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Gut dysbiosis-related thrombosis in inflammatory bowel disease: Potential disease mechanisms and emerging therapeutic strategies

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ABSTRACT

Patients with inflammatory bowel disease (IBD) have an increased risk of developing venous thromboembolic events, which have a considerable impact on morbidity and mortality. Chronic inflammation plays a crucial role in the pathogenesis of thrombotic events in patients with IBD. However, many unresolved questions remain, particularly regarding the mechanisms that determine the persistent inflammatory state independent of disease activity. This review explored the role of gut microbiota dysbiosis and intestinal barrier dysfunction, which are considered distinctive features of IBD, in determining pro-thrombotic tendencies. Gut-derived endotoxemia due to the translocation of bacterial lipopolysaccharides (LPS) from the intestine to the bloodstream and the bacterial metabolite trimethylamine-N-oxide (TMAO) are the most important molecules involved in gut dysbiosis-related thrombosis. The pathogenic prothrombotic pathways linked to LPS and TMAO have been discussed. Finally, we present emerging therapeutic approaches that can help reduce LPS-mediated endotoxemia and TMAO, such as restoring intestinal eubiosis, normalizing intestinal barrier function, and counterbalancing the effects of LPS and TMAO.

1. Introduction

Inflammatory bowel disease (IBD) is a chronic immune-mediated disorder with typical onset at a young age and a lifelong natural history characterized by alternating exacerbation and remission phases [1]. IBD is classified into two main clinical entities: ulcerative colitis (UC) and Crohn's disease (CD). UC continuously affects the colon, starting from the rectum, with variable extension from proctitis to the entire colon. In contrast, CD can affect the entire digestive tract segmentally, localizing at the terminal ileum and colon in most cases. In addition to gastrointestinal involvement, IBD is characterized by several extra-intestinal manifestations [2]. Venous thromboembolism (VTE) has a substantial clinical impact on the prognosis of IBD.

As in the general population, the most frequent clinical presentation of VTE in patients with IBD is deep vein thrombosis (DVT) of the lower limbs or pulmonary embolism (PE) [3,4]. However, the high thromboembolic burden also determines thrombotic episodes in unusual sites, such as cerebral [5,6], portal [7–9], splenic [7,9], mesenteric [10], or ovarian [7,11,12] veins; Budd-Chiari syndrome [7,9,13,14], retinal vein occlusion [5,15,16], or upper extremity deep vein thrombosis [3,17,18].

The association between IBD and VTE was first reported nearly a century ago in 18 arterial and venous thromboembolic episodes in a cohort of 1500 patients with UC [19]. Since then, numerous studies have followed, although heterogeneous, have provided robust evidence of an increased VTE risk in patients with IBD [20,21]. In the last decade, three meta-analyses reported an overall twofold increase in VTE risk in patients with IBD [21–23].

Arvanitakis et al. showed that the relative risk (RR) of VTE in IBD

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compared with non-IBD was further increased after adjustment for smoking and body mass index (BMI) (RR 2.65, 95%CI 1.51–4.65) [5]. However, sex does not affect this [21]. Furthermore, despite the low overall incidence, the risk of VTE is significantly increased in pediatric patients with IBD [24]. As regards the absolute risk, the prevalence rate of VTE ranges from 5.6 % [3] to 7.6 % [25], with an incidence between 2.4 [26] and 6 cases per 1000 person-years [PY] [3]. Recently, a population-based Canadian study including 3593 children with IBD compared age- and sex-matched children to children without IBD, and found a 5-year incidence of VTE of 31.2 (95%CI 23.7–41.0) per 10,000 PY compared to 0.8 (95%CI 0.4–1.7) among 16,289 children without IBD [adjusted hazard ratio (HR) 22.91 (95%CI 11.50–45.63)] [27]. These data confirmed the highest RR of VTE in pediatric patients among all age groups.

In patients with IBD, evidence relating to mortality and morbidity for VTE is impressive, with a significant age- and comorbidity-adjusted excess mortality of 2.1-fold higher for IBD than for non-IBD hospitalized patients [13]. Additionally, VTE in hospitalized patients with IBD was associated with a 2.5-fold increased odds ratio (OR) of mortality compared to non-VTE-related hospitalizations, with only IBD-related surgery carrying a higher risk of in-hospital mortality (OR = 4.8) [28].

Moreover, the recurrence of thromboembolic disease over time has a substantial clinical impact on the course of IBD. Novacek et al. reported a 5-year probability of VTE recurrence of 33 % after the first episode of unprovoked VTE, compared to 21 % in patients without IBD (HR of 2.5, $P = 0.01$) [29].

Although a large body of evidence suggests that the chronic inflammatory state is crucial for the pathogenesis of VTE in IBD [30], many unresolved questions remain, particularly regarding the mechanisms that determine a persistent inflammatory condition independent of disease activity.

This review aims to explore gut dysbiosis-related factors determining a prothrombotic state in patients with IBD. Consequently, we focused on the role of altered gut microbiome (GM) and impaired intestinal permeability in enhancing translocation of bacterial metabolites capable of promoting thrombosis, such as bacterial lipopolysaccharide (LPS) and trimethylamine-N-oxide (TMAO). Finally, the role of intestinal barrier integrity and eubiosis relief was explored in providing possible therapeutic approaches, counterbalancing the effects of LPS and TMAO.

1.1. Risk factors of VTE in patients with IBD

VTE in patients with IBD are often attributed to multiple risk factors (Fig. 1). Active disease is the most critical risk factor for VTE in patients with IBD. The so-called “inflammatory burden” typical of the phases of disease flare-ups determines a significant procoagulant tendency attributable to the strict interdependency between inflammation and coagulation factors [30]. To clarify this topic, Grainge et al. conducted an epidemiological study to quantify the risk of VTE during different phases of the disease. They observed the highest risk of VTE at the flare time with an HR of 8.4 (95%CI 5.5–12.8) compared with controls, although an increased risk persisted during disease quiescence (HR of

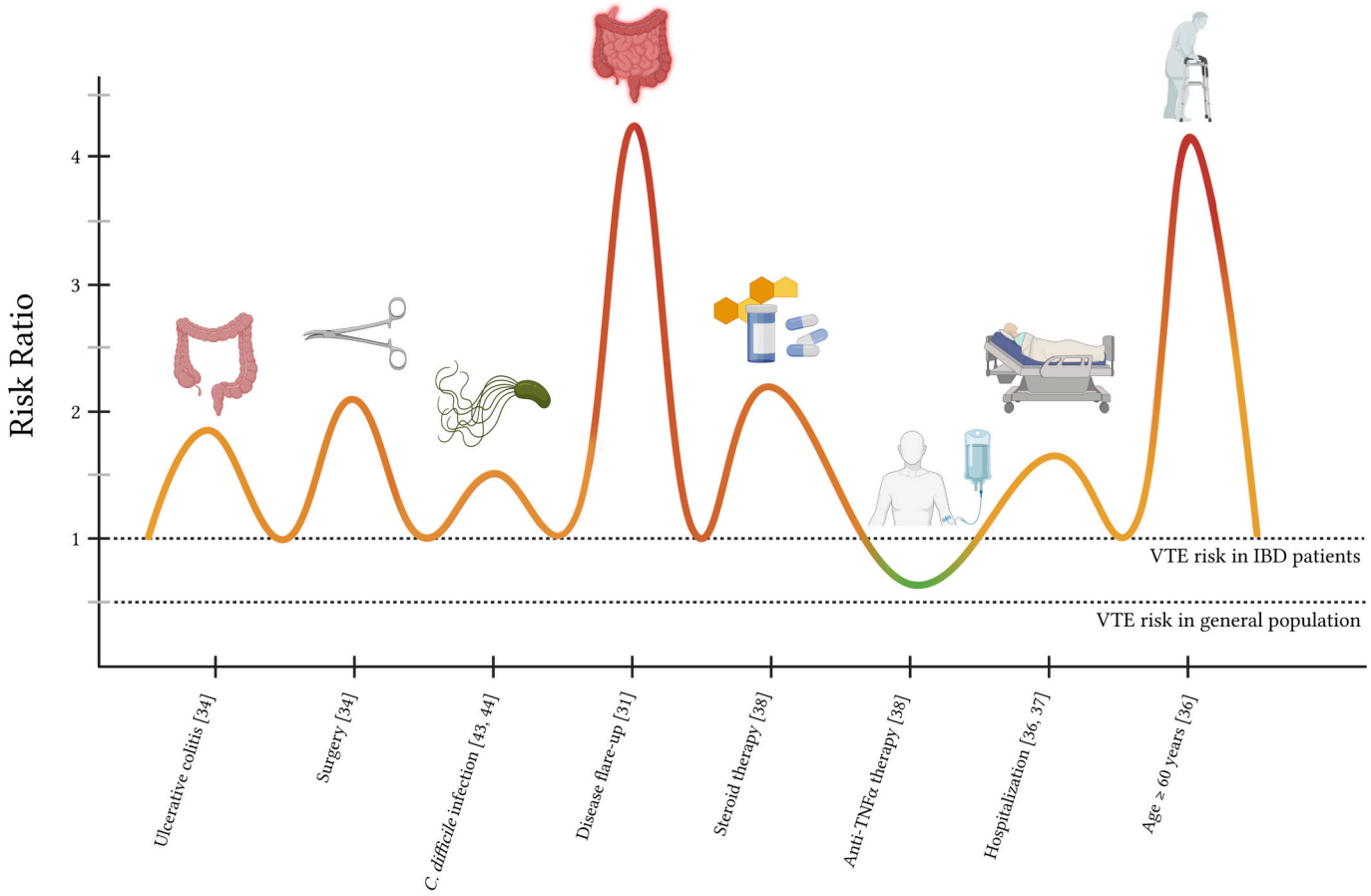

Fig. 1. Factors influencing venous thromboembolic risk throughout inflammatory bowel disease. The VTE risk ratio for each clinical condition is compared to the VTE risk in the general population and in patients with IBD. Data refer to original studies and meta-analyses identified by the references.
Abbreviations: VTE, venous thromboembolism; IBD, inflammatory bowel disease.

2.1, 95%CI 1.6–2.9) [31]. In addition, Miehsler et al. demonstrated that VTE is a specific feature of IBD because neither rheumatoid arthritis, another chronic inflammatory disease, nor celiac disease, another chronic bowel disease, was accompanied by an increased risk of VTE compared to controls [32].

The risk of VTE in IBD is also influenced by the disease subtype and location. UC shows a higher risk of thromboembolic events with respect to CD patients, with an HR of 1.81 (95%CI: 1.56–2.09, $P < 0.001$) [33].

Hospitalization is another crucial risk factor of venous thrombosis in patients with IBD. Kim et al., in a population-based cohort study using Korean National Health Insurance data, found that hospitalization was a significant risk factor for VTE in patients with IBD with an adjusted HR of 1.56 (95%CI 1.22–1.98, $P < 0.0001$) [34]. Similarly, Ananthakrishnan et al. reported that an IBD-related hospitalization was the strongest independent predictor of a venous thromboembolic event (OR 1.72, 95%CI 1.39–2.12) [35]. However, the hospitalization-associated risk of VTE should be cautiously considered. Indeed, a non-negligible rate of thrombotic events occurs in outpatients. For example, in a case-control study, Scoville and colleagues showed that a large number of VTE occurred in ambulatory patients (129 out of 204), with one-third (36 %) of them experiencing ambulatory disease flares at the time of VTE diagnosis [36].

IBD is a recognized risk factor for the development of *Clostridioides difficile* infection and is associated with a significantly higher risk of VTE. In a retrospective study on 312,147 IBD hospitalized patients, a multivariate analysis with propensity-score matching found an adjusted OR of 1.7 (95%CI 1.4–2.2, $P < 0.001$) for VTE in patients with *C. difficile* infection [37].

The therapeutic armamentarium for IBD also plays an essential role in influencing the balance between prothrombotic and antithrombotic factors. Corticosteroids (CS), anti-tumor necrosis factor (TNF)-α, and the newer oral small molecules, such as Janus-Kinase (JAK) inhibitors, have a different effect in modulating the overall thrombotic risk [49,50].

CS, despite their anti-inflammatory effect, increase the risk of VTE, and a Danish population-based case-control study, including 38,765 VTE cases, found an adjusted incidence rate ratio of 2.31 for VTE in patients taking CS [38]. This finding was reinforced by a recent meta-analysis involving 58,518 IBD patients with overall 3260 thromboembolic events, reporting a significant association between systemic CS and VTE compared to patients not treated with CS with OR 2.20 (95%CI 1.70–2.85, $P < 0.001$) [39].

Conversely, the same meta-analysis found that the treatment with anti-TNF-α agents resulted in a 5-fold decreased risk of VTE compared to CS with OR 0.267 (95%CI 0.106–0.674, $P = 0.005$) [39]. TNFα is indeed a pro-inflammatory cytokine which has been reported to link inflammation and thrombosis in IBD. Regarding the hypothesized prothrombotic risk of oral anti-JAK small molecules, the available evidence, particularly in patients with IBD, is insufficient to draw definitive conclusions [40,41]. However, until further evidence of anti-JAK safety is available, prudent behavior is advisable, including avoiding its use in patients with thrombotic risk factors, especially if alternative therapeutic options are available.

1.2. Pathophysiology of VTE in IBD

As mentioned above, the pathophysiology of VTE in IBD is multifactorial and needs to be understood entirely [42]. Individuals diagnosed with IBD exhibit several alterations in the hemostatic system, including the widely acknowledged Virchow's triad. These include venous flow stasis, endothelial injury, and hypercoagulability [41,43]. Increasing evidence underscores the existence of a solid interconnected system in which inflammation, coagulation, and fibrinolysis contribute interdependently to various physiological processes. Coagulation activation serves as a component of the inflammatory response by directly facilitating cytokine responses. Conversely, specific pro-inflammatory cytokines such as interleukin (IL) 6, influence the coagulation cascade, regulate platelet count, and function at different regulatory points, and diminish the role of endogenous anticoagulants [30]. This reduction in anticoagulant activity promotes thrombotic events and exacerbates the inflammatory response [44]. Hypofibrinolysis promotes blood clotting and is a hallmark of inflammation [30]. However, the mere existence of an active inflammatory process cannot solely account for this phenomenon, because of the variety of prothrombotic abnormalities that may occur in individuals with IBD. This observation suggests that specific disease features play a role in the thrombotic risk of IBD.

1.3. Gut dysbiosis in IBD

The potential link between the GM imbalance and IBD has been extensively studied [45–47]. However, the cause-effect relationship has not been fully elucidated. GM is a complex ecosystem of bacteria, viruses, and fungi that populates the intestinal surface and plays a crucial role in homeostasis of the human immune system and pathogenesis of several diseases, including IBD and colorectal cancer [48–50]. Dysbiosis can occur when the balance, diversity, and function of the GM are disturbed. A healthy microbiota is primarily composed (up to 90 %) of *Bacteroides* and *Firmicutes*, with smaller amounts of *Proteobacteria* and *Actinobacteria* making up the rest [51].

One of the hallmarks of dysbiosis in IBD is a reduction in GM diversity compared to that in healthy individuals [52]. However, it is important to note that changes in microbiome composition may be influenced by factors such as the location and duration of the disease, as well as an individual's genetic background [53].

The intestinal barrier, which comprises different layers and prevents the translocation of bacteria and their products into the bloodstream, is strictly related to GM. Mucus on the epithelial cell surface is the first defense layer [54]. The epithelial layer comprises enterocytes held together by several junction proteins, such as tight junction proteins (TJPs) [55]. The deepest layer is the gut–vascular barrier interface, immediately below the epithelial barrier [56]. Maintaining the integrity and permeability of the gut barrier is crucial and involves both intrinsic and extrinsic mechanisms. Additionally, bacterial metabolites actively maintain intestinal barrier homeostasis [57]. However, when the integrity of the intestinal barrier is compromised, bacteria and/or bacterial metabolites can enter the bloodstream, leading to a leaky gut [58]. This condition is often associated with dysbiosis, which is a distinctive feature of IBD.

1.3.1. Dysbiosis can impair intestinal immune function and barrier integrity

Decreased biodiversity due to dysbiosis can result in reduced intestinal immune function and impaired barrier integrity [59]. Furthermore, disruption of the intestinal barrier integrity is necessary for the development of several diseases, including IBD [60]. Notably, a dysbiotic gut microbiome influences the immune response. Indeed, in patients with IBD, the altered microbiota promotes an imbalance between Th17 and Treg cells in favor of upregulating Th17 cells, resulting in a pro-inflammatory response [61–63]. In conclusion, GM alterations reported in patients with IBD determine the impairment of the intestinal barrier, resulting in a leaky gut and a pro-inflammatory dysbiotic shift. Both conditions predispose to increased translocation of bacterial products, such as LPS, from the intestinal lumen into the bloodstream, and increased production of bacterial metabolites with prothrombotic properties, such as trimethylamine (TMA).

1.3.2. Microbiota metabolites and IBD

Remodeling in microbiota leads to altered metabolite production, which may play a role in IBD pathogenesis. Comparing microbiota in healthy and IBD patients, up to 12 % of metabolites were significantly different [64]. Short-chain fatty acids (SCFAs), generally produced by bacteria from dietary fibers, are essential for gut epithelium homeostasis [65]. In particular, butyrate significantly promotes colonocyte differentiation, regulation of intestinal barrier integrity, and immune

homeostasis [66]. Tryptophan synthesis is another metabolic pathway involved in IBD. Tryptophan is an essential aromatic amino acid that is processed into indole by microbiota [67]. Indoles are ligands of the aryl hydrocarbon receptor (AhR), a transcription factor involved in several physiological processes, improving the expression of TJPs [68,69].

Finally, the GM plays a crucial role in bile acid (BAs) metabolism. The microbiome transforms primary BAs (cholic acid and chenodeoxycholic acid) into secondary BAs, such as lithocholic acid and deoxycholic acid. Secondary BAs exert anti-inflammatory and immunomodulatory effects [70].

Alongside the microbial metabolites and metabolic pathways capable of maintaining homeostasis of the intestinal barrier and endowed with anti-inflammatory properties, other metabolites and microbial components described below play prothrombotic and inflammatory roles.

1.3.3. Trimethylamine-N-oxide (TMAO)

The GM also produces other metabolites involved in thrombotic risks, such as TMAO [71]. Bacteria can convert dietary lipids, such as choline, phosphatidylcholine, and L-alpha glyceryl phosphorylcholine into TMA and transform it into TMAO in the liver [72]. TMAO triggers pro-atherogenic pathways by activating *E*-selectin, cyclooxygenase-2, IL-6, and intracellular adhesion molecule-1 [73]. Moreover, in mouse models, plasma TMAO concentrations correlated with the early stages of atherosclerotic plaques. Several studies have shown that TMAO is associated with cardiovascular disease (CVD), triggering platelet hyperreactivity and promoting thrombus formation; thus increasing cardiovascular risk [74–76].

In a cross-sectional study of patients with acute VTE, higher TMAO levels were associated with mortality [77]. The same study highlighted a trend for an increased risk of recurrent VTE in older people but without statistical significance. Of note, several confounding factors could mask the presence of a relationship due to decreased TMAO levels from concomitant infectious disease and the related use of antibiotic therapy or a state of malnutrition, with reduced intake of fish, as well as phosphatidylcholine and L-carnitine present in dairy products such as eggs and red meat [77].

Patients with IBD show a high atherosclerotic CVD risk [78,79]. More recently, Kul et al. examined the association between TMAO and endothelial and coronary microvascular dysfunction by measuring TMAO concentrations, flow-mediated vasodilatation (FMD), and coronary flow velocity reserve (CFVR) [80]. In patients with UC, a significant correlation between TMAO and CFVR and FMD was observed, and this partly explains the CVD in these patients, even though TMAO concentrations were lower than those in non-IBD patients. In contrast, patients with CD, had no such association [191]. Wilson et al. first noted that patients with IBD, especially those with active UC, had a low mean level of TMAO [81]. They attributed this result to gut dysbiosis and proposed that TMAO in these patients had a "mechanistically different" role in the pathogenesis of atherosclerosis. A recent study found a link between gut dysbiosis and the reduction of TMAO in one-episode stroke patients [82]. The results reported by Kul et al. suggested that similar conditions may exist in patients with IBD [80].

1.3.4. Lipopolysaccharide (LPS) and IBD: a bi-directional interaction

LPS is a glycolipid component of the outer membrane of gram-negative gut bacteria, comprising carbohydrates and lipid A. It circulates at a very low concentration of approximately 20 pg/mL and is quickly eliminated by Kupffer cells in the liver [83]. Increased intestinal permeability with enhanced LPS translocation and the failure of liver cells to ultimately convert LPS into bile causes low-grade endotoxemia [84]. This condition is defined as circulating levels of LPS >20 ng/mL [83,85], and is comparable to the septic state of low-grade endotoxemia which is characterized by at least two-fold and up to 10–50 times lower blood LPS levels [86,87].

Moreover, as it is the first bacterial component to contact the immune system, it is involved in immune system modulation [88]. LPS induces extracellular matrix protein (ECM)-1 expression in intestinal macrophages, promotes the production IL-8, and directly damages the integrity of the gut barrier [89,90]. In addition, following the interaction with the Toll-like-receptor (TLR) 4, LPS may activate the expression of NFkB, which is involved in several inflammatory pathways, such as TNF-α, IL-12, and the release of interferon- β (IFN- β), stimulating the differentiation in Th1 and Th17 [91–93].

Several studies have supported the crucial role of the LPS-TLR4 pathway in modulating the integrity of the gut barrier in patients with IBD. LPS is directly involved in gut barrier impairment; the binding of TLR4 and LPS downregulation of TJPs expression, favoring its transition into the bloodstream. Furthermore, different studies have largely supported the critical role of the LPS-TLR4 pathway in modulating gut barrier integrity in IBD. The interaction between LPS and IBD is bidirectional. LPS is involved in the pathogenesis of IBD, and LPS endotoxemia mediated by leaky gut and dysbiosis determines an increase in LPS production [94]. LPS is mainly produced by the GM and, to a minor extent, by exogenous sources such as diet [95]. Moreover, not all LPS have the same function. LPS produced by *E. coli* is highly toxic; however, *Bacteroides*-produced LPS has an immunomodulatory action. It has been widely demonstrated that patients with IBD show an increase in *Enterobacteriaceae* and consequently, pro-inflammatory LPS levels produced [96–98].

LPS stimulates the progression of IBD by acting on the immune system [99]. In damaging epithelial barrier conditions such as IBD, LPS crosses the gut barrier and enters the bloodstream, inducing low-grade endotoxemia [94,100]. LPS in blood circulation can contact endothelial cells and circulating PLTs. As endothelial cells and PLTs express TLR2, TLR4, and LPS, which act as pathogen-associated molecular patterns (PAMP), they can activate the molecular pathways of coagulation [101,102]. These findings support the hypothesis that gut barrier impairment and LPS levels lead to the activation of the coagulation cascade, even if available experimental data are scarce. Finally, Pastorelli et al. studied the correlations between LPS levels, TLR concentrations, and coagulatory markers in patients with IBD, and a correlation between LPS, D-dimer, and prothrombin fragment F1 + 2 concentrations was shown [44].

1.4. How dysbiosis could influence venous thromboembolic risk in IBD

IBD alters intestinal permeability to varying degrees depending on the stage of disease progression [53]. The VTE burden is dynamic throughout the clinical course of the disease and is accompanied by GM dysbiosis [33]. In patients with IBD, dysbiosis and a prothrombotic state frequently coexist, and clinical risk factors for thrombosis are associated with dysbiosis or bacterial translocation from the gastrointestinal tract (Fig. 2).

For example, abdominal surgery is one of the most recognized thrombotic risk factors [33,103]. It is accompanied by a significant alteration in the GM in the postsurgical period and even after several months in both the general and IBD populations [104]. Similarly, *C. difficile* infection is significantly associated with an increased risk of VTE in IBD [37,105] and non-IBD [106] patients. Moreover, it is a consequence and manifestation of severe dysbiosis [107].

Furthermore, the increased thrombotic risk linked to IBD colonic involvement [33,108] could likewise be interpreted in light of a different and more representative bacterial composition at this level compared with other parts of the gastrointestinal tract [51]. Moreover, disease location is a significant determinant of the GM, with significantly reduced diversity in composition compared to that in CD patients with colonic or ileal involvement [53]. Disease flare-ups carry an increased risk of venous thrombosis [31] and could be associated with a different microbiome than that in the remission phase [109–111].

Finally, thromboembolic risk factors unrelated to IBD, such as obesity, smoking, and age [33], are significantly associated with

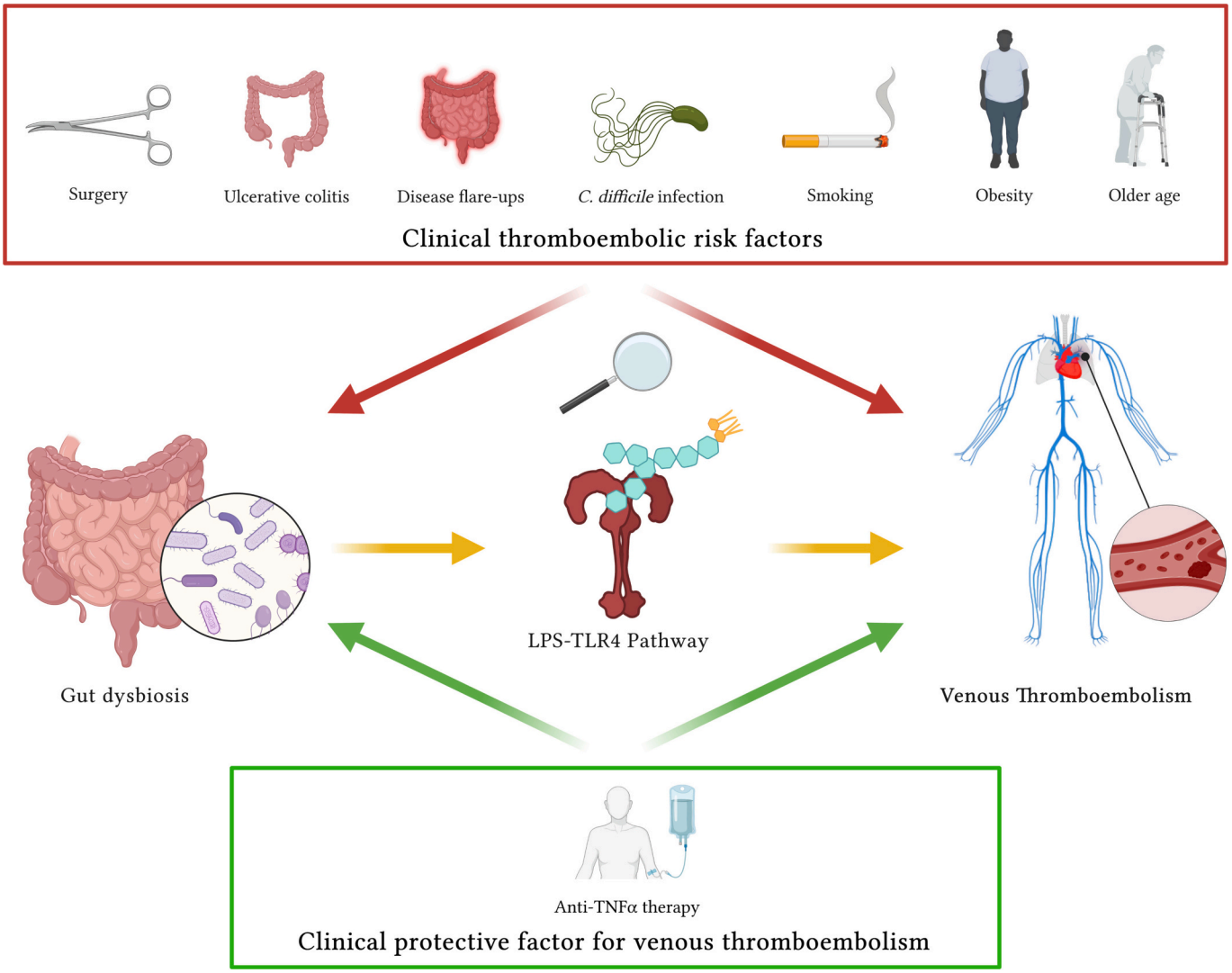

Fig. 2. Association of clinical factors, gut dysbiosis, and venous thromboembolism in inflammatory bowel disease. Clinical risk factors associated with gut dysbiosis and VTE are identified within the red box. A clinical protective factor related to eubiosis restoration and decreased VTE risk (i.e., anti-TNFα therapy) is represented inside the green box. Yellow arrows represent the putative pathophysiological mechanism that could link the presence of dysbiosis with the increased risk of VTE, constituted by the signaling pathway elicited by the binding of LPS with its receptor TLR4.
Abbreviations: IBD, inflammatory bowel disease; LPS, lipopolysaccharide; TNF-α, Tumor Necrosis Factor α; TLR4, Toll-Like Receptor 4; VTE, venous thromboembolism. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

changes in the intestinal bacterial flora of dysbiotic significance [112–116].

Conversely, the treatment with infliximab reduced VTE risk [39,117], and several reports suggest a partial recovery of microbial diversity and microbiome's biochemical functionality in anti-TNF-α treated patients [118].

1.5. Low-grade endotoxemia as a potential pathophysiological determinant in IBD-related VTE

LPS has long been studied as a critical factor in thrombo-inflammation, mainly because of the activation of the inflammatory process secondary to its interaction with the TLR pathway [119,120]. Initially, theories regarding the connection between low-grade endotoxemia and thrombosis were investigated in advanced liver disease, a condition characterized by an elevated risk of thrombosis and bleeding [121,122]. In these patients, hemostatic alterations affect portal and peripheral venous circulation levels, with contextual detection of low-grade endotoxemia in both vascular districts [123].

Low-grade endotoxemia alters the hemostatic process in a procoagulant manner through several mechanisms (Fig. 3). The prothrombotic activity of LPS is determined by its interaction with several cell lines, such as endothelial cells (EC), leukocytes, and PLTs, affecting every component of the Virchow triad [124–126].

In this context, the elicitation of the extrinsic coagulation pathway appears to be decisive through its interaction with TLR4. In vitro incubation of human EC with a scalar concentration of LPS resulted in a dose-dependent increase in the release of vWF and factor VIII via the formation and secretion of Weibel-Palade bodies. Notably, this phenomenon was mitigated by the inhibition of TLR4 [125]. In addition, the same endothelial phenotype underwent prothrombotic changes in the presence of LPS. LPS-incubated EC shows an over-expression of TF and generation of TAFI and PAI [127,128]. In addition, this cascade of events is mediated by the central role of TLR4 and its binding to LPS. Indeed, TF activity and mRNA were significantly greater in wild-type EC than in TLR4-/- EC, and were inhibited in wild-type EC by pretreatment with an anti-TLR4 antibody [129].

LPS can also interact with leukocytes, which contribute to

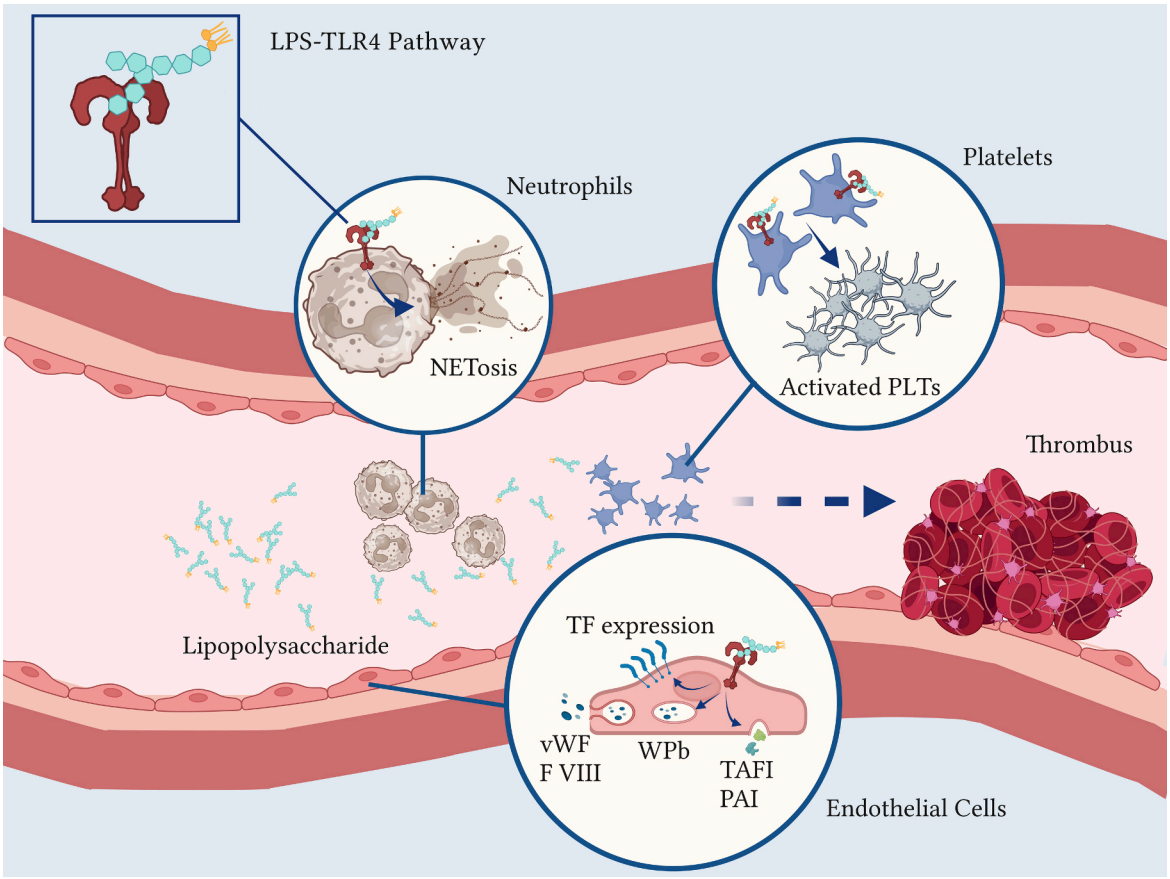

Fig. 3. Mechanism of lipopolysaccharide-mediated hypercoagulable state in inflammatory bowel disease. Low-grade endotoxemia caused by LPS circulation determines a hypercoagulable state and eventually venous thrombosis by binding LPS with TLR4 at the level of different cell lines. In neutrophils, LPS-TLR4 binding stimulates NETs release in a dose-dependent manner. The interaction between LPS and TLR4 in platelets enhances platelet activation in response to typical agonists. In endothelial cells, LPS-TLR4 pathway activation determines the formation and secretion of Weibel-Palade bodies by releasing vWF and FVIII. Moreover, the same pathway stimulates the over-expression of TF over endothelial cells' surface and the generation and release of TAFI and PAI. Abbreviations: FVIII, Factor VIII; NETs, Neutrophil Extracellular Traps; LPS, lipopolysaccharide; PAI, Plasminogen Activator Inhibitor; PLTs, platelets; TAFI, Thrombin-Activatable Fibrinolysis Inhibitor; TF, Tissue Factor; TLR4, Toll-Like Receptor 4; vWF, von Willebrand Factor; WPb, Weibel-Palade bodies.

thrombosis by stimulating the formation of neutrophil extracellular traps (NETs) [130]. LPS enhances NET formation in vitro in a dose-dependent manner [131], as evidenced by the fact that the TLR4 inhibitor TAK242 decreases LPS-mediated NETosis [132].

LPS also contributes to the formation of the prothrombotic milieu via platelet activation. Experiments on normal PLTs revealed that at concentrations >15 pg/mL, LPS does not prompt aggregation, but enhances the platelet response to typical agonists such as collagen and adenosine diphosphate (ADP) [124]. A TLR4-mediated oxidative stress mechanism seems to be involved, as this result was linked to an increase in eicosanoids such as thromboxane A2 and 8-isoPGF2alpha-III, as well as oxidants such as H_2O_2 and was inhibited by a TLR4 inhibitor. Moreover, a significant correlation between circulating LPS and ex vivo TLR4-mediated platelet overactivation has been detected in patients with arterial thrombosis [133].

The relevance of the prothrombotic activity of LPS has been demonstrated in vivo using an experimental model mimicking low-grade endotoxemia in humans. Thus, a mouse model with an intraperitoneal injection of LPS was used to investigate whether LPS enhances thrombus growth in experimental thrombosis. Accelerated thrombus growth, coinciding with systemic biomarkers of platelet activation, was also detected. Both changes were inhibited by the co-administration of a TLR4 inhibitor, reinforcing the hypothesis that TLR4 plays a pivotal role in the prothrombotic effects of LPS [83]. Moreover, a murine inferior vena cava stenosis model of deep vein thrombosis and an LPS model of endotoxemia were used to investigate the role of vWF in inflammation-associated venous thrombosis. Choi et al. showed that (lipo) polysaccharide LPS-treated mice had a significantly higher incidence of venous thrombosis. This effect was mitigated when vWF was inhibited using inhibitory αvWF antibodies [134].

Preliminary clinical evidence regarding the association between LPS, markers of intestinal permeability, hypercoagulability, and venous thrombosis has been reported. To study the correlation between these variables, Cangemi et al. conducted a case-control study of patients with community-acquired pneumonia (CAP) compared to patients matched for sex, age, and comorbidities but without infections. It was shown that a marker of thrombin generation (i.e., F1 + F2) was higher in patients who did not present with an infectious disease and were characterized by a significant reduction at discharge. Similarly, baseline serum endotoxin and zonulin levels, a marker of gut permeability, were significantly higher in patients with CAP than in controls. As a result, their levels significantly decreased at discharge, with a significant correlation between serum endotoxins and zonulin [135]. Moreover, another case-control study by the same group showed that sP-selectin, a marker of in vivo platelet activation, serum LPS, and serum zonulin at admission were higher in CAP patients than in controls. Subsequently, plasma sP-selectin, LPS, and zonulin levels significantly decrease upon hospital discharge [136]. Notably, LPS levels can predict thrombotic events in COVID-19 (COVID-19) patients [137]. Oliva et al. measured the serum levels of zonulin, LPS, and D-dimer in 81 hospitalized patients with COVID-19 and 81 healthy subjects. Among the 81 patients with COVID-19, 11 (14 %) experienced arterial ($n = 5$) and venous ($n = 6$)

thrombotic events during their hospital stay, and a logistic regression analysis showed that LPS and D-dimer independently predicted thrombotic events.

Finally, an elegant study by Leskelä et al. used a genome-wide association meta-analysis to generate a composed genetic risk score of endotoxemia. In this way, it was possible to identify a significant genome-wide association between lipopolysaccharide activity and 741 single-nucleotide polymorphisms (SNPs) in five independent *loci*, which were mainly located in genes affecting contact activation of the coagulation cascade and lipoprotein metabolism. In the subsequent phase, the association of the composed genetic risk score of endotoxemia with thrombosis-related clinical endpoints was analyzed in 195,170 participants in the FinnGen study. The genetic risk score for endotoxemia is associated with deep vein thrombosis, pulmonary embolism, pulmonary heart disease, and VTE [138]. A Mendelian randomization (MR) approach was employed to illustrate this relationship. MR uses genetic risk score SNPs as instrumental variables, allowing researchers to explore the causality between endotoxemia and clinical endpoints in a manner analogous to that of a randomized controlled trial. This conclusion is exciting because the use of genetic variants as instrumental variables produces consistent regression estimates that are not biased by reverse causation or missing confounders.

1.6. Emerging therapeutical strategies to reduce gut dysbiosis-related hypercoagulation

As previously reported, gut dysbiosis and a leaky gut can trigger the onset of LPS-mediated endotoxemia, leading to prothrombotic effects, and in turn, an increased risk of VTE in patients with IBD. Researchers are exploring new therapeutic strategies to reduce this risk, by restoring intestinal eubiosis and barrier function (Table 1). Another synergistic approach involves counterbalancing the LPS toxicity (Table 1). A potential option to achieve eubiosis is to use the poorly absorbed broad-spectrum antibiotic, rifaximin [139]. In addition, rifaximin can reduce circulating LPS and exert an anti-inflammatory effect by lowering TNF-α or leukocyte TLR4 [140]. Probiotics and prebiotics have shown promise in positively manipulating the GM and augmenting gut barrier function. Specifically, certain strains of probiotics, such as *Lactobacillus plantarum*, *Akkermansia muciniphila*, lactose-fermenting *Lactobacilli* and *Bifidobacteria* have been shown to improve the gut barrier function and reduce endotoxemia [57,141]. Prebiotics are poorly absorbed and fermentable food elements that provide essential nutrients to beneficial bacteria, such as *Bifidobacterium* and *Lactobacillus*, which can, in turn, exert an anti-inflammatory action and help protect against harmful pathogens in the gut. Paone et al. demonstrated in a model of obese/diabetic mice that the prebiotic oligofructose improves gut barrier function, by inducing significant changes in intestinal mucus layer production, glycosylation, and secretion, and increasing TJPs [142]. In addition, prebiotic-treated mice exhibit lower plasma LPS and cytokine levels via an intestinotrophic proglucagon-derived peptide (GLP-2)-dependent mechanism [143]. Dietary cellulose supplements have also proven promising in murine models and can ameliorate LPS-mediated intestinal barrier damage and protect against gut epithelial apoptosis [144].

Although the beneficial activities of microbial metabolites in regulating the gut barrier function have been demonstrated in animal models, to date, no microbial metabolites or their analogs have been used clinically. However, experimental studies have shown that SCFAs can improve the intestinal barrier function [57]. In addition, other microbial metabolites such as urolithin-A (URO-A) and oxyberberine (OBB) favor homeostasis of the intestinal barrier [145,146].

Statins can also benefit gut barrier dysfunction by modulating gut dysbiosis or upregulating intestinal adhesive proteins [147,148].

An attractive therapeutic alternative is to favor the rapid metabolism of LPS to lower its circulatory levels and toxicity. Epithelial cells physiologically synthesize intestinal alkaline phosphatase (IAP), which removes one of the two phosphate groups of the lipid A portion of LPS, forming monophosphoryl-LPS; this molecule is able to bind to TLR4 but acts as an antagonist [149]. In animals fed a high-fat diet, IAP overexpression maintained intestinal mucosal integrity, reduced LPS translocation into the systemic circulation and lipid accumulation in the liver, and attenuated atherosclerotic plaques [150]. Other metabolic pathways that reduce LPS activity have also been investigated. Acyloxyacyl hydrolase (AOAH) is a highly conserved host lipase that is mainly produced by leukocytes and can inactivate LPS by cleaving secondary fatty acyl chains from the diglucosamine backbone of lipid A. The resulting tetraacyl LPS is non-stimulatory and may inhibit LPS signaling. In animal models, AOAH has been proven to prevent LPS-induced cholesterol accumulation in macrophages; therefore, reducing prolonged inflammation after LPS exposure [151].

In addition, the effect of diet on GM composition and related fecal metabolomics cannot be overstated to attenuate the adverse effects of endotoxemia. A recent interventional study indicated that healthy young adults who consume higher amounts of fat experience unfavorable changes in their GM, including an increase in *Alistipes* and *Bacteroides* and a decrease in *Faecalibacterium* [152]. Further support for the

Table 1
Emerging therapeutical strategies to reduce gut dysbiosis and impaired permeability.

Therapy	Category	Mechanism of action
Lipopolysaccharide reduction strategies		
Rifaximin	Antibiotic	Eubiosis restoration and anti-inflammatory effect
Lactobacillus plantarum, *Akkermansia muciniphila*, and lactose-fermenting *Lactobacilli* and *Bifidobacteria*	Probiotics	Improvement of gut barrier function
Oligofructose	Prebiotic	Improvement of gut barrier function
Dietary cellulose supplements	Prebiotic	Improvement of gut barrier function
Short-chain fatty acids, urolithin-A, oxyberberine	Microbial metabolites	Improvement of gut barrier function
Statins	Pharmacological agent (catabolic enzyme)	Up-regulation of intestinal adhesive proteins
Intestinal Alkaline Phosphatase	Pharmacological agent	Dephosphorylation of LPS, forming monophosphoryl-LPS (antagonist properties)
Acyloxyacyl Hydrolase	Pharmacological agent (catabolic enzyme)	Cleavage of secondary fatty acyl chains from lipid A, forming tetraacyl LPS (nonstimulatory)
Mediterranean diet	Dietary habits	Eubiosis restoration
Polyphenol-rich pomegranate	Dietary habits	Eubiosis restoration
Albumin supplementation	Blood product	Reduction of LPS circulating levels
Trimethylamine-*N*-oxide reduction strategies		
Restriction of dietary choline, carnitine, and betaine	Dietary habits	Reduction of choline conversion to trimethylamine (TMAO precursor)
Lactobacillus rhamnosus GG	Probiotic	Reduction of choline conversion to trimethylamine (TMAO precursor)
Resveratrol	Prebiotic	Restoring eubiosis
3,3-Dimethyl-1-Butanol	Pharmacological agent	Choline analogue with subsequent inhibition of TMA formation
Iodomethylcholine and Fluoromethylcholine	Pharmacological agent	Inhibition of TMA lyase
Meldonium	Pharmacological agent	Inhibition of butyrobetaine hydroxylase with subsequent decrease of circulating L-carnitine

role of diet in defining the individual GM profile was demonstrated by the beneficial effect of the Mediterranean diet on microbiota composition. Recently, three dietary clusters (DCs) were identified in a cohort of 2, 289 healthy first-degree relatives of patients with CD. DC3, which resembles the Mediterranean diet, was strongly associated with a defined microbial composition with an increased abundance of fiber-degrading bacteria such as *Ruminococcus* and taxa such as *Faecalibacterium* [153]. Another study involving 1425 individuals spanning four cohorts (the general population, patients with CD and UC, and patients with irritable bowel syndrome) explored the associations between dietary patterns and microbial clusters. The study found that processed foods and animal-derived foods were consistently associated with higher abundances of *Firmicutes* and *Ruminococcus* species of the *Blautia* genus and endotoxin synthesis pathways [154]. Conversely, a higher abundance of commensals such as *Roseburia*, *Faecalibacterium*, and *Eubacterium* spp. was observed with the consumption of nuts, oily fish, fruits, vegetables, cereals, and red wine across all cohorts [154]. These bacteria are known for their anti-inflammatory effects in the intestine through fiber fermentation of SCFAs, thus confirming the potential anti-inflammatory effects of the Mediterranean diet [154].

Moreover, administration of a polyphenol-rich pomegranate extract preserved gut barrier architecture and reversed GM dysbiosis, mainly through the modulation of *Faecalibacterium*, *Odoribacter*, and *Parvimonas* [155].

An adjunctive therapeutic option to mitigate the biological effects of endotoxemia is to maintain adequate blood albumin levels, because albumin is able to neutralize endotoxins. However, patients with IBD often develop hypoalbuminemia, which can compromise their ability to counteract the toxic effects of LPS. Therefore, preventing and treating hypoalbuminemia may reduce the risk of thrombosis because albumin also has anticoagulant and antiplatelet activities [156]. Although the role of TMAO in VTE pathogenesis remains debatable, its well-established role in arterial CVD has led to the search for therapeutic strategies aimed at its reduction (Table 1). One of the most straightforward ways to reduce TMAO levels is through the diet. Studies have shown that restricting dietary choline, carnitine, and betaine (TMA precursors) can reduce TMAO levels [157]. Moreover, the effects of probiotics on TMAO levels have been evaluated in both animal models and humans and provide promising evidence for specific bacterial strains that can reduce circulating TMAO levels. Only the *Lactobacillus rhamnosus* GG strain exhibited this beneficial effect [158].

Prebiotics have been evaluated as potential therapeutic strategies for lowering TMAO levels, and are non-digestible dietary products that GM can ferment; thus, promoting eubiosis. Chen et al. showed a positive effect of resveratrol (RSV), a natural polyphenol with prebiotic benefits, present in grapes, berries, and other dietary constituents, but with low bioavailability. In a mouse model, RSV attenuated TMAO-induced atherosclerosis by decreasing TMAO levels and increasing hepatic BAs biosynthesis through the remodeling of GM [159].

Furthermore, a double-blind, randomized, controlled pilot study in 20 male patients with metabolic syndrome treated with single lean vegan-donor or autologous fecal microbiota transplantation failed to document a significant change in TMAO production capacity or parameters related to vascular inflammation [160].

Pharmacological treatments have also been proposed to reduce the TMAO levels. Microbial enzymes are promising drug targets that convert choline and carnitine to TMA. Inhibitors of this enzyme have been identified and tested in animal studies with good results. One such inhibitor is 3,3-dimethyl-1-butanol (DMB), which reduces TMAO levels and improves cardiovascular function in animal models [161,162]. Other investigational pharmacological agents include iodomethylcholine (IMC) and fluoromethylcholine (FMC), two second-generation TMA lyase inhibitors capable of suppressing TMA and TMAO levels and minimizing thrombus formation without any noticeable toxicity in vivo [75]. Meldonium, a γ-butyrobetaine hydroxylase inhibitor that decreases circulating L-carnitine levels, is also being evaluated for its capacity to decrease plasma TMAO concentration through increased urinary excretion [163].

Future research is needed to identify the most effective and safe approaches for reducing LPS and TMAO levels and to evaluate the impact of this strategy on gut dysbiosis-related thrombosis in patients with IBD.

2. Conclusions

In conclusion, GM dysbiosis and intestinal barrier dysfunction, which are distinctive features of IBD, may be critical for increasing LPS translocation into the systemic circulation and determining higher TMAO levels. These two mediators can cause inflammation and are involved in cellular pathways implicated in clotting and platelet activation. Thus, the causative link between gut dysbiosis, a leaky gut, and prothrombotic tendencies should be addressed in novel therapeutic strategies to reduce circulating LPS and TMAO levels or counteract their toxic effects to reduce the risk of VTE in patients with IBD.

However, further research is required to better understand the correlation between LPS-mediated endotoxemia and TMAO, GM dysbiosis, impaired intestinal permeability, and potential prothrombotic effects.

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