The Association of Inflammatory Gut Diseases with Neuroinflammatory and Auditory Disorders

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Abstract

Disorders such as inflammatory bowel disease (IBD) and celiac disease (CeD) result in intestinal hyperpermeability or ‘leaky’ gut. The increased permeability of the intestinal barrier allows microbial metabolites, toxins, and pathogens to infiltrate the bloodstream and extraintestinal tissues, causing systemic inflammation. Despite differences in aetiology and pathophysiology, IBD and CeD share several extraintestinal manifestations such as neuroinflammation, neurological and psychiatric manifestations, and sensorineural hearing loss (SNHL). This narrative review focuses on the association between intestinal hyperpermeability with the brain and inner ear diseases. We postulate that the microbial metabolites and pathogens released from the gut increase the permeability of natural barriers, such as the blood-brain barrier (BBB) and blood-labyrinth barrier (BLB). The barrier breakdown allows the spreading of inflammatory processes to the brain and inner ear, leading to disease.

Keywords: inflammatory bowel disease; celiac disease; gut dysbiosis; microbiota; neuroinflammation; hearing loss

1. Introduction

If an inflammatory response in the gut does not naturally resolve, it may lead to a state of chronic inflammation. This development may result in pathologies such as inflammatory bowel disease (IBD) and celiac disease (CeD) [1]. Evidence shows that these conditions are associated with a pathological shift in gut bacteria [2–4].

An imbalance of intestinal flora results in gut dysbiosis, bringing about changes to the permeability of the intestinal barrier (IB) [5,6]. Consequently, pathogens can then infiltrate the circulation, enabling them to spread to other organ systems, thus resulting in secondary extraintestinal infections, which are often life-threatening [5]. Indeed, both IBD and CeD have been linked with extraintestinal manifestations (EIMs), including neuroinflammatory diseases and sensorineural hearing loss (SNHL) [7–9]. However, despite reported associations between diet and hearing loss, the current literature does not recognise IBD-induced gut dysbiosis as an aetiology of SNHL. Instead, it advocates that SNHL in IBD has an autoimmune background [10].

IBD is an umbrella term used to label two disorders that involve chronic inflammation of the gastrointestinal tract (GIT): Crohn’s disease (CD) and ulcerative colitis (UC) [11]. Interestingly, IBD and sub-clinical manifestations of the inflammatory gut disease have been associated with gut dysbiosis and significantly increased levels of bacterial plasma components such as lipopolysaccharide (LPS) [12–14]. These findings provide evidence for IB hyperpermeability. In both IBD and CeD, bacterial metabolites leak from the intestinal lumen into the bloodstream, where they can potentially infiltrate the brain, producing local neuroinflammatory processes [15,16] and other neurological conditions, including the so-called “celiac brain” [15]. Similarly, we previously postulated that, in gut dysbiosis caused by a high-fat diet (HFD), systemic immune responses might enhance the permeability of the blood-labyrinth barrier (BLB), thus causing cochlear inflammation following the infiltration of inflammatory cells and cytokines and the deposition of immune complexes [17]. However, IBD and CeD do not rely on HFD to trigger increased IB permeability. Instead, these disorders are multifactorial “leaky gut” diseases resulting from immune system malfunctioning and autoimmunity [18–22].

This review entails the existence of a gut-inner ear axis that links IBD and CeD with SNHL. This concept is analogous to the gut-brain axis, linking inflammatory gut diseases with brain disorders.

A broad literature search spanning from 1998 to 2021 was conducted using PubMed, Google Scholar, and Embase medical databases. References from the relevant papers were used. Following Boolean search logic, the main keywords included: “inflammatory bowel disease” OR “Crohn’s disease” OR “ulcerative colitis” OR “celiac disease” OR “coeliac disease” OR “gut dysbiosis”) AND (“hearing loss” OR “sensorineural hearing loss” OR “cochlea” OR “blood-labyrinth barrier” OR “blood-brain barrier” OR inflammation OR lipopolysaccharides). The search results were subsequently examined according to their relevance to this review. Only publications in the English language were included.
2. A “Leaky Gut” does not only Affect the Gut

Since first described by Samuel Wilks in 1859, IBD has been associated with altering the gut microbiome [23, 24]. Even though the aetiology of IBD is not yet fully understood, it has been tightly linked with IB hyperpermeability (“leaky gut”) [25], similar to CeD [2,26]. Consequently, these conditions are often referred to as “leaky gut disorders” [27–29].

A compromised IB can result in systemic pathological processes, such as increased oxidative stress (OS) [30], inflammation [31], and decreased insulin sensitivity, affecting various organs and tissues [32]. Interestingly, it appears that CeD represents a risk factor for IBD and vice versa [33]. Pinto-Sanchez et al. [34] found a 9-fold increase in the risk of developing IBD in CeD patients compared with the control population.

However, CeD and IBD are very different in their aetiology and pathophysiology. Nevertheless, they share similarities, such as gut dysbiosis, increased IB permeability, and inflammatory responses. In addition, both diseases present with similar EIMs, including neuroinflammation, neurodegeneration, and hearing loss. Based on the similarities between CeD and IBD, it is prudent to assume their EIMs might have comparable pathophysiology. Here, we discuss the links between these gut diseases and the potential mechanisms of their EIMs.

2.1 Intestinal Barrier

The intestinal wall coating is a single epithelial layer that connects the host to the external environment, known as the IB. Intestinal epithelial cells (IECs) are responsible for maintaining a functional barrier. The lining of intestinal epithelium exhibits distinctive intercellular connections known as tight junctions (TJs), desmosomes, and adherent junctions. These connections have a role in the selective permeability of gut lining by permitting the passage of nutrients and fluid absorption while preventing the displacement of microbial metabolites and antigens from the gut [35,36]. TJs function as an active structural barrier in the paracellular space [36]. TJ protein composition includes claudins, occludins, and junctional adhesion molecules (JAM) [35]. The cytokines that regulate the immune system, such as tumour necrosis factor-α (TNF-α), interleukins (IL), interferon-γ (IFN-γ), and the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, fulfill a role in regulating TJs’ function [37].

The lamina propria beneath the IECs contains an array of immune cells, including T-cells, B-cells, macrophages, and dendritic cells, that contribute to the maintenance of tissue homeostasis [38]. In addition, mucin, a highly glycosylated protein that coats the gut lumen, contributes to tissue defence by trapping pathogens and preventing microbial colonisation [39].

2.2 The Immune System in the Gut

The mammalian immune system comprises two integrated subsystems: the innate and adaptive (Fig. 1). The innate immune system is the first to respond to pathogens and is evolutionarily older. If the pathogenic challenge persists, the adaptive immune system will engage with the pathogen with specificity and memory [40–42]. The innate immune system in the gut includes several physiological barriers that protect the body from the insurgence of pathogens. These barriers include mucus, TJs, IECs, antimicrobial enzymes, pattern recognition receptors, transforming growth factor-β (TGF-β) releasing stromal cells, and mesenchymal cells, to name a few [40,43,44]. Pattern recognition receptors, such as Toll-like receptors (TLRs) or Nucleotide-binding Oligomerization Domain-like receptors (NODs), recognise pathogens and their metabolites such as LPS via pathogen associated-molecular patterns (PAMPs) [45]. These receptors also recognise reactive oxygen species (ROS) produced by microbiota [46]. Activation of TLRs can lead to stimulation of cytoplasmic protein NF-κB, a ubiquitous transcription factor involved in inflammatory and immune responses and the regulation of the expression of many other genes related to cell survival, proliferation, and differentiation [47,48]. Activation of the NF-κB pathway triggers a pro-inflammatory response by upregulating the release of pro-inflammatory mediators such as adhesion molecules and multiple cytokines (TNF-α, IL-1, IL-6 and IL-8) to neutralise the pathogen [37,40,49]. The immune system development and functioning are conditioned by the microbiome that colonises the intestinal lumen and prevents infections [50]. However, oral antibiotics, high-fat or high-sugar diet can negatively affect the microbibial landscape, promoting IB’ hyperpermeability [50]. Experimental studies have shown that introducing a healthy microbiome in germ-free (GF) animals can reverse some immunological abnormalities associated with IBD [51] and CeD [52–54]. For example, Cinova et al. [54] have demonstrated that the intestinal tissue of GF rats, when exposed to enterobacteria, bifidobacteria and/or CeD-triggering agents (gliadin and IFN-γ), reacts differently to each of these elements. Intestinal tissue in the presence of gliadin alone or with IFN-γ, E. Coli CBL2 or Shigella CBDB8 had altered mucin production and presented with impaired TJs, allowing the penetration of gliadin deeper into the tissue, increasing IB permeability. However, a spontaneous addition of B. bifidum IATA-ES2 increased the number of goblet cells and production of chemotactic factors and inhibitors of metalloproteinases, which play a role in mucosal protection, thus decreasing IB permeability [54].

2.3 Critical Time for the Development of Gut Health: Early Childhood and Microbiome

In the first 2–3 years of life, the microbial landscape of the gut rapidly changes, by the end reaching similar functionality to the one seen in adults [55]. During this period
of weaning from breastmilk to solid food, the changing microbiota leads to “weaning rejection” of the immune system. At this point, several studies have observed shifts in the global gene expression in the intestines, including genes encoding defensins (a major family of host defence peptides expressed predominantly in neutrophils and epithelial cells), chemokine receptors, and mucins [56]. At the weaning stage, commensal microbiota induces gene expression of the pro-inflammatory cytokines (TNF-α, IL-1β, and IFN-γ) in rodents [56,57]. Antibiotic administration in early childhood may impact the microbiome for life via so-called pathological imprinting [56,58]. In South Korea, children up to two years of age receive an average of 3.4 courses of antibiotics per year [59]. In New Zealand, clinical studies demonstrated that 94% of children received at least one course of antibiotics by the age of five, with an average of eight courses by the same age [60]. Several studies have identified multiple early childhood factors that are directly associated with the risk of developing IBD later in life, such as mode of delivery [61], feeding type [62], childhood hygiene [63], and antibiotic use [64]. Antibiotics in infancy also increase the chance of developing obesity [65] and CeD [66], both linked with gut dysbiosis.

2.4 Inflammatory Bowel Disease (IBD)

IBD denotes diseases that involve chronic inflammation within the GIT, with two apparent phenotypes [67]. In the first phenotype (CD), the inflammation can develop in any part of the GIT, often characterised by patchy and transmural damage through the IB. The second phenotype (UC) involves confluent inflammation in the colonic mucosa [68]. IBD impairment leads to a leaky gut in both cases [11]. IBD is considered by many as having an autoimmune origin [69]; however, some authors have suggested a novel, autoinflammatory background [70].

IBD’s aetiology is multifactorial, complex, and still not fully understood. It combines genetic, environmental, and microbial factors, which influence the immune system; however, none of these factors can cause disease alone [68]. The genetic factors constitute only a relatively small proportion of IBD cases [68,71]. Therefore, if the host carries genetic risk variants, they must be exposed to environmental or microbial challenges to develop IBD [68]. Rapidly increasing IBD incidence in the modern world indicates the significance of diet, lifestyle, and a changing environment [72].

The increased incidence of IBD parallels the “westernisation” of countries [73,74]. IBD affects around 3.1 million people in the USA alone, with cases increasing worldwide. Between 2003 and 2013, the number of new IBD cases in NZ increased by an average of 8.1% per year [75]. The incidence of IBD in NZ among adults and children is considered very high [76–78], with NZ and Australia among the top five countries for incidence of CD [78]. In Asia, the incidence rate for UC has risen by 60% since 1988 and 70% for CD [79]. The number of new IBD cases in South Korea is one of the highest globally and rapidly increases [80].
2.5 Celiac Disease

Another inflammatory gut disorder that results in a “leaky gut” is celiac disease (CeD). It is an autoimmune condition that results from an immune response to gluten in genetically predisposed adults and children [81]. CeD affects approximately 1% of the global population [82]. Over the past 50 years, CeD prevalence has increased 4-fold [83].

The severity of the disease might be influenced by genetic and environmental factors and immune imbalance [84]. Like IBD, genetic background on its own is insufficient to develop the disorder; gluten is a crucial contributor [85]. However, gut dysbiosis may trigger pathogenic pathways leading to CeD progression [81]. In response to the build-up of gluten fragments (such as gliadin) in the intestines, the adaptive and innate immune responses lead to villous atrophy, crypt hyperplasia, and IB hyperpermeability [86].

3. Pathogenesis of IBD and Celiac Disease - Where is the Common Ground?

Several established factors can alter homeostasis between gut microbiota and the immune system; however, the multifactorial aetiology of IBD is still not fully understood [40].

IBD and CeD have common immunological, genetic, and environmental factors contributing to their manifestations. Genome-wide association studies (GWAS) have shown that CeD and CD share genetic risk loci [87]. Moreover, CeD and IBD share elements of aetiology such as increased IB permeability [88], compromised regulatory T cell (Treg) function [89,90], upregulation of pro-inflammatory cytokines (IL-13, IL-17, IL-21 and IFN-γ) [1,91,92] and a paradigm shift in the microbiome [93,94].

In a healthy individual, commensal microbiota, IECs, and immune cells function in concinnity. When a soluble antigen enters the GIT, local immunity is suppressed due to immune tolerance. However, many factors can disturb this homeostasis between pro-, and anti-inflammatory mediators, favouring pro-inflammatory responses in susceptible individuals. Prolonged activation of the innate immune system leads to a state of unresolved, chronic inflammation, such as IBD. IB hyperpermeability in IBD allows harmful molecules (such as LPS, CpG motifs, pathogens, luminal antigens) to infiltrate the bloodstream, causing the release of pro-inflammatory cytokines, which can alter homeostasis in distant organs [59,72,95]. In CD, increased IB permeability has been observed prior to clinical relapse, suggesting its role in disease exacerbation [96,97]. However, it is still unclear if the immune activation in IBD results from gut dysbiosis or loss of immune tolerance in the gut’s immune system [40].

The prevalence of genetic factors in IBD is relatively low, making environmental factors a key player. Interestingly, the incidence of IBD is higher in urban than rural areas [98,99], and there is a clear association between diet and incidence [73,100–104]. Factors that impact gut microbiota, such as early exposure to animals, having many siblings [105,106], natural mode of delivery [61], and breastfeeding [107], effectively decrease the chances of developing IBD in contrast to the mode of delivery via C-section [61,74], excessive paediatric hygiene [63] and early-life antibiotic therapies [64,108,109]. Furthermore, treatments that typically affect microbiota, such as faecal diversion and antibiotic therapy, are often used for IBD management [110–115]. However, an extensive nested case-control analysis of the population-based University of Manitoba Inflammatory Bowel Disease Epidemiologic Database has demonstrated that antibiotic use may be a risk factor for developing IBD, as a significant number of patients included in this study had been prescribed antibiotics 2–5 years prior to being diagnosed with IBD [108]. Moreover, a random-effects meta-analysis demonstrated that antibiotic use increases the risk of CD development [116]. Interestingly, the lesions characteristic for IBD coincide with higher concentrations of commensal bacteria [117,118], and IBD patients present higher yields of antibodies against commensal bacteria than healthy individuals [119].

Over the years, the increase in IBD incidence has been associated with the increased consumption of the western diet, which is higher in fats and additives, but with a decreased amount of fruits, vegetables, and fibre [59,72,120–122]. Even though regional differences of the western diet have been observed [72,123,124], dietary factors associated with that diet commonly induce gut dysbiosis in obesity and metabolic syndrome [122,125–128]. Moreover, many pro-inflammatory cytokines common for CeD and IBD (e.g., TNF-α, IFN-γ, IL-6, IL-17) are altered by a high-fat diet [129]. However, there is a lack of studies on the specific dietary components (other than gluten) influencing IBD development. Other environmental risk factors may also contribute to increasing IBD prevalence. Modern agricultural practices have been proposed as contributing factors for gastrointestinal disorders [130]. Crop desiccation using glyphosate has been attributed to carcinogenic and cytotoxic effects on the body [131]. Moreover, it has been suggested that glyphosate negatively affects gut microbiota and is especially harmful to commensal bacteria [130]. Ingestion of glyphosate has been associated with an impact on mental health via altering the microbiome landscape [130].

The other established aspect of IBD aetiology is a failure of the immune regulatory control in the active phases of the disease [132]. The increased population of T-cells and increased expression of pro-inflammatory cytokines, including TNF-α, IL-6, IFN-γ (15), promote chronic inflammation instead of resolution and recovery processes [40]. Inflammatory processes in the epithelial gut layer facilitate microbiome infiltration of the deeper gut tissue and elicit a local immune response [43]. Gut dysbiosis and IB hyperpermeability are thus significant factors causing activation of the immune system [40]. Immune system acti-
IB permeability, enabling gluten peptides to infiltrate lamina propria and nearby circulation, where cell adhesion molecules (selectins and integrins) on endothelial cells facilitate the homing of effector cells [40]. Macrophages activate the adaptive immune system locally, whereas dendritic cells migrate to lymphoid tissue and activate T helper (Th1) cells and cytotoxic T cells and allow for maturation of regulatory T-cells. IBD immunopathology can thus be defined as the dysfunctional immune response and activation of either Th1 or Th2 cells in the mucosa, particularly in CD [133]. Cytokines such as IL-1, IL-6, IL-23, and transforming growth factor β (TGF-β) can activate Th17 pathways responsible for the secretion of the pro-inflammatory IL-17 family of cytokines that recruit Treg cells and neutrophils contributing to UC pathogenesis [134–136]. IL-23 may play an essential role in controlling the Th1/Th17 balance in both UC and CD [135].

Interestingly, GF animals tend to have impaired Th17 cell development, decreased IL-17 cytokine production in the colon [137], and impaired Treg cells [138], suggesting an essential role for microbiota in IBD immunopathology. GF animals also have an altered mucus layer [139], further implicating gut microbiota in IBD pathophysiology. While healthy subjects can generally tolerate autologous microbiome, in some cases, the breakdown of this symbiosis is associated with chronic intestinal inflammation [40,140,141]. It was proposed that gut dysbiosis negatively impacts the interaction between the immune response and microbiome, leading to an overactivation of the immune system [40].

In comparison, dietary gluten in CeD stimulates innate and adaptive immune systems in a susceptible individual, increasing the production of IL-15, which plays a major role in developing inflammatory and protective immune responses to microbial invaders and parasites. IL-15 also causes epithelial cell death in the gut and increases IB permeability, enabling gluten peptides to infiltrate lamina propria [142,143]. At the same time, transglutaminase type 2 stimulates deamination of gluten-derived peptides producing epitopes that bind to HLA-DQ2/DQ8 heterodimers on antigen-presenting cells, thus provoking a T-cell response [144,145]. Moreover, glialin (a proline component of gluten) accelerates the disassembly of intracellular junctional proteins via epidermal growth factor receptor (EGFR) pathway activation [3,146,147]. As a consequence of uncontrolled antigen trafficking from the lumen through the IB, immunoregulatory deficits are further escalated. It was suggested that the onset of inflammation with a secondary production of pro-inflammatory cytokines (TNF-α, IFN-γ) increases the IB permeability by activating the myosin light chain kinase (MLCK) pathway [146,148,149]. Activation of this pathway may lead to the onset of chronic inflammatory disease depending on host genetic predisposition [146].

Interestingly, CeD and IBD share genetic backgrounds associated with the innate immune response against pathogens and pro-inflammatory activation [133]. However, the Th17 response pathways and autophagy (natural cell degradation that removes unnecessary or dysfunctional components through a lysosome mechanism) are only involved in IBD. Autophagy also plays a role in recognising and eliminating pathogens [133,150,151].

3.1 Gut Dysbiosis in IBD and Celiac Disease

It is now well established that CeD and IBD need external, environmental stimuli to activate the immune system. Known environmental triggers include diet [152,153], smoking, microorganisms, hygiene, early antibiotic exposure, and urban living, to mention a few [154]. Not surprisingly, the initial trigger is different for each disorder [133].

The bacterial species Bacteroides and Firmicutes make up 90% of eubiotic human gut microbiota [155], where along with other phyla, they orchestrate pro-and anti-inflammatory responses [156]. For example, in a healthy microbiome, Bacteroides engage in the recruitment of cytotoxic T cells to target immune cells (microbial antigen-loaded, antigen-presenting cells) that can trigger IBD, thus preventing IBD development [157]. Gut dysbiosis in CD is characterised by a decrease in Bacteroides and Firmicutes and an increase in Gammaproteobacteria and Actinobacteria, which leads to disease progression [71]. Interestingly, enterotoxigenic Bacteroides fragilis has been strongly associated with IBD and colorectal cancer [158–160]. In addition, 33% of IBD patients have an increased quantity of E. coli in the gut [161]. These strains of bacteria can cross the mucosal barrier, disturbing the epithelial lining [4,71], thus allowing bacterial metabolites and pathogens to translocate into the systemic circulation [4,25,39,156,162]. Gram-negative bacterial metabolites such as LPS can also induce colitis and local inflammation in the intestines [163].

Gut dysbiosis in CeD is characterised by an increase of Gram-negative and a decrease of Gram-positive bacteria [2]. The increased presence of Bacteroides fragilis has been found in celiac patients and was associated with IB hyperpermeability and CeD pathogenesis [164]. Intriguingly, celiac patients presenting with EIM and those with typical GIT symptoms have different microbiome landscapes [165]. Wacklin et al. [165] demonstrated that CeD patients with only GIT symptoms had lower microbial diversity dominated by Proteobacteria compared to those with EIMs. The latter had a high abundance of Firmicutes [165].

CeD facilitates barrier breaches in the immune-privileged organs (brain, cochlea); however, the mechanism is unknown [16,166,167]. CeD can also increase the risk of developing sepsis due to the increased mucosal permeability and altered composition of the intestinal glycoalyx (the layer of gut epithelial cells considered the primary site for adhesion of commensal bacteria) [167].

![Image](Image.png)
GUT DYSBIOSIS: alteration of the gut microbiome can result in an enhanced innate immune response, infiltration of pathogens and bacterial metabolites into the circulation, and systemic inflammation.

Fig. 2. Extraintestinal manifestations of gut dysbiosis. Gut dysbiosis contributes to intestinal tissue damage, leading to intestinal barrier hyperpermeability (leaky gut). The pathogens and their metabolites infiltrