into systemic circulation is emerging as pathogenic factor of nonalcoholic fatty liver disease (NAFLD). Experimental and clinical studies suggested a potential role of LPS as a trigger eliciting in situ liver inflammation upon interaction with its receptor toll-like receptor 4. Also, LPS has been reported to prime platelets to respond to the common agonists indicating that it behaves as a prothrombotic molecule. Of note, recent studies suggested platelet-related intrahepatic thrombosis triggered by LPS as a mechanism implicated in the process of liver inflammation. This review describes: 1) the impact of gut barrier dysfunction and endotoxemia in the process of NAFLD; 2) the relationship between endotoxemia and platelet activation in NAFLD; 3) clinical evidence for the use of antiplatelet drugs in NAFLD/nonalcoholic steatohepatitis patients; and 4) the potential therapeutic approach to modulate endotoxemia and eventually platelet activation. (J Am Coll Cardiol Basic Trans Science 2024;9:404–413) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Nonalcoholic fatty liver disease (NAFLD) is characterized by accumulation of fatty acids within liver cells that may progress to nonalcoholic steatohepatitis (NASH), cirrhosis, and eventually liver cancer.[1] In the general population, the prevalence of NAFLD is 20% to 29%, and 20% to 30% of these patients may progress to NASH.[2]

NAFLD is more prevalent in men compared with women, but after menopause the prevalence is similar; also, NAFLD may be an early liver disease in children with metabolic disease such obesity.[3] Thus, NAFLD is closely associated with metabolic diseases such as type 2 diabetes mellitus, obesity, metabolic syndrome, and dyslipidemia and is characterized by

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local and systemic low-grade inflammation, which may affect clotting and platelet activation, favoring the occurrence of atherosclerosis and cardiovascular diseases.[3,4]

Gut dysbiosis with ensuing enhanced gut permeability is emerging as an important pathogenic factor of NAFLD via translocation of bacteria or bacteria products such as lipopolysaccharide (LPS) into systemic circulation.[5,6] Thus, changes of gut microbiota typically occur in patients with metabolic diseases favoring gut barrier dysfunction, which is a prerequisite for systemic endotoxemia.[7]

Experimental and clinical studies suggested a potential role for endotoxemia, as detected by elevated circulating levels of LPS as a mechanism eliciting in situ liver inflammation via interaction with its receptor, toll-like receptor 4 (TLR4).[8-10] Interestingly, LPS has been reported to prime platelets to respond to the common agonists, indicating that it behaves like a prothrombotic molecule. Such a proaggregating effect was achieved by incubating platelets with LPS at concentrations detectable in the peripheral circulation of patients with liver disease.[11] Furthermore, recent studies pointed to platelets as blood cells implicated in the process of local liver inflammation predisposing to the classic NAFLD/NASH histological features in animals and humans.[10,12] As it is possible that the LPS-platelet axis may represent a mechanism involved in the pathogenesis on NAFLD, in this review we analyze: 1) the impact of gut barrier dysfunction and endotoxemia in the process of NAFLD; 2) the relationship between endotoxemia and platelet activation in NAFLD; 3) clinical evidence for the use of antiplatelet drugs in NAFLD/NASH patients; and 4) the potential therapeutic approach to modulate endotoxemia and eventually platelet activation.

INTESTINAL BARRIER DYSFUNCTION, ENDOTOXEMIA, AND NAFLD

There are several intestinal strata separating epithelial cells from gut microbiota such as mucus stratum, intestinal cell barrier including adherent junction proteins, tight junction proteins, gap junction proteins and desmosomes, and third protective stratum (ie, the gut-vascular barrier).[13,14]

