BIOCELL
2021 45(3): 461-481

Tech Science Press

Extraintestinal manifestations of inflammatory bowel disease, nitroxidative stress and dysbiosis: What is the link between them?

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Key words: Oxidative stress, Microbiota, Bacterial translocation, Ulcerative colitis, Crohn disease

Abstract: Inflammatory bowel disease (IBD), which includes Crohn's disease and ulcerative colitis, has a not yet completely defined aetiology and is characterized by a progressive chronic inflammation that involves nitroxidative stress and dysbiosis. Extraintestinal manifestations can occur and affect several organs, including the liver and bile ducts, joints, skin, eyes, and less frequently, the heart, brain, and kidneys, increasing the risk of morbidity and mortality. These repercussions may be associated with the activity or severity of IBD. The present review proposes to report and analyse the participation of dysbiosis and nitroxidative stress in the genesis of extraintestinal manifestations, aiming to contribute to a better understanding of the disease and to focus on the development of individualized preventive and therapeutic strategies.

Abbreviations

4-HNE:	4-hydroxy-2-nonenal
AP-1:	activating protein-1
HLA-B27:	B27-human leukocyte antigen
BBB:	blood-brain barrier
BDNF:	brain-derived neurotrophic factor
BMD:	bone mineral density
CAT:	catalase
CCL25:	C-C motif chemokine ligand 25
CNS:	central nervous system
CCR6:	chemokine receptors 6
D161:	cluster of differentiation 161
CRP:	C-reactive protein
CD:	crohn disease
CYP27A1:	cytochrome P450 family 27 subfamily A member 1
CYP7A1:	cytochrome P450 family 7 subfamily A member 1
EIMs:	extraintestinal manifestations
GPx:	glutathione peroxidase
HM:	hepatobiliary manifestations
HCy:	homocysteine
HLA-DR1:	human leukocyte antigen-DR1
IgA:	immunoglobulin A
iNOS:	inducible nitric oxide synthase
IBD:	inflammatory bowel disease
ICAM-1:	intercellular Adhesion Molecule-1
IFN-γ:	interferon gamma
IL:	interleukin
LRR:	leucine rich repeats
LPS:	lipopolysaccharide
MDA:	malondialdehyde
MAPK:	mitogen activated protein kinase
MCP-1:	monocyte chemoattractant protein-1
MAdCAM-1:	mucosal vascular addressin cell adhesion molecule-1
MAIT:	mucosal associated invariant T cells
MS:	multiple sclerosis
NAFLD:	non-alcoholic fatty liver disease
NFκB:	nuclear factor kappa B

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Received: 17 September 2020; Accepted: 20 November 2020

Doi: 10.32604/biocell.2021.014332

NLRP3: nucleotide-binding domain, leucine-rich-repeat-containing receptor 3
NOD: nucleotide-binding oligomerization domain
OmpC: outer membrane protein C
oxLDL: oxidized low density lipoprotein
PAMP: pathogen-associated molecular patterns
PD: parkinson disease
PPARs: peroxisome Proliferator-Activated Receptors
PRR: pattern recognition receptors
ONOO-: peroxynitrite
PSC: primary sclerosing cholangitis
RONS: reactive Oxygen and Nitrogen Species
ROS: reactive Oxygen Species
SCFA: short chain fatty acids
STAT3: signal transducer and activator of transcription 3
SpA: spondyloarthropathies
SREBP: sterol Regulatory Element Binding Protein
TLR4: toll like receptor 4
TRAF3IP2: tumor necrosis factor alfa receptor-associated factor interacting protein 2
TMA: trimethylamine
TMAO: trimethylamine-N-oxide
TNF-α: tumor necrosis factor alfa
UC: ulcerative colitis
VCAM-1: vascular adhesion molecule-1
VAP-1: vascular adhesion protein-1
VEGF: vascular endothelial growth factor.

Introduction

Inflammatory bowel disease (IBD) is a chronic and recurrent disease that includes Crohn's disease (CD) and ulcerative colitis (UC). The IBD aetiology is not fully elucidated, however, it is known that there is an intimate interaction between genetic, immunological, and environmental factors (diet, smoking, circadian cycle), the intestinal microbiota and nitroxidative stress (Manichanh *et al.*, 2012; Moura *et al.*, 2016; Garber and Regueiro, 2019; Feuerstein and Cheifetz, 2014).

Intestinal microbiota comprises more than 150.000 species of commensal microorganisms that inhabit the gastrointestinal tract and perform beneficial functions to the host, such as the synthesis of substances important for energy metabolism, defense against luminal pathogens, and modulation of the immune response (Qin *et al.*, 2010; Nishida *et al.*, 2018).

The participation of the microbiota in the modulation of innate and adaptive immunity of the mucosa is fundamental to maintain the integrity of the epithelial barrier and occurs through the interaction between the pathogen-associated molecular patterns (PAMPs) and the pattern recognition receptors (PRR), such as Toll-like receptors (TLR), present in immune cells, as well as by the action of their metabolites, especially short-chain fatty acids (SCFA), which act to induce immunological tolerance by stimulating, mainly, the polarization of regulatory T lymphocytes.

In addition, they secrete or promote the secretion of antimicrobial factors, such as defensins and immunoglobulin A (IgA) (Kamada and Núñez, 2013; Hart *et al.*, 2005; Nishida *et al.*, 2018).

Imbalance in microbial diversity and density, known as dysbiosis, can alter the interaction between the host-microbiota-immune system and has been associated with the appearance of many inflammatory and autoimmune disorders, including IBD. Some studies have reported that IBD patients have changes in microbial composition, when compared to healthy individuals, with a decrease in SCFA producing commensal bacteria, such as *Faecalibacterium prausnitzii*, and an increase in mucolytic, sulfate-producing, and pathogenic bacteria (Fujimoto *et al.*, 2013; Takahashi *et al.*, 2016; Nishino *et al.*, 2018; Nishida *et al.*, 2018).

It has been described that the increase in intestinal permeability and the unregulated immune response causes a continuous inflammatory process (with neutrophilic infiltration) and a redox imbalance, generating nitroxidative stress, production of pro-inflammatory cytokines, and consequent impairment of the intestinal barrier, characterized by the destruction of tight junctions and oxidative damage caused by lipid peroxidation (Fig. 1) (Moura *et al.*, 2015). This scenario allows pathogenic bacteria and their products, such as lipopolysaccharide (LPS), not only to enter the sterile submucosa and activate immune cells through the binding and recognition of their PAMPs in the respective PRRs but also favour microbial translocation, via current blood, to other organs and tissues, characterizing extraintestinal manifestations (EIM), with an impact on the functional status of the patients and their quality of life (Fig. 2) (Knutson *et al.*, 2013; Hussein *et al.*, 2008).

EIM can be identified in 25–40% of patients with IBD. The variation between remission and activity of symptoms is linked to morbidity and mortality. The main described manifestations include those that affect the liver and bile ducts, the skin, joints, eyes, and blood vessels. The heart, brain, and kidney are also affected (Annese, 2019; Garber and Regueiro, 2019). In addition, a common link regarding the microbial composition/nitroxidative stress of IBD and some diseases involving extraintestinal organs has been reported. This review aims to elucidate the participation of nitroxidative stress and dysbiosis in EIM genesis.

Materials and Methods

A narrative review of the literature was carried out on the association of inflammation, oxidative and nitrosative stress, and dysbiosis in the onset of EIM of IBD using the PubMed database. Systematic reviews, *in vivo* and *in vitro* studies (rats and mice) were included, with a total of 200 papers. Studies carried out on dogs, rabbits, pigs, or monkeys were not included in this review. The following keywords were used: oxidative stress, intestinal microbiota, dysbiosis, ulcerative colitis, Crohn's disease, inflammatory bowel disease, liver, hepatic, joint, skin, eyes, ophthalmological, thromboembolism, cardiovascular diseases, heart, brain, cerebral, neurologic, renal, kidney, lipopolysaccharide, endotoxin.

Systematic description

After an extensive review, the results are displayed in the following topics: hepatobiliary; osteoarticular, dermatological

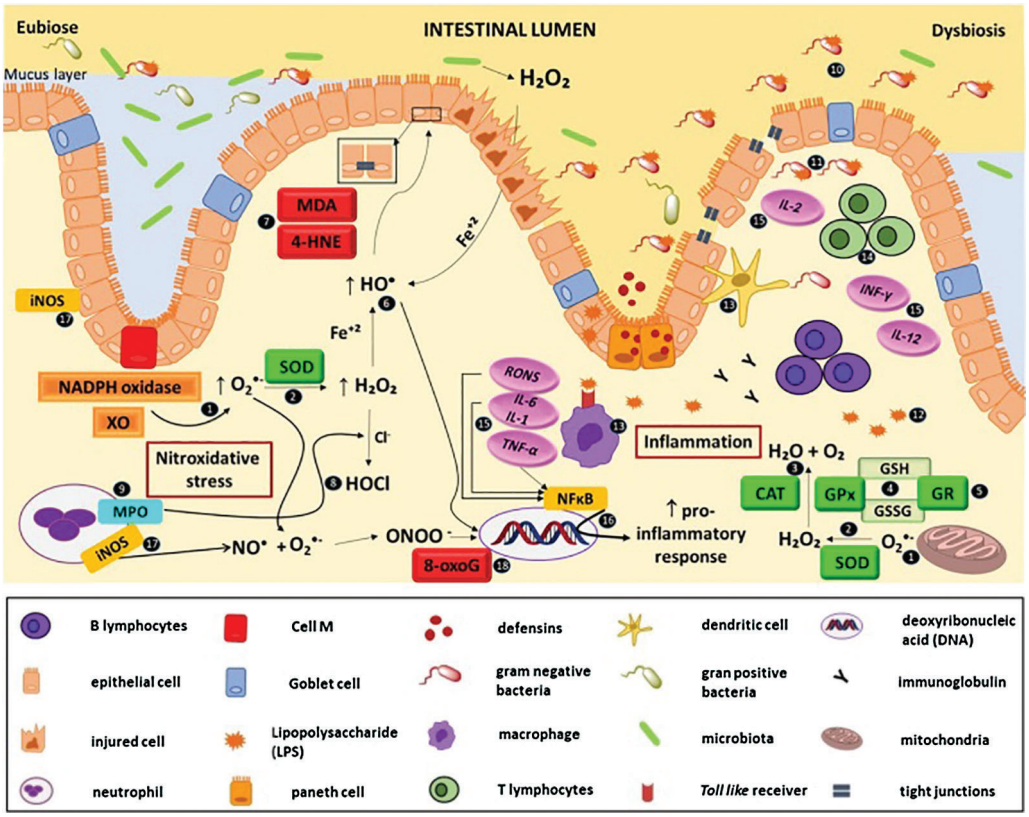

FIGURE 1. Interaction between dysbiosis, nitroxidative stress and inflammation in inflammatory bowel disease.
Legend: Representation of the interaction between dysbiosis, nitroxidative stress and inflammation involved in the pathophysiology of inflammatory bowel disease (IBD). The activation of xanthine oxidase (XO), NADPH (nicotinamide adenine dinucleotide phosphate) oxidase enzyme complex, and mitochondrial stimuli generate significant amounts of the superoxide radical anion ($O_2^{\bullet-}$) (1). In the cytosol, this reactive species, through superoxide dismutase (SOD), is quickly converted into hydrogen peroxide (H_2O_2) (2), which in turn is decomposed into H_2O and O_2, through the activity of catalase (CAT) and glutathione peroxidase (GPx) –formed by oxidation of GSH (glutathione reduced) to GSSG (glutathione oxidized) (4). GSSG is converted back to GSH by glutathione reductase (GR) (5). The generated redox imbalance causes a decrease in these antioxidant defences. The presence of transition metals, such as ferrous ion (Fe^{2+}), converts H_2O_2 into the hydroxyl radical (HO•) (6) that indiscriminately oxidizes cell membrane proteins and phospholipids (lipid peroxidation), causing epithelial barrier dysfunction. The lipid peroxidation generates toxic aldehydes, such as malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE) (7), which are also the result of the action of hypochlorous acid (HOCl) (8) formed from the reaction between H_2O_2 and chloride (Cl-), through the activity of myeloperoxidase (MPO), secreted from neutrophil granules (9). All those alterations, associated with dysbiosis (10), make the environment conducive to bacterial translocation (11), which consists of the entry of bacteria, mostly gram-negative, and their endotoxins, such as lipopolysaccharide (LPS), in the sterile sub-mucous (12). These microbes interact with immune cells (dendritic cells and macrophages) (13), through the link between pathogen-associated molecular patterns (PAMPs) and pattern recognition receptors (PRRs), respectively, and activate T lymphocytes (14), which promote the secretion of proinflammatory cytokines (15) that contribute to the maintenance of the inflammatory arsenal. These inflammatory cytokines and RONS activate the nuclear factor kappa B (NfκB) (16), which in turn stimulates, even more, the proinflammatory response. Reactive nitrogen species also participate, where the nitric oxide (•NO) derived from inducible nitric oxide synthase (iNOS) (17), can react with $O_2^{\bullet-}$ and generate peroxynitrite (ONOO-), which in turn, acts causing deoxyribonucleic acid (DNA) fragmentation, increasing metabolites such as 8-oxoguanine (8-oxoG) (19). Additionally, nitroxidative stress causes recruitment of inflammatory cells that generate additional damage and injury into intestinal microenvironment.

and ophthalmological; thromboembolic; cardiovascular; neurological; and renal manifestations.

Hepatobiliary manifestations

Hepatobiliary manifestations (HM) comprise one of the most common repercussions in IBD, with a prevalence of 3–50%, especially in those with UC. In addition, up to 5% of adults with IBD will develop some liver disease (Mendes *et al.*, 2007; Restellini *et al.*, 2017; Silva *et al.*, 2019; Venkatesh *et al.*, 2011). Primary sclerosing cholangitis (PSC) and non-alcoholic fatty liver disease (NAFLD) are the most common forms and can occur at any time during the course of intestinal disease or before its diagnosis (Annese, 2019; Fousekis *et al.*, 2018).

PSC is a progressive chronic cholestatic disease, characterized by inflammation, stenosis, fibrosis, and obstruction of the intra- and extrahepatic ducts, which can progress with complications such as cirrhosis, liver failure, and portal hypertension, in addition to an increased risk of cholangiocarcinoma and colorectal cancer (Eaton and Talwalkar, 2013; Maggs and Chapman, 2008; Tsaitas *et al.*, 2014). Epidemiological studies demonstrate that 60–80% of patients with PSC have IBD, especially UC (approximately 75%), and up to 8% of patients with IBD have PSC (Hirschfield *et al.*, 2013; Mendes *et al.*, 2007; Tsaitas *et al.*, 2014).

NAFLD, in turn, characterized by excess fat deposited in the liver, is responsible for up to 40% of the hepatic repercussions of

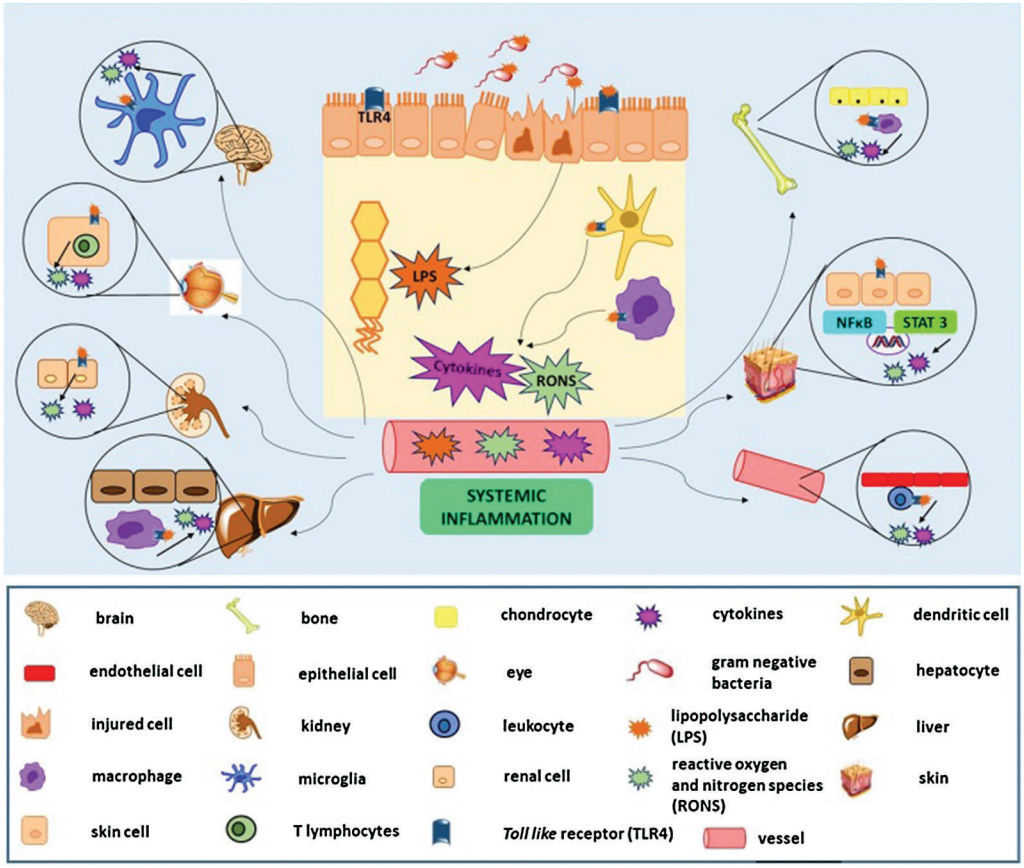

FIGURE 2. Microbiota translocation in inflammatory bowel disease promotes systematic inflammation and affects several tissues, causing local production of reactive oxygen and nitrogen species (RONS) and cytokines.
Legend: Bacterial translocation and nitroxidative stress contribute significantly to unregulated and exacerbated inflammatory response. The interaction between endotoxins, such as LPS, and their pattern recognition receptors, Toll like receptors, in particular TLR 4, in immune cells, causes secretion of pro-inflammatory cytokines and RONS, which cause harmful damage to all intestinal barriers and allow the spread of these toxic products through the bloodstream, which can be deposited and activate the immune response in extraintestinal organs. In these organs, LPS finds its TLR on the surface of innate immunity cells, causing the secretion of molecules with inflammatory profile and RONS, with consequent recruitment of other cells of the immune system, which intensifies the inflammatory cascade, generating local damage and contributing to the appearance of diseases. NFκB: nuclear factor kappa B; STAT 3: signal transducers and activators of transcription 3.

the non-alcoholic subtype in patients with IBD (Magri *et al.*, 2019; Vernon *et al.*, 2011). The prevalence is higher when compared to the general population, ranging between 1.5% and 55% (Chao *et al.*, 2016; Palumbo *et al.*, 2019).

The link between HM and IBD is still not well understood; however, multiple factors are involved, including genetic predisposition (HLA-B8, HLA-DRB1* 0301, HLA-DRB3* 0101, HLA-DRB1* 0401, REL, IL2 and CARD9) and hepatotoxicity induced by the use of drugs (corticosteroids, aminosalicylates, methotrexate, thiopurine, and antitumour necrosis factor-alpha) (Chapman *et al.*, 2010; Eaton and Talwalkar, 2013; Janse *et al.*, 2011; Karlsen *et al.*, 2010). However, the role of intestinal dysbiosis, inflammation, and nitroxidative stress also stands out, resulting from immune-mediated processes (Fousekis *et al.*, 2018; Navaneethan, 2014; Restellini *et al.*, 2017).

Bacterial translocation, evidenced by the significant increase in the levels of endotoxins and LPS in the portal vein in humans and animal models, implies the participation of the intestinal microbiota in the pathogenesis of HM (Nakamoto *et al.*, 2019).

Changes in the intestinal microbiota and dysfunction of the epithelial barrier play a crucial role in PSCs concomitant with IBD, as evidenced in humans. Intestinal dysbiosis– generally called dysbiosis– is an inherent characteristic of IBD, participating in the perpetuation and maintenance of chronic intestinal inflammation (Fujimoto *et al.*, 2013; Nishida *et al.*, 2018).

In humans, cohort studies have reported changes in microbial diversity and composition and have identified distinct phenotypes among patients with PSC and/or IBD when compared to healthy controls. It is noteworthy the significant decrease in the strain Faecalibacterium prausnitzi, present in both PCS and patients with IBD (Bajer *et al.*, 2017; Quevrain *et al.*, 2016; Sabino *et al.*, 2016). This dysbiosis may be associated with an unregulated mucosal immune response and altered permeability that directs a local and extraintestinal inflammatory response through bacterial translocation. It has been suggested that in the liver, endotoxins, especially LPS, bind to Toll-like receptor 4 (TLR 4) and activate dendritic cells and macrophages, which are involved in the secretion of pro-inflammatory cytokines, such as tumour necrosis factor-alpha (TNF-α) and reactive oxygen and nitrogen species (RONS); the expression of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and vascular

adhesion molecule 1 (VCAM-1); and in the initiation and progression of the fibrotic process characteristic of PSC (Reyes-Gordillo *et al.*, 2017).

In an animal model of PSC, dysbiosis was associated with changes in the enterohepatic circulation of bile acids, damage to the mucus layer, reduced expression of tight junction proteins, and increased bacterial translocation (Liao *et al.*, 2019).

Furthermore, a review showed that activation of the inflammasome nucleotide-binding domain, leucine-rich containing family, pyrin domain-containing-3 (NLRP3) in the intestine-liver axis by bacterial products contributed to the progression of liver damage through secretion of interleukin (IL)-1β and IL-18 via caspase-1 activity (Liao *et al.*, 2019), which is related to the amplification of hepatocellular damage (Zmora *et al.*, 2017).

Intestinal dysbiosis has also been recognized as a predisposing factor for NAFLD. The binding of bacterial DNA to TLR9 in Kupffer cells has been reported in animal studies to stimulate the secretion of IL-1β, which amplifies steatosis and liver fibrosis, in a MyD88-dependent mechanism (Miura *et al.*, 2010; Muruve *et al.*, 2008; Purchiaroni *et al.*, 2013).

The involvement of *Klebsiella pneumoniae* in NAFLD, a gram-negative bacterium associated with lung infections, has also been investigated. Recurrent infections by this resistant pathogenic bacterium stimulate an influx of pro-inflammatory cytokines in the colon and ileum, and the increased colonization of *K. pneumoniae* induced UC in an animal model, where it was able to increase the expression of cyclooxygenase- 2 (COX-2), IL-6, IL-1β and TNF-α and the levels of nitric oxide ($NO^{\bullet}$) and reduce tight junction proteins (Kaur *et al.*, 2018; Lee and Kim, 2011; Zhou *et al.*, 2009). Additionally, a study in mice demonstrated that these animals developed liver steatosis after faecal microbiota transplant containing *K. pneumoniae* isolated from a patient with NAFLD. Lastly, a cohort study reported a strong association between this bacterium and the severity of NAFLD in 61% of individuals. This result suggested that dysbiosis causes this condition due to excessive alcohol production, as this bacterium is associated with ethanol production in the faeces of patients with NAFLD when compared to healthy patients, and, consequently, ROS production and mitochondrial dysfunction (Chen *et al.*, 2020; Yuan *et al.*, 2019).

In dysbiosis, redox imbalance plays a crucial role in the damage, apoptosis/necrosis, and formation of toxic aldehydes (lipid peroxidation) (Leung and Nieto, 2013; Shearn *et al.*, 2018).

Significant periportal inflammation in the PSC marked by neutrophilic infiltrate and activation of NADPH oxidase is related to the generation of elevated levels of lipid peroxidation products and derivatives, such as malondialdehyde (MDA), acrolein, and 4-hydroxy-2-nonenal (4 HNE), which are important markers in the liver associated with protein and deoxyribonucleic acid (DNA) damage. Toxic aldehydes can cause post-translational changes in certain proteins, causing protein carbonylation, which determines the toxicity and degree of inflammation/fibrosis in the liver (Osna *et al.*, 2016; Shearn *et al.*, 2018; Shearn *et al.*, 2019).

In an animal model of PSC, an increase in periportal oxidative stress depending on the stage of cholestasis was demonstrated (Shearn *et al.*, 2019). Corroborating these findings, human studies carried out in patients with PSC concomitant with IBD showed an increase in periportal oxidative stress, with the elevated presence of toxic aldehydes, inflammation (↑ lymphocytes, ↑ Kupffer cells and ↑ MPO), and unregulated antioxidant response (Shearn *et al.*, 2018).

Additionally, the increase in intestinal permeability observed in IBD patients allows lymphocytes, activated in the intestine, to enter the enterohepatic circulation and cause inflammation in the liver. This promotes the recruitment of adhesion molecules and chemokines, such as MAdCAM-1 (mucosal vascular addressin cell adhesion molecule-1) and CCL25 (C-C motif chemokine ligand 25), which are chemotactic for other inflammatory cells, such as macrophages and dendritic cells (Adams and Eksteen, 2006; Eksteen *et al.*, 2004; Grant *et al.*, 2002).

In NAFLD, increased β-oxidation in peroxisomes and microsomes generates hydrogen peroxide (H_2O_2) not coupled to phosphorylation and cytochromes P4502E1 and P4504A, respectively (Bellanti *et al.*, 2017; Robertson *et al.*, 2001). The imminent redox imbalance and the elevation of lipids, associated with glutathione reductase (GR) depletion, can lead to the formation of intermediate lipids and cause stress of the endoplasmic reticulum, which in turn are related to inflammation and apoptosis (Bellanti *et al.*, 2017; Higa and Chevet, 2012; Mari *et al.*, 2006; Pagliassotti, 2012).

In humans, it was seen that the accumulation of lipids in the liver, especially cholesterol, alters the cellular redox status by prominently activating the oxidative pathways in the mitochondria, causing a significant increase in the formation of ROS that surpasses the neutralizing capacity of endogenous antioxidant defenses, leading to mitochondrial dysfunction (Muriel, 2009; Serviddio *et al.*, 2011; Sunny *et al.*, 2011).

Moreover, lipid peroxidation products, due to overproduction of ROS, influence the progression of NAFLD by complex inflammatory mechanisms, including inhibition of the peroxisome proliferator-activated receptors (PPARs) and TLR 7 pathways and activation of nuclear factor kappa B (NFκB) and activating protein 1 (AP-1) Green and Wahli (1994). These factors stimulate the production of pro-inflammatory cytokines, especially TNF-α and IL-1β, which increase the expression of sterol regulatory element-binding protein (SREBP), responsible for the transcription of genes that encode enzymes involved in the synthesis of lipids and the later appearance of steatosis (Bellanti *et al.*, 2017; Chen *et al.*, 2008; Kohjima *et al.*, 2007).

Therefore, the involvement of dysbiosis/inflammation/nitroxidative stress as mediators of hepatobiliary lesions triggered by IBD seems to be increasingly consistent and should be considered in clinical practice.

Osteoarticular, dermatological and ophthalmological manifestations

These manifestations occur even before the diagnosis of UC, correlating or not with disease activity (Olpin *et al.*, 2017). Genetic susceptibility has been proposed to explain the link between then and IBD, such as TNF-α and variations in TNF receptor-associated factor interacting protein 2 (TRAF3IP2) that occur in erythema nodosum (Ciccacci *et al.*, 2013;

Orchard *et al.*, 2002; Suh *et al.*, 2019; Timani and Mutasim, 2008). In this context, in some of these diseases, genetic alterations related to microbiota disruption have been described, including ankylosing spondylitis and uveitis, which were identified as the presence of B27 human leukocyte antigen (HLA-B27) that predisposes individuals to dysbiosis (Ciccia *et al.*, 2016; Costello *et al.*, 2015; Hermann *et al.*, 1993; Lin *et al.*, 2014a; Pimentel-Santos *et al.*, 2013; Sheth *et al.*, 2015; Speca and Dubuquoy, 2017).

However, genetic factors alone are unable to elucidate the pathophysiological pathways, suggesting the involvement of environmental factors. It has been proposed that intestinal lumen antigens can form circulating immune complexes and could be deposited in these organs, causing an inflammatory response and RONS production, which are responsible for the characteristic lesions of the disease (Lin *et al.*, 2014a; Lin *et al.*, 2014b; Yang *et al.*, 2016).

Osteoarticular manifestations: Spondyloarthropathies (SpA), including ankylosing spondylitis and peripheral arthritis, are found in 10–39% of patients with IBD, especially in patients with CD (Fantini *et al.*, 2009; Gionchetti *et al.*, 2015; Karreman *et al.*, 2017). Some mechanisms are described to explain this association. One of these findings suggests that lymphocytes and macrophages activated in the Payer plate and in the mesenteric lymph nodes start to express and stimulate cell and vascular adhesion molecules (α4β7 and αEβ7 integrins, cadherin E, vascular adhesion protein 1 [VAP-1], ICAM-1) that promote the adherence of these immune cells in the synovial endothelium and inside the joints, releasing cytokines directed to synovial fibroblasts. These findings were corroborated in samples from the affected part of the intestine of patients with CD and CU, where it was demonstrated that the leukocyte populations of the inflamed intestine were avidly bound to synovial vessels, evidenced by the expression of adhesion molecules and ligands (ICAM-1 and P-selectin) (Jacques and Elewaut, 2008; Salmi and Jalkanen, 2001).

Another link described in some studies suggests that the mechanisms of IBD-associated SpA involve a hypothesis of "intestine-synovia-joint axis", including changes in the intestinal microbiota and activation of T cells in the intestine for liquid synovial joint in genetically predisposed individuals (Arvikar and Fisher, 2011; Fragoulis *et al.*, 2019; Brakenhoff *et al.*, 2010).

In this context, germ-free and transgenic animals for the HLA-B27 gene (related to joint disease) did not develop inflammation or lesions characteristic of colitis and spondyloarthritis (Gilis *et al.*, 2018; Scher *et al.*, 2016; Taurog *et al.*, 1994).

Additionally, it has been reported in patients with IBD and SPA overexpression of E-cadherin, the major component of adhering junctions, responsible for maintaining intestinal homeostasis and barrier function, indicating the participation of microbiota/endotoxins in these conditions (Demetter *et al.*, 2000; Demetter *et al.*, 2005).

These changes in microbiota and intestinal permeability allow the translocation of bacteria and endotoxins, such as LPS, to the synovial fluid and joints, causing local inflammation (Asquith *et al.*, 2014). Dysbiosis induces the M1 phenotype in macrophages, which are responsible for increasing the production of pro-inflammatory cytokines (Yang *et al.*, 2016). Ciccia *et al.* indicated in intestinal biopsy samples from patients with SpA that infiltrating monocytes were responsible for the increased IL-23 expression, and overexpression of IL-23 is an important characteristic of subclinical gut inflammation in SpA. Further, to confirm this theory of "intestine-synovia-joint axis", a reduction in the number of Faecalibacterium praustnizii species, which are beneficial species for intestinal health and the immune system, has been described in the faeces of patients with SpA and IBD (Tito *et al.*, 2017).

Together, these findings (in experimental and human studies) suggest the involvement of microbiota homeostasis in the immune response and molecular mimicry in patients with SpA and IBD.

Osteoporosis is another osteoarticular disease common in patients with IBD and has been identified in 18–42% of these, increasing the fracture risk, especially in older patients (>60 years). However, it is not clear if IBD patients have an increased risk of reduced bone mineral density (BMD) (van Hogezand and Hamdy, 2006).

Osteoporosis in IBD is multifactorial, but medications used in IBD treatment seems to be the main cause of BMD in these patients. Chronic steroid therapy may decrease BMD, damage bone tissue structure, increase the risk of fractures (van Staa *et al.*, 2005), and, by the other side, decrease intestinal calcium absorption and calcium kidney reabsorption, leading to an increase in the parathormone level, responsible for the stimulation of osteoclasts and increasing bone loss (van Staa, 2006).

The link between osteoporosis/IBD/oxidative stress/microbiota is not evident. However, in a recent review of Ratajczak *et al.* (Ratajczak *et al.*, 2020), the authors did an association between vitamin C deficiency and risk of osteoporosis in IBD patients. According to then, as an antioxidant, vitamin C: (1) Decreases the level of ROS, which increase bone resorption, throughout the activation of (NF-κB) which is a crucial mediator of TNF-α and osteoclastogenesis; (2) Creates a redox state and modulates gut microbiota increasing Firmicutes and a decreased Bacteroides level. All dates together suggest an important role of antioxidant status in bone health to IBD patients. However, the exact mechanism is unclear and must be studied posteriorly.

Dermatological manifestations: Erythema nodosum and pyoderma gangrenosum are the most frequent EIM on the skin of IBD (Greuter and Vavricka, 2019; Vavricka *et al.*, 2011). Nodosum erythema is the most common symptom, more present in CD than in UC, especially in women (Farhi *et al.*, 2008; Vavricka *et al.*, 2011; Vavricka *et al.*, 2015). Its relationship with IBD is more associated with genetic factors (Suh *et al.*, 2019; Timani and Mutasim, 2008).

Gangrenous pyoderma, in turn, mainly affects patients with UC to the detriment of those with CD and can appear before or after the diagnosis of IBD (Ahn *et al.*, 2018; Annese, 2019). The pathophysiological link is still unclear, but an unregulated inflammatory response is proposed, involving neutrophils and T cells against antigens common to the organs. Data from immunohistochemistry and analysis of proteins in necrotic tissue in patients with gangrenous pyoderma have demonstrated overexpression of

the TNF-α, NF-κB, and signal transducer and activator of transcription 3 (STAT3) pathways (Vavricka *et al.*, 2015).

Psoriasis, a chronic inflammatory skin disease, has also been associated with IBD and is more prevalent in patients with CD than in those with UC (Fu *et al.*, 2018; Suh *et al.*, 2019). A recent meta-analysis also showed that psoriasis was significantly related to IBD (Fu *et al.*, 2018), being more prevalent in these patients than in the general population.

Despite the genetic link (IL23R and IL12B), it has been proposed that the intestinal microbiota plays an important role in this context (Capon *et al.*, 2007; Cho, 2008; Cottone *et al.*, 2019; Ellinghaus *et al.*, 2012). The decrease in the genus Faecali bacterium prausnitzii (a beneficial bacterium for the maintenance of intestinal homeostasis, as already mentioned in this review), observed in both patients with CD and psoriasis, demonstrates the relevance of an interaction between the microbiome and an adequate immune response (Eppinga *et al.*, 2016).

Ophthalmological manifestations: Ophthalmological manifestations may be present in 4–12% of patients with IBD; however, the reported prevalence rate can reach up to 29%, especially in CD. The most common conditions reported are anterior uveitis and episcleritis, present in 0.3–10% of patients with IBD (Greuter and Vavricka, 2019; Harbord *et al.*, 2016; Larsen *et al.*, 2010; Taleban *et al.*, 2016).

The hypothesis of the microbiota-intestine-eye has been proposed and investigated. In animal models of autoimmune uveitis, it has been shown that dysbiosis induces the activation of retinal-specific autoreactive T cells and intraocular inflammation (Horai and Caspi, 2019; Horai *et al.*, 2015; Nakamura *et al.*, 2016). In addition, there was an increase in intestinal permeability and antimicrobial peptide expression concomitant with the effector T cell response in the initial stage of uveitis (Janowitz *et al.*, 2019).

In addition, nitroxidative stress, identified through MDA elevation levels in the aqueous humour and decreased antioxidant defense (superoxide dismutase [SOD], catalase [CAT] and glutathione peroxidase [GPx]), has been confirmed in an endotoxin-induced anterior uveitis model (Rahman and Biswas, 2004).

Recent cohorts, including individuals with autoimmune anterior uveitis, identified changes in the composition of the intestinal microbiota and a faecal metabolic phenotype that significantly differed when compared to that of healthy controls (Huang *et al.*, 2018; Chakravarthy *et al.*, 2018). However, the scarcity of studies in humans that have evaluated the intestine in eye diseases hinders the effective association.

Despite these molecular findings suggesting the close link between microbiota, nitroxidative stress, intestinal inflammation and osteoarticular, dermatological and ophthalmological manifestations in patients with IBD, these crosslinks are not yet well understood, and additional studies, especially in humans, are still needed.

Thromboembolic manifestations

The prothrombotic state is considered a characteristic of patients with IBD, especially during the symptomatic phase (Nguyen *et al.*, 2014). The most common manifestations are deep venous thromboembolism and pulmonary embolism (van Assche *et al.*, 2013). Chronic inflammation (monocyte chemoattractant protein-1 [MCP-1], IL-6 and IL-8) activates hemostasis and causes hypercoagulation and, consequently, abnormalities in the microvascular tissue characteristic of endothelial dysfunction (Danese *et al.*, 2007; Esmon, 2005; Levi *et al.*, 2012; Papa *et al.*, 2008; Roifman *et al.*, 2009; Zezos *et al.*, 2014).

Several factors cause lesions in the gut microvascular endothelium, among which the most important described are the bacterial endotoxins present in the gut lumen, pro-inflammatory cytokines, and hypoxia (Danese, 2007; Joseph *et al.*, 2002; Levi *et al.*, 2012; Makrides, 1998; Stadnicki, 2012; Zezos *et al.*, 2014).

Once activated, the vascular endothelium starts to express a large amount of cell adhesion molecules (ICAM-1, VCAM-1, and PCAM-1) and adhesins (selectins and integrins) that allow the recruitment and transmigration of leukocytes through the vessel, platelet activation, and aggregation (Davis *et al.*, 2003; Panes and Granger, 1998; Schuermann *et al.*, 1993). This scenario promotes the coagulation cascade, with an evident increase in the factors involved in this process (factors V, VIII, von Willebrand, and fibrinogen), thus enabling the formation of thrombi. Vascular and tissue damage spread through a vicious cycle characterized by an increase in the production of cytokines, especially TNF-α, IL-6 and vascular endothelial growth factor (VEGF), RONS and chemokines (Danese, 2007; Hudson *et al.*, 1992; Jorens *et al.*, 1990; Scaldaferri *et al.*, 2011; Zezos *et al.*, 2014). Increased expression of VEGF and its receptor was seen in samples from patients with IBD when compared to healthy individuals (Scaldaferri *et al.*, 2009).

Furthermore, vascular dysfunction in IBD was associated with an imbalance in RONS levels. Inflammatory and immunological stimuli, bacteria and LPS have been shown to activate inducible nitric oxide synthase (iNOS), which induces the production of large amounts of $^{\bullet}NO$–a potent vasodilator and anti-aggregation agent that causes indirect harmful effects through the generation of other species, such as nitroxyl anion (NO^{-}) and peroxynitrite ($^{-}OONO$), which is able to cause lipoperoxidation and damage to DNA molecules (Beckman and Koppenol, 1996; Kolios *et al.*, 2004). Studies with colonic biopsies of patients with CD and UC, showed overexpression of iNOS in the inflamed epithelium and nitrotyrosine, suggesting that this finding is associated with the formation of –OONO and the nitration of cellular proteins (Singer *et al.*, 1996; Dijkstra *et al.*, 1998).

In addition, literature reviews show that in the endothelial cells of the chronically inflamed microvasculature, there is a decrease in the production of $NO^{\bullet}$, mainly due to the selective inhibition of iNOS and the non-selective inhibition of the constitutive forms of nitric oxide synthase (NOS), and an increase in superoxide anion radical ($O2^{\bullet-}$), which was proportional to the increase in recruitment and leukocyte adhesion (Binion *et al.*, 1998; Binion *et al.*, 2000; Hatoum *et al.*, 2003).

The increase in the serum levels of homocysteine (HCy), a sulfur-containing amino acid resulting from the demethylation of methionine, is also associated with an elevated risk of venous thromboembolism by inducing platelet activation in the endothelium and increasing prothrombotic components (Zhang *et al.*, 2014). In a dysbiotic environment, the bacteria

that synthesize methionine contribute to excessive HCy formation (Kurilshikov *et al.*, 2019).

Intestinal dysbiosis and bacterial translocation have also been linked to endothelial dysfunction. A review described that, in the bloodstream, microbial endotoxins present in the outer membrane of gram-negative bacteria, especially LPS, bind to TLR4 in immune cells, forming a complex that binds to the MD-2 protein and CD14. This complex formation results in the production of pro-inflammatory cytokines and other mediators involved in endothelial damage, the procoagulant state, the recruitment and transformation of macrophages into foam cells, and the initiation of atherosclerotic plaque (Szeto *et al.*, 2018a; Szeto *et al.*, 2018b).

Therefore, the activation of the endothelium associated with chronic bowel inflammation and dysbiosis may be critically implicated in triggering hypercoagulability and subsequent onset of thromboembolic events.

Cardiovascular manifestations

Patients with IBD have a high risk of coronary artery disease, in part, attributed to a greater susceptibility to the occurrence of thromboembolic events and nutrient malabsorption, especially selenium (Benstoem *et al.*, 2015; Castro Aguilar-Tablada *et al.*, 2016; Hansson, 2005; Wu *et al.*, 2017). On the other hand, it has been suggested that the risk of atherosclerosis and other cardiovascular diseases is associated with endothelial dysfunction caused by systemic inflammation, dysbiosis, and nitroxidative stress (Aniwan *et al.*, 2018; Bigeh *et al.*, 2019; Horowitz *et al.*, 2007; Wu *et al.*, 2017).

Systemic inflammation in IBD leads to RONS generation and nitroxidative stress (Wu *et al.*, 2017; Zanoli *et al.*, 2015). A study in patients with CD observed high levels of pro-inflammatory molecules such as TNF-α, IL-1, IL-6 and C-reactive protein (CRP) contribute to endothelial dysfunction, characterized by vascular smooth muscle cell hyperplasia and decreased $^{\bullet}$NO production, resulting in a reduction in vessel relaxation. This induces the infiltration of neutrophils into the blood vessels, causing changes in the smooth muscle cell phenotype, an increase in matrix metalloproteinase production, and a decrease in elastin and collagen fibres due to the activation of collagenases and elastases, thus leading to the formation of rigid fragments that induce atherosclerotic processes (Schinzari *et al.*, 2008). Moreover, TNF-α signaling pathways induce the expression of osteoblast markers (osteocalcin and osteopontin) in endothelial cells, which leads to an increase in calcification and reduced vascular elasticity, resulting in arterial stiffening, coronary artery disease, and heart failure (Floege and Ketteler, 2004; Wu *et al.*, 2017; Zanoli *et al.*, 2015; Zieman *et al.*, 2005).

Intestinal dysbiosis, in turn, associated with increased permeability, allows bacterial translocation. Has been demonstrated in *in vitro* assays (Howell *et al.*, 2011; Maziere *et al.*, 1999) and an animal model (Wiesner *et al.*, 2010) that high levels of LPS and bacterial products directly induce the atherosclerotic process through the formation of oxidized low-density lipoprotein (oxLDL), a key atherosclerotic lesion component, activation of macrophages and adhesion molecules and, consequently, the formation of foam cells and stimulation of pro-inflammatory cytokine expression. The latter, in association with other cellular mediators such as VEGF, CRP, and platelets, cause endothelial dysfunction and eventual atherosclerosis.

A recent cohort study exploring the relationship of intestinal microbiota with plasma metabolites, cardiovascular metabolic risk score, and cardiometabolic phenotypes demonstrated that L-methionine-producing bacteria were associated with atherosclerosis in obese individuals. It is suggested that methionine causes this effect through its direct conversion to HCy, contributing to serum elevation, which is a known cardiovascular risk factor that will be addressed later (Kurilshikov *et al.*, 2019).

The presence of bacterial DNA in human plasma has been addressed in some reviews and associated with endotoxin levels to trigger systemic inflammation and increase the instability of atherosclerotic plaques. It binds to TLR-9, stimulating inflammatory intracellular signaling pathways such as mitogen-activated protein kinase (MAPK), NF-κB, PI3-kinase, and Jun N-terminal kinase (El Kebir *et al.*, 2008; Szeto *et al.*, 2018a).

The intestinal microbiota is also related to the trimethylamine/N-trimethylamide (TMA/TMAO) pathway (Hansen *et al.*, 2015; Wang and Zhao, 2018). *Proteus mirabilis* is a gram-negative bacterium, a component of the fecal microbiota, but in a dysbiotic environment, it is found in higher numbers. These species, from the carbon extraction of some compounds such as choline, phosphatidylcholine, glycerol phosphocholine, carnitine, betaine, and γ-butyrobetaine, produce the metabolite TMA by TMA lyases (Tang and Hazen, 2014; Wang *et al.*, 2015; Wang and Zhao, 2018). TMA is oxidized to TMAO in the liver by flavin monooxygenase and transported to the systemic circulation (Bennett *et al.*, 2013; Koeth *et al.*, 2013; Tang and Hazen, 2014; Wang and Zhao, 2018) and activates smooth muscle cells of the vessels, endothelial MAPK and the NF-κB pathway, leading to the expression of pro-inflammatory cytokines and leukocyte adhesion in addition to inducing transformation of macrophages to foam cells to activate NOD (nucleotide-binding oligomerization domain), LRR (leucine-rich repeats) and NLRP3 (nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3) (Chen *et al.*, 2017; Seldin *et al.*, 2016; Wang and Zhao, 2018; Wei *et al.*, 2017). Additionally, TMAO reduces the expression of the genes CYP7A1 (cytochrome P450 family 7 subfamily A member 1) and CYP27A1 (cytochrome P450 family 27 subfamily A member 1), affecting the metabolism of cholesterol and bile salts and the release of calcium in the platelet endoplasmic reticulum, facilitating the formation of thrombi (Koeth *et al.*, 2013; Zhu *et al.*, 2016).

Furthermore, hyperhomocysteinaemia is an independent cardiovascular risk factor and has been observed in both patients with UC and CD at concentrations 4–5 times higher than those in healthy individuals (Drzewoski *et al.*, 2006; Oussalah *et al.*, 2011; Tyagi *et al.*, 2005; Wu *et al.*, 2017).

High levels of HCy cause nitroxidative stress and endothelial dysfunction through self-oxidation catalysed by cationic metals, which results in the formation of $O_2^{\bullet}$- and, when reacting with $^{\bullet}$NO, forms (ONOO-), which reduces

the bioavailability of •NO (Sen *et al.*, 2010; Tyagi *et al.*, 2005). Studies in cell culture (Liu *et al.*, 2013; Zhu *et al.*, 2016) and animals (Sen *et al.*, 2010) have shown that high levels of HCy induce RONS formation, causing an increase in the concentrations of H_2O_2 and MDA and mitochondrial damage by decreasing the expression of cytochrome c oxidase III/ATPase 6/8 and heat shock protein 60 and impairing the antioxidant defence system (GPx, hemeoxygenase and SOD), thus leading to redox imbalance (Liu *et al.*, 2013; Tyagi *et al.*, 2005). It also activates the NFκB pathway, adhesion molecules (ICAM-1, VCAM-1) and MCP-1. These, in turn, interact with inflammatory cells of the endothelium, leading to the atherosclerotic process (Silverman *et al.*, 2002; Wang *et al.*, 2002).

Neurological manifestations

Malabsorption, nutritional deficiencies (vitamins B1, B12, D and E, folic acid and nicotinamide), infections, thromboembolism, adverse drug effects (metronidazole, sulfasalazine, steroids, cyclosporine), and immunological abnormalities are related to changes in the bowel-brain axis (Casella *et al.*, 2014; Moris, 2014). The pathophysiology of neurological manifestations of IBD and their prevalence are not yet fully understood. Neurologic and neuromuscular complications in IBD (peripheral neuropathies, multiple sclerosis, cerebrovascular diseases, and others including psychiatric disorders) have been estimated from 0.25 to 35.7% due to the different forms of diagnosis (Elsehety and Bertorini, 1997; Gondim *et al.*, 2005; Lossos *et al.*, 1995).

A link has been proposed between chronic intestinal inflammation and neuropathy onset. The deregulated immune response involving mainly T cells towards the autoantigens that crossed the blood-brain barrier (BBB) induces central nervous system activation of astrocytes and microglia, which stimulates the production of pro-inflammatory cytokines, RONS, glutamatergic excitotoxicity, and autoantibody generation against the myelin sheath, causing axonal injury and neuronal dysfunction (Casella *et al.*, 2014; Moris, 2014; Singh *et al.*, 2013). According to Nemati *et al.* (2019), the development of neurological disease in IBD may be coincidental (chance association) or the consequence of the primary disease and this differentiation is necessary because they may require different treatments. Furthermore, investigations in this context are not yet routine in clinical practice.

An intimate link between the microbiota-gut-brain axis has been proposed. The microbiota influences several brain activities, including the modulation of neuroimmune responses and maintenance of the integrity of the epithelial barrier and the BBB, through the expression of occludin and claudin, demonstrated in an animal model (Braniste *et al.*, 2014). Changes in the microbiota and bowel permeability allow the spread of bacteria, toxins such as LPS, and other metabolites (TMAO, for example) towards the BBB. This causes an unregulated immune response, with activation of the microglia that alters its secretory profile and stimulates the production of pro-inflammatory chemokines and cytokines (MCP-1, interferon-gamma [IFN-γ], IL-6, IL-8, and TNF-α), as well as increases RONS (Block *et al.*, 2007; Del Rio *et al.*, 2017; Shemer *et al.*, 2015).

Multiple sclerosis (MS), characterized by demyelination and neuroinflammation, has been closely related to IBD. Studies indicate that first-degree relatives of patients with MS are at risk for CD development (risk of 1.4), while IBD patients have a risk of 1.7 of developing MS (Gupta *et al.*, 2005; Nielsen *et al.*, 2008; Noseworthy *et al.*, 2000). Changes in the microbiota in patients with MS have been identified in this process, such as an increase in antibodies against intestinal microbial components (Banati *et al.*, 2013). Furthermore, in cell culture, the activation of mucosal-associated invariant T cells (MAIT), seen in IBD, also plays a role in MS, as they can interact with microbial components and stimulate the innate and adaptive response, including CD8+ T cells and the production of pro-inflammatory cytokines, such as IL-17. Moreover, these cells express high levels of CD161 (cluster of differentiation 161), CCR6 (chemokine receptor 6), and IL-18 (Moreira *et al.*, 2017).

Neurodegenerative diseases, such as Parkinson's disease (PD), have also been associated with intestinal dysbiosis and increased intestinal permeability, seen in IBD Animal studies have shown that the increase in LPS in UC causes an overactivation of microglia, TNF-α secretion and iNOS activation. The identification of α-synuclein (Parkinson's disease–PD–marker protein) in the enteric nervous system and later in the neurons of the central nervous system (CNS) reinforced the link (de La Serre *et al.*, 2015; Hoban *et al.*, 2013; Qin *et al.*, 2013; Villaran *et al.*, 2010).

In humans, this relationship has also been confirmed. According to Villumsen *et al.* (2019), patients with IBD have up to 22% risk of developing PD when compared to healthy individuals.

The reduced integrity of the BBB in model animals and PD individuals has been reported, and it is possible that concomitant epithelial barrier dysfunction increases microbiota communication with CNS cells (Gray and Woulfe, 2015; Zhao *et al.*, 2007).

On the other hand, studies have shown that patients with IBD have a 2–3 times higher risk of developing anxiety and depression than the general population, affecting 30% and 25%, respectively, of these patients, especially in the active phase (Mikocka-Walus *et al.*, 2016; Walker *et al.*, 2008).

The intimate connection and communication of the microbiota–gut–brain axis is proposed to explain this prevalence. The hypothalamic-pituitary-adrenal axis perceives and responds to the stimulus of stress and inflammation, leading to a decrease in the effector response of the vagus nerve and an increase in intestinal permeability. This favors bacterial translocation that activates the mucosal immune response, as well as other cells of the innate immune system in the brain, increasing microglia activity, pro-inflammatory cytokine levels and nitroxidative stress, which generate changes in brain functions and damage to neuroplasticity (Abautret-Daly *et al.*, 2018; Bailey *et al.*, 2006; Maes *et al.*, 2012; Santos *et al.*, 1999).

In cell culture and animal model assays, dysbiosis impairs its appropriate interaction with the host and influences neural activities in brain areas related to stress and behavior, with changes in brain-derived neurotrophic factor (BDNF) in the hypothalamus and amygdala, in addition to the decrease in SCFA-producing bacteria, which, in turn, are immunomodulatory metabolites. The participation of the microbiota seems to be related to the

gamma-aminobutyric acid (GABA), serotonin and dopamine pathways, which are implicated in depressive and anxiety disorders (Bernstein, 2017; Foster and McVey Neufeld, 2013; Lyte *et al.*, 2011).

Renal manifestations

The link between IBD and renal manifestations, although less frequent, has been demonstrated in both CD and UC. The reported diseases are nephrolithiasis, glomerulonephritis, and tubule-interstitial nephritis (Ambruzs *et al.*, 2014; Corica and Romano, 2016).

Nephrolithiasis affects 12–28% of patients with IBD, and few studies report a 9–18% higher risk than in the general population. The frequency is higher in CD and patients submitted to surgical procedures such as colectomy with ileostomy and intestinal resection (Bianchi *et al.*, 2018; Gkentzis *et al.*, 2016; McConnell *et al.*, 2002; Parks *et al.*, 2003). In this context, a small cohort of 83 patients demonstrated an incidence of 24% IgA glomerulonephritis and 19% tubule-interstitial nephritis, especially in CD (Ambruzs *et al.*, 2014).

Some links between renal manifestations and IBD have been described that seem to have an important role, including genetics by identifying the HLA-DR1 (human leukocyte antigen-DR1) and HLA-DR1/DQw5 genes present in both IgA glomerulonephritis and CD; adverse effects of drugs such as aminosalicylates and its derivatives, especially in tubule-interstitial nephritis; and a reduction in anti-lithogenic factors (citrate and magnesium) in nephrolithiasis, mainly due to chronic diarrhea (Ambruzs *et al.*, 2014; Ganji-Arjenaki *et al.*, 2017; Hueppelshaeuser *et al.*, 2012; Kane, 2006; Oikonomou *et al.*, 2011; Takemura *et al.*, 2002; Worcester, 2002). However, these factors cannot fully explain the renal manifestations in patients with IBD.

In relation to nephrolithiasis, intestinal dysbiosis seems to be involved in the formation of calcium oxalate stones in the kidneys. It has been observed that individuals with IBD, who have a smaller population of *Oxalobacter formigenes* in their intestinal microbiota, have a high prevalence of nephrolithiasis (Kumar *et al.*, 2004). *O. formigenes* is a gram-negative, anaerobic, commensal bacterium from the gastrointestinal tract that acts on the regulation of oxalate homeostasis; it degrades oxalate through the enzymes oxalyl-coenzyme A decarboxylase and formyl-coenzyme transferase and interacts with the intestinal mucosa, stimulating the secretion of endogenous oxalate into the lumen, a transport mechanism through the epithelium, thus contributing to the excretion of this compound (Arvans *et al.*, 2017; Liu *et al.*, 2017; Siener *et al.*, 2013; Siva *et al.*, 2009; Stewart *et al.*, 2004).

It has been observed, especially in patients with CD, that decolonization of TGI by *O. formigenes* leads to a reduction in the intestinal catabolism of oxalate and the subsequent appearance of hyperoxaluria, the main mechanism involved in the formation of kidney stones. In addition, an increase in urinary oxalate was observed in these patients when compared to healthy controls. It occurs more frequently in individuals who have undergone ileum resection and colon-jejunal anastomoses (Hueppelshaeuser *et al.*, 2012; Kane, 2006; Kumar *et al.*, 2004; Oikonomou *et al.*, 2011; Siva *et al.*, 2009). The causes that lead to the decolonization of this bacterium have not yet been elucidated. However, it has been proposed that the possible reasons are precisely associated with changes in the composition of the intestinal microbiota, typical of IBD, which is the result of an inflammatory response exacerbated against these commensals, which results in a break in immunological tolerance (Kumar *et al.*, 2004).

Nevertheless, other commensal bacteria, such as Lactobacillus and Bifidobacterium, also secrete enzymes capable of degrading oxalate in a medium that contains glucose and lactose (Campieri *et al.*, 2001). The role of oxalate-degrading bacteria in the treatment of kidney stones has become of great interest in the scientific community, aiming at their use as a probiotic. Animal and human research using *O. formigenes* or their enzymes have shown promising results; however, data security is still required through well-controlled and larger-scale clinical trials. Other studies investigating the species Lactobacillus and Bifidobacterium have also shown a reduction in oxalate excretion, but the results are still controversial. The importance of additional standardized studies that determine the direct relationship between the decolonization of these bacteria and the presence of hyperoxaluria and consequent kidney stones and their influence as a risk factor for the identification of possible probiotics in the treatment of this condition is emphasized. It is said that functional and molecular approaches are needed to choose the best species that also have the ability to effectively colonize the intestine (Abratt and Reid, 2010; Mehta *et al.*, 2016; Sadaf *et al.*, 2017).

Oxalate generates toxic responses that result in the activation of phospholipase A2, which culminates in the production of arachidonic acid and various lysophospholipids. These factors, in turn, lead to mitochondrial dysfunction, an increase of RONS production, and the induction of changes in the expression of genes involved in the synthesis of molecules that inhibit the formation of calcium oxalate stones and in the activation of caspases, which are involved in apoptotic cell death (Cao *et al.*, 2000; Cao *et al.*, 2004; Jonassen *et al.*, 2005; Oikonomou *et al.*, 2011). In addition, the presence of TLRs, especially TLR4, expressed in renal epithelial cells and the identification of significant amounts of endotoxins in kidney stones suggest that this interaction generates activation of inflammatory pathways (Anders *et al.*, 2004a; Anders *et al.*, 2004b; McAleer *et al.*, 2003; Oikonomou *et al.*, 2011).

In IgA nephropathy, the intimate relationship of the microbiota-intestine-kidney axis has been implicated. The breakdown of the intestinal barrier and the increase in pro-inflammatory cytokines leads to bacterial translocation, facilitating the diffusion of microbial endotoxins and DNA through the bloodstream, which become established in the renal glomeruli. It was proposed that the deposited immune complexes react with luminal antigens and that there is a loss of exclusion and antigenic tolerance, sustained immune response and deregulation in the production and transport of IgA. Evidence shows that patients with CD present high levels of IgG and IgA due to an inflammatory response of the mucosa to *K. pneumoniae* (Anders *et al.*, 2004a; Corica and Romano, 2016; Forshaw *et al.*, 2005; O'Mahony *et al.*, 1992; Takemura *et al.*, 2002).

Finally, in tubule-interstitial nephritis, a deregulated immune and inflammatory response, the presence of

autoantibodies and immunocomplexes against epitopes common to the intestine and kidney and molecular mimicry are likely pathophysiological mechanisms (Ambruzs *et al.*, 2014; Corica and Romano, 2016; Fraser *et al.*, 2001; Mahmud *et al.*, 2002; Oikonomou *et al.*, 2011; Poulou *et al.*, 2006).

The diseases addressed may progress to renal failure and end-stage renal disease if the inflammation persists and/or is not contained. A few epidemiological studies have reported the incidence of renal failure between 2 and 15.9% in patients with IBD, and there is an elevated risk for end-stage renal disease in CD that is five times higher than that in CU and healthy controls, suggesting that IBD, especially CD, is an independent risk factor (Park *et al.*, 2018; Primas *et al.*, 2013). Some mechanisms have been proposed to explain the increased risk in patients with CD, including systemic inflammation resulting from the unregulated immune response in the intestine and the transmural character that can exacerbate renal damage, as has been reported with the increase in serum levels of IL-6 and CRP, in addition to autoimmunity (Cioffi *et al.*, 2015; Fried *et al.*, 2004). Therefore, it is essential to monitor renal function in patients with IBD to identify early signs of renal damage and guide the choice of appropriate and effective therapy.

Study limitations

There are few prospective studies in humans that assess the microbiota and nitroxidative stress in EIM of IBD. In some studies, associated comorbidities, such as diabetes mellitus and arterial hypertension, were not mentioned as a possible confounding factor. Thus, in this review, we propose a crosslink between redox imbalance and dysbiosis, using mainly *in vitro* and experimental reports, as well as physiological and biochemical established routes.

Prospects and future direction

Evidence suggests that chronic continuous nitroxidative stress and alteration of the intestinal microbiota may be strongly associated with the appearance of EIM inherent to patients with IBD (Fig. 3). Despite the involvement of genetic factors, it is necessary that other variables act to stimulate and/or to facilitate the expression of this phenotype, and the chronic inflammatory environment associated with increased intestinal permeability becomes decisive in determining these manifestations of the disease.

However, the studies carried out in humans, herein described, demonstrate the association and the presence of dysbiosis in the hepatic (PSC), osteoarticular, and dermatological manifestations (psoriasis) and as a contributing factor for the formation of kidney stones. It is associated with the nitroxidative stress and lipid peroxidation in triggering NAFLD and endothelial dysfunction described in the pathophysiology of thromboembolic events. Nevertheless, according to the evidence presented, it is possible that an imbalance in the intestinal microbiota and nitroxidative stress are also implicated in cardiac, ophthalmological, and neurological outcomes, including psychological disorders. However, there are still gaps to explore in regard to the mechanisms and pathways that culminate in such conditions.

The absence of standardized clinical studies and the scarcity of large, prospective studies make it impossible to establish a cause-and-effect link, hindering a clinical intervention in this dimension. In view of this, well-designed clinical studies are necessary to further investigate the influence of nitroxidative stress and dysbiosis, as well as other factors mentioned in this work, such as the current pharmacological therapy used to trigger EIM. The understanding of the intrinsic pathophysiological pathways is urgently required for the development of effective

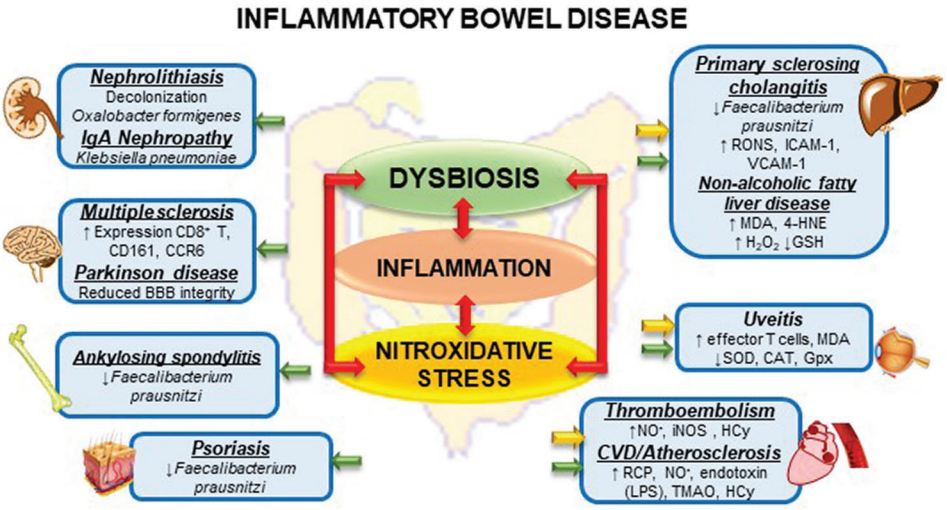

FIGURE 3. Interactions between dysbiosis, inflammation and nitroxidative stress and Extraintestinal Manifestation in inflammatory Bowel Disease. Legend: Green arrows: dysbiosis influence; Yellow arrows: nitroxidative stress influence; BBB: blood-brain barrier; CAT: catalase; CCR6: chemokine receptor 6; CD161: cluster of differentiations 161- lecithin-like receptor; CD8+ T: CD8+ T lymphocytes; CVD: cardiovascular disease; HCy: homocysteine; GPx: glutathione peroxidase; GSH: reduced glutathione; ICAM-1: intercellular adhesion molecule 1; IgA: immunoglobulin A; LPS: lipopolysaccharide; MDA: malondialdehyde; •NO: nitric oxid; RCP: reactive C protein; RONS: reactive oxygen and nitrogen species; SOD: superoxide dismutase; TMAO: N-trimethylamine-N-oxide; VCAM-1: vascular cell adhesion molecule 1; 4-HNE: 4-hydroxynonenal; iNOS: inducible nitric oxide synthase.

preventive and therapeutic strategies aimed at manipulating the intestinal microbiota and controlling inflammation/ nitroxidative stress.

Units: Units of measurement should be used concisely according to the International System of Units (SI). All units should be converted to SI units whenever possible.

Statistical Analysis: Appropriate statistical treatment of the data is essential. When statistical analysis is performed, the name of the statistical test used, the number for each analysis, the comparisons of interest, the alpha level and the actual *p*-value for each test should be provided.

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Funding Statement: This work was supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq–Brazil) [435704/2018-4] and Fundação de Amparo à Pesquisa do Estado de Alagoas (FAPEAL)/ PPSUS/Ministério da Saúde (MS) [60030-000876/2016].

Conflicts of Interest: The authors declare that they have no conflicts of interest to report regarding the present study.

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