The gut microbiota protects intestinal barrier by secreting metabolites maintaining barrier integrity such as short-chain fatty acids (SCFAs), indole and indole derivatives, and polyamines and polyphenols.[15] However, overgrowth of pathogen bacteria or reduction of microbiota biodiversity generate gut dysbiosis, which is a prerequisite for gut barrier dysfunctionality and translocation of microorganisms or microbial products into the systemic circulation.[7] Small intestine bacterial overgrowth (SIBO) is among the most important mechanisms contributing to gut dysbiosis-related increased intestinal barrier permeability and is caused by impaired bile secretion and/or delayed gastrointestinal transition-related mucus layer thinning or down-regulation of adhesion proteins.[16] Thus, a significant association between SIBO, as assessed by xylose and lactulose breathing testing, and NASH has been reported.[17] However, analysis of the interplay between gut dysbiosis typology and NAFLD provided equivocal data, as it is unclear if specific microbiota are connected with NAFLD pathogenesis.[16,18,19]

The relationship between gut dysbiosis and gut permeability was extensively investigated by Miele et al[8] in 35 consecutive biopsy-proven NAFLD patients presenting with SIBO and showing reduced expression of tight junctions in duodenal biopsy specimens. Impaired gut barrier functionality may have deleterious effects because it allows LPS to translocate into the portal circulation and eventually causes liver damage.[10] On the other hand, LPS, which is a glycolipid component of outer bacteria membrane of Gram-negative bacteria comprising of carbohydrates and lipid A portion, may further exacerbate gut permeability upon interaction with intestinal TLR4.[7] Upon LPS recognition, which occurs via binding of its lipid moiety (ie, lipid A),[20] TLR4 undergoes oligomerization and increases the production of proinflammatory cytokines, such as interleukin-8 and tumor necrosis factor (TNF)[21] and oxidative stress via upregulation of NOX2-derived reactive oxidant species, which ultimately elicit formation of powerful proaggregating eicosanoids such as F2-isoprostanes and thromboxane A2.[11] There are several mechanisms that may contribute to detoxify the human body from LPS. The intestinal epithelium encompasses, in fact, the enzyme intestinal alkaline phosphatase (IAP), which removes 1 of the 2 phosphate groups of lipid A moiety, resulting in LPS degradation to monophosphoryl-LPS; this molecule still binds to TLR4 but acts as an antagonist (**Figure 1**).[22] In animals given a high-fat diet, IAP overexpression resulted in maintaining intestinal mucosa integrity and lowering LPS translocation[23]; a similar detoxification pathway is retained by liver cells that contributes to lower endotoxemia also via LPS excretion into the bile through scavenger receptors.[24] The other 2 mechanisms detoxicating LPS occur at level of intestinal or

ABBREVIATIONS AND ACRONYMS

HCC = hepatocellular carcinoma

HDL3 = high density lipoprotein 3

LBP = lipopolysaccharide-binding protein

LPS = lipopolysaccharide

NAFLD = nonalcoholic fatty liver disease

NASH = nonalcoholic steatohepatitis

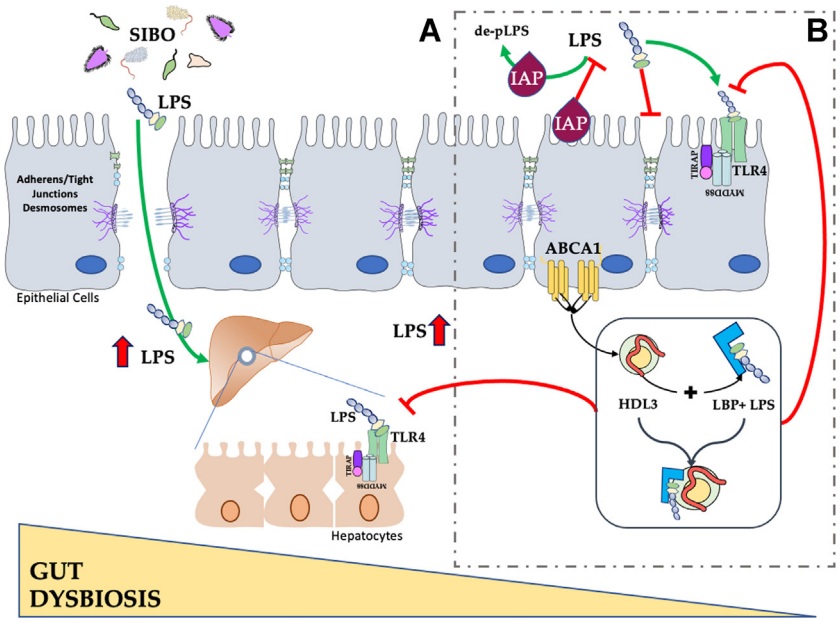
NET = neutrophil extracellular trap

SCFA = short-chain fatty acids

SIBO = small intestine bacterial overgrowth

TLR4 = toll-like receptor 4

FIGURE 1 Gut Dysfunction and Endotoxemia in NAFLD



(A) In nonalcoholic fatty liver disease (NAFLD), small intestine bacterial overgrowth increases gut permeability down-regulating adhesion proteins. An impaired gut barrier allows lipopolysaccharide (LPS) translocation into the portal circulation and eventually causes liver damage interacting with its receptor toll-like receptor 4 (TLR4) on hepatocytes. (B) The mechanisms that contribute to detoxify the human body from LPS include: 1) remotion, by the enzyme intestinal alkaline phosphatase (IAP) of 1 of the 2 phosphate groups of lipid A moiety resulting in LPS degradation to monophosphoryl-LPS; and 2) expression of the cholesterol transporter ABCA1 on intestinal epithelial cells, thus generating high-density lipoprotein 3 (HDL3), which is able to bind lipopolysaccharide-binding protein (LBP), thus failing LPS recognition by TLR4 at the level of hepatocytes and intestinal epithelial cells. SIBO = small intestine bacterial overgrowth.

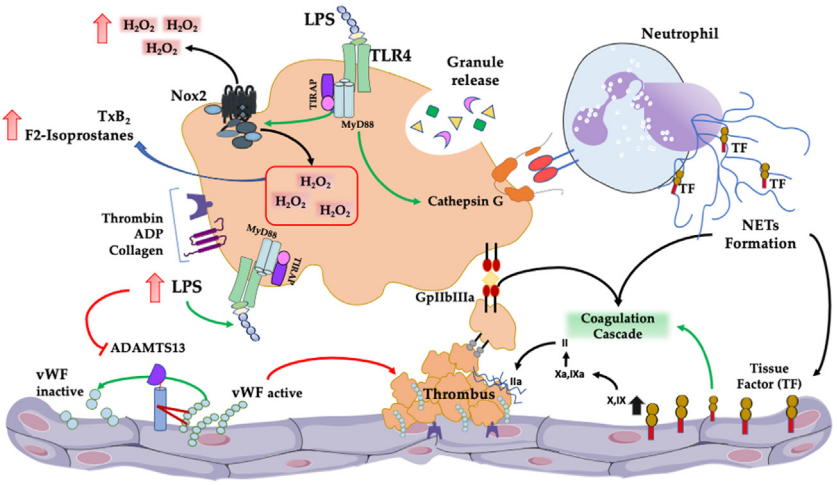
liver cells. Thus, epithelial cells express the cholesterol transporter ABCA1, which is essential for the biogenesis of high-density lipoprotein 3 (HDL3); once secreted, HDL3 binds lipopolysaccharide-binding protein (LBP), failing LPS recognition by its receptor TLR4 at level of hepatocytes and Kupffer cells.[25] A further inactivation of LPS may occur through liver acyloxyacylhydrolase, which deacylates fatty acid residues critical for LPS recognition (**Figure 1**).[26]

Enhanced levels of circulating LPS have been detected in children and adults with NAFLD, showing a significant association between circulating LPS and the severity of liver steatosis and between serum LBP and liver steatosis.[27] The role of LPS as mediator of liver inflammation has been documented in mice on methionine and choline-deficient diet-induced NASH, in which administration of rifaximin, a nonabsorbable antibiotic, resulted in reduced gut dysbiosis, endotoxemia, liver inflammation, and eventually NASH[28]; the importance of the LPS-TLR4 axis has been further corroborated by experiments withTLR4 knockout mice displaying a resistance to experimentally induced NAFLD.[2] We recapitulated these findings in patients with NAFLD/NASH, reporting higher serum LPS and LPS localization in patients compared with control subjects as well as macrophage and platelet TLR4 overexpression, which significantly correlated with serum LPS; also, reduced liver inflammation was detected in experimentally induced NASH in animals treated with a TLR4 inhibitor.[10] Together, these data indicated that LPS may behave as trigger of liver damage upon interaction with platelet TLR4 receptor and eventually release of mediators with inflammatory properties including S-1-P, CXCL4, platelet-derived growth factor, and transforming growth factor-β[29]; it remains to be established if one or more of these mediators play a role in eliciting liver inflammation by platelets.

PLATELET ACTIVATION AND NAFLD

The relevance of platelet activation in NAFLD/NASH comes from immunohistochemical analysis of liver samples taken from patients or experimentally

FIGURE 2 **LPS-Mediated Prothrombotic Effects in NAFLD**



LPS and platelet TLR4 play a role as trigger of platelet activation. LPS interaction with TLR4 with ensuing recruitment of the adaptor proteins TIRAP and MyD88 promotes activation of downstream signaling, resulting in stimulation of platelet granule secretion leading to potentiation and amplification of platelet activation and aggregation to the common agonists by overproduction of eicosanoids, such as thromboxane A2 and F2-isoprostanes, and oxidant species produced by Nox2. In addition, LPS may also act indirectly eliciting a proaggregating effect via reducing ADAMTS13 activity. Finally, after stimulation of LPS, platelets are able to interact with neutrophils resulting in neutrophil extracellular traps (NETs); tissue factor (TF) by NETs results in activation of coagulation cascade. ADP = adenosine diphosphate; TxB_2 = thromboxane B2; vWF = Von Willebrand factor; other abbreviations as in Figure 2.

induced NAFLD/NASH. Miele et al[30] compared platelet behavior in 24 consecutives nonobese and nondiabetic biopsy-proven NAFLD/NASH patients vs 17 control subjects and found a higher number of platelets and platelet aggregates in the sinusoids of NASH patients compared with control subjects. These findings were paralleled by enhanced systemic levels of von Willebrand factor (vWF), LPS, and platelet transcripts such as CXCR1, TLR4, MPO, and ICAM1; also, a significant higher deposition of neutrophil extracellular traps (NETs) was detected in livers presenting inflammation with a significant correlation between NETs and platelet aggregates.[30] Platelets may have an important role in this context, as shown by their interaction with neutrophils to give formation of NETs in a murine model of LPS-induced endotoxemia; such interplay was highly dependent on β2 integrins.[31] Thus, the relationship among LPS, platelets and leukocytes may also be implicated in the microthrombosis occurring in the hepatic sinusoids of NAFLD, as leucocytes express tissue factor, a key factor of extrinsic coagulation cascade via activation of factor X to Xa (Figure 2).[32]

The impact of platelet activation on liver disease has been extensively investigated by Malehmir et al,[12] who demonstrated an increased infiltration of platelets in the hepatic tissue along with signs of platelet activation; these changes were observed in liver tissue taken from NASH patients and high-fat diet-treated mice. The role of platelets in the pathogenesis of NAFLD/NASH was further investigated in animals treated with antiplatelet drugs such as aspirin, which inhibits platelet thromboxane A_2 by irreversible acetylation of COX1,[33] and clopidogrel, which inhibits the adenosine diphosphate receptor $P2Y_{12}$.[34] The study showed a significant reduction of intrahepatic platelet number and activation along with an amelioration of liver steatosis and NASH; also, in patients with cardiovascular disease and coexistent NAFLD, antiplatelet treatment resulted in lower liver volume and liver fat mass.[12] Further support to the role of platelets in NAFLD/NASH was provided by our group, showing that in biopsy-proven patients a higher number of platelets was detected in the liver sinusoids of patients with liver steatosis and NASH, which highly expressed TLR4; a significant correlation was detected between LPS and platelet TLR4, suggesting LPS as pivotal trigger of platelet TLR4 overexpression.[10] Two separate experiments in high-fat diet-treated mice provided support to the role of platelets and TLR4 in the pathogenesis of NAFLD/NASH animals; thus, administration of a

TLR4 inhibitor resulted in lowered liver inflammation, while aspirin treatment showed no changes of liver steatosis but a significant reduction of fibrosis score.[10]

In addition to the role of platelets in the pathogenesis of NAFLD, other studies showed that NAFLD is associated with a hypercoagulation state, which in turn may favor liver damage progression and fibrosis[3]; in this context, the role of enhanced thrombin generation could be of relevance via interaction with the platelet receptor agonist PAR-1/2.[35] Experimental study supported the role of clotting activation in the progression of liver disease, showing that impaired thrombin generation was associated with reduced systemic and liver inflammation and protection from liver disease development[36]; also, administration of dabigatran, a direct thrombin inhibitor, resulted in lower hepatic inflammation and disease progression.[36]

ENDOTOXEMIA AND PLATELET ACTIVATION

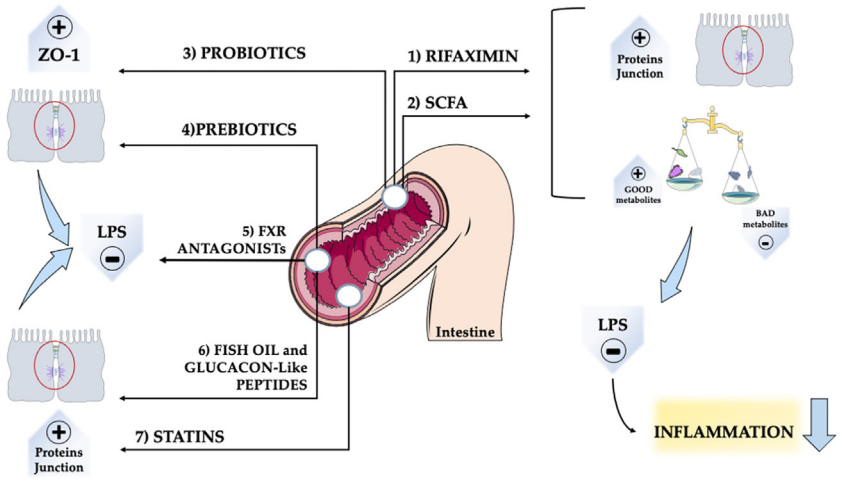
Studies performed in patients with advanced liver disease documented enhanced platelet activation in peripheral and the portal circulation.[37,38] However, this novel finding, which is in contrast with previous papers reporting platelet functional defects in cirrhosis,[39] has not been fully accepted.[40] Conversely, a recent large study including 203 patients with cirrhosis supported our view, showing that platelets are overactivated in cirrhosis, overall in the case of decompensated patients.[41] To investigate the underlying mechanism, we focused on the potential interplay between LPS and platelet activation, as detection of a correlation between circulating LPS and in vivo platelet activation suggested a cause-effect relationship.[42] This hypothesis was supported by experiments conducted in normal platelets showing that LPS, per se, at concentrations detectable in human circulation, is unable to promote aggregation but amplifies platelet response to common agonists such as collagen and adenosine diphosphate at concentrations as low as 15 pg/mL.[11] This effect was associated with overproduction of eicosanoids, that are implicated in platelet aggregation such as thromboxane A2 and 8-iso-PGF2α-III, as well as oxidant species such as hydrogen peroxide.[11] Of note, LPS-promoted platelet aggregation was associated with lower production of eicosanoids and oxidant species in platelets incubated with a TLR4 inhibitor, suggesting that LPS amplifies the platelet response to the agonists via TLR4-mediated oxidative stress mechanism; in accordance with this hypothesis, the previously reported platelet functional changes were prevented by an inhibitor of Nox2 (**Figure 2**).[11] The putative association between LPS and platelet activation was further corroborated by a significant association between elevated circulating LPS and TLR4-mediated platelet overactivation in patients with coronary thrombosis.[43] Modification of redox status via activation of Nox2 may be an impact in artery functionality, as Nox2 is a powerful arterial vasoconstrictor via production of oxidant species and inactivation of nitric oxide[44]; further study should be done to assess the interplay between redox status and artery vasodilatation in NAFLD.

Additional support to the interplay between LPS and platelet activation was provided by a study performed in 13 healthy male subjects who received an intravenous administration of LPS (20 IU/kg). Several markers on platelet activation were measured at baseline and at 1, 2, 4, 6, and 24 hours after LPS infusion. Platelet-monocyte aggregates, tissue-factor binding on monocytes, and surface expression of platelet CD40L significantly increased after LPS administration reaching peak values 1 hour after infusion. All values returned to baseline after 24 hours.[45]

Alternatively, LPS may indirectly elicit a proaggregating effect via reducing disintegrin-like and metalloprotease with ADAMTS13 activity as suggested by an inverse relationship between endotoxin blood levels and ADAMTS13 activity in patients with severe liver alcohol hepatitis.[46] ADAMTS13, which is primarily synthesized and released from hepatic stellate[47] and endothelial cells,[48] binds and cleaves large and highly reactive vWF into smaller and less active multimers.[49] In case of lowered ADAMTS13 activity, a persistent elevated concentration of vWF multimer leads to a hypercoagulated state, as vWF is a proaggregating molecule (**Figure 2**).[50] The potential role of ADAMTS13 in the pathogenesis of NAFLD was suggested by an experimental model of NAFLD in which animals knocked out for ADAMTS13 were more prone to intrahepatic microthrombosis.[51] However, it is still to be defined if ADAMTS13 lowering in advanced liver cirrhosis is dependent on impaired biosynthesis or enhanced degradation.

Despite these interesting findings, a cause-effect relationship between LPS and intrahepatic platelet activation is still lacking, and further study is necessary to assess if lowering LPS results in reduced platelet-dependent intrahepatic microthrombosis and eventually liver inflammation. Of note, however, an experimental model mimicking low-grade endotoxemia in humans demonstrated that injection of LPS (0.5 mg/kg), resulting in a systemic concentration of 40 pg/mL, accelerated thrombus growth

FIGURE 3 **Detoxification of LPS: Therapeutic Strategies**



Reduction of levels lipopolysaccharide (LPS) or counteraction of LPS toxicity could occur by: 1) rifaximin, a nonabsorbable antibiotic; 2) short-chain fatty acids (SCFAs) such as propionate, butyrate, and acetate; 3) probiotics (live bacteria or microbial metabolites including *Lactobacillus plantarum* or *Akkermansia muciniphila*), microbial metabolites such as urolithin A, or oxyberberine or lactose-fermenting Lactobacilli and Bifidobacteria; 4) prebiotics (fermentable fiver [oligofructose]); 5) fish oils and glucagon-like peptides; and 6) statins. FXR = farnesoid X receptor; ZO-1 = zonula occludens-1.

coincidentally with increased systemic biomarkers of platelet activation, an effect blunted by coadministration of TLR4 inhibitor.[52]

ANTIPLATELET TREATMENT IN NAFLD

There is a growing interest on the role of antiplatelet drugs, especially aspirin, in patients with NAFLD.[53]

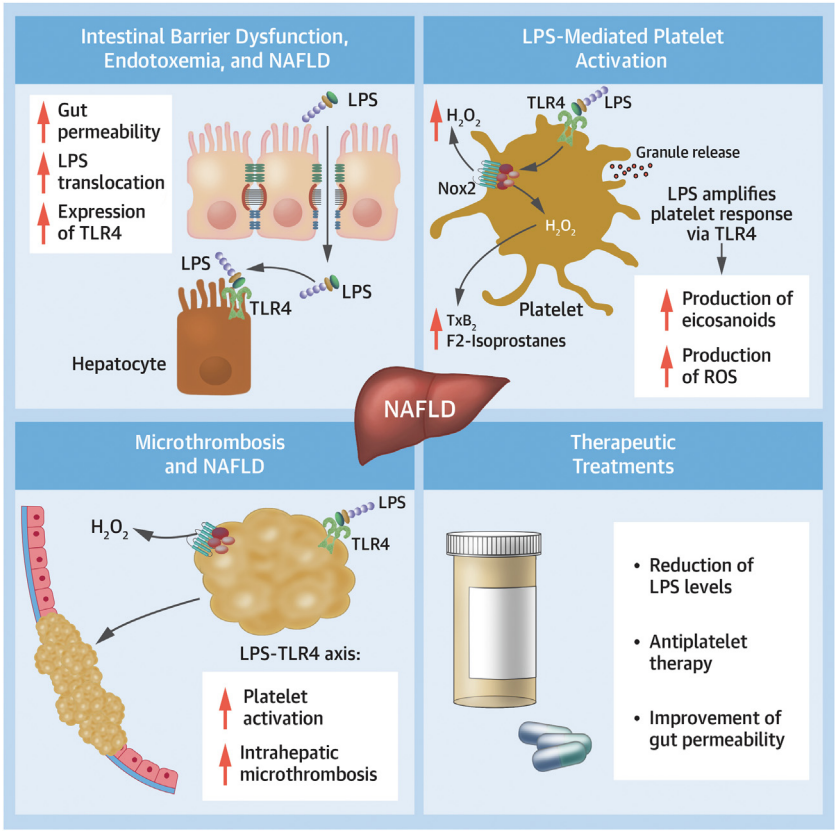
Experimental studies showed that aspirin/thienopyridine treatment may modify the progression of liver steatosis, by reducing the development of NAFLD and liver fibrosis,[10] which are known to be associated with cardiovascular and liver-related outcomes.[54] In 344 male rats given a choline-deficient, l-amino acid-defined diet or a high-fat, high-calorie diet, the addition antiplatelet drugs such aspirin, ticlopidine, or cilostazol for 16 weeks significantly attenuated liver steatosis, inflammation, and fibrosis, with cilostazol being the most effective antiplatelet agent.[55]

In the general population, data from the NHANES III (Third National Health and Nutrition Examination Survey) that included 11,416 adults 20 to 74 years of age showed that aspirin use was inversely associated with the prevalence of ultrasonography-based NAFLD (OR: 0.62; 95% CI: 0.51-0.74; $P = 0.04$), especially in men (OR: 0.32; 95% CI: 0.23-0.45) and in subjects >60 years of age (OR: 0.21; 95% CI: 0.14-0.30).[56]

Furthermore, a study including 361 adults with biopsy-confirmed NAFLD, of whom 151 were on aspirin, showed that aspirin use was associated with a lower risk of developing NASH (OR: 0.68; 95% CI: 0.37-0.89) and fibrosis (OR: 0.54; 95% CI: 0.31-0.82).[57] In particular, aspirin users had a significant lower risk for developing incident advanced fibrosis (HR: 0.63; 95% CI: 0.43-0.85), with the greatest benefit seen after at least 4 years of treatment (HR: 0.50; 95% CI: 0.35-0.73).[57] Results of observational studies were recently pooled in a metanalysis including 4 studies with 2,593 NAFLD patients, of whom 949 were treated with antiplatelet agents. The use of aspirin and/or $P2Y_{12}$ receptor inhibitors was associated with a lower risk of advanced liver fibrosis (OR: 0.66; 95% CI: 0.53-0.81; $I^2 = 0.0\%$; $P < 0.001$).[58]

NAFLD patients have also an increased risk of developing hepatocellular carcinoma (HCC) compared with the general population.[59] In a study including 18,080 patients, the 10-year cumulative incidence of HCC was 2.73% (95% CI: 1.69%-3.76%).[60] The HCC incidence was highest in patients >55 years of age with alanine aminotransferase elevation (12.41%; 95% CI: 5.99%-18.83%).[61] Data from patients with chronic viral hepatitis in Sweden showed that the use of low-dose aspirin was associated with a significantly lower risk of HCC and lower liver-related mortality compared with nonaspirin use.[61]

CENTRAL ILLUSTRATION **Gut-Derived Low-Grade Endotoxaemia and Platelet Activation in NAFLD**



Violi F, et al. J Am Coll Cardiol Basic Trans Science. 2024;9(3):404–413.

Schematic representation of the impact of gut barrier dysfunction and endotoxemia in NAFLD process; the relationship between endotoxemia platelet activation and micro-thrombosis in NAFLD; the potential therapeutic approach to modulate endotoxemia and eventually platelet activation. LPS = lipopolysaccharide; NAFLD = nonalcoholic fatty liver disease.

The relationship between aspirin and HCC seems to be dose dependent, with a dose of at least 650 mg/wk being associated with reduced HCC risk (adjusted HR: 0.51; 95% CI: 0.34-0.77).[62] In addition, the risk of HCC decreased with the duration of aspirin treatment with an HR of 0.41 (95% CI: 0.21-0.77) for 5 or more years of treatment.[62] Data on patients with NAFLD are lacking, but aspirin might be a promising option for these patients.[63]

THERAPEUTIC PERSPECTIVES

Considering the negative effect of endotoxemia on the vascular tree, reducing the circulating levels or counteracting LPS toxicity would be the mainstream approach to lower its proinflammatory and prothrombotic activity. Reduction of systemic LPS may occur at 3 levels, that is: 1) lowering dysbiosis; 2) improving gut permeability; or 3) enhancing LPS degradation (**Figure 3**).

Regarding the first point, gut dysbiosis lowering by nonabsorbable antibiotics may be an interesting option. Thus, administration of rifaximin reduced the circulating levels of LPS via shift from pathogen to beneficial gut metabolites and exerted an anti-inflammatory effect by lowering TNF-α or leucocyte TLR4 (**Central Illustration**).[64]

Gut permeability may be improved by using microbiota metabolites with a protective role of gut barrier permeability such as SCFA; thus, experiments in vitro by incubation of intestinal epithelial cells with SCFA such as propionate, butyrate, and acetate improved gut barrier dysfunction.[15] Also, administration of a diet rich in SCFAs to patients with metabolic syndrome resulted in up-regulation of epithelial adhesive protein.[15,65]

Other approaches to improve gut permeability include probiotics, such as live bacteria, or prebiotics, which are plant-derived fivers. Regarding probiotics, *Lactobacillus plantarum* or *Akkermansia muciniphila*[15] or lactose-fermenting Lactobacilli and Bifidobacteria are capable of improving gut permeability and thus lowering endotoxemia.[66] Other probiotics that protect gut barrier permeability include *L. plantarum* or *A. muciniphila*, or microbial metabolites such as urolithin A or oxyberberine.[15] Regarding prebiotics, a diet added with a fermentable fiver (oligofructose) resulted in improved gut barrier dysfunction and reduced circulating LPS via up-regulation of zonula occludens-1 and occluding.[67] Administration of fish oils, statins, or glucagon-like peptides may also improve gut permeability and thereby could be candidates to prevent or treat NAFLD.[67]

LPS catabolism to lower its circulating levels and eventually its toxicity is an alternative therapeutic approach. In animals given a high-fat diet, IAP overexpression resulted in maintaining intestinal mucosa integrity and lowering LPS translocation; however, it was not investigated if IAP overexpression resulted in improving fatty acid accumulation in the liver.[23]

CONCLUSIONS

There is consistent evidence that both increased circulating LPS and platelet activation are detectable in the intrahepatic tissue of patients with NAFLD/NASH and may be implicated in the pathogenesis of inflammation-related liver damage. Interventional studies with rifaximin or antiplatelet drugs that resulted in lowered liver inflammation and amelioration of liver damage provided indirect support on this pathogenetic mechanism. These findings may provide the rationale to develop novel strategies to slow liver steatosis progression and its sequelae inhibiting the endotoxemia-mediated platelet activation.

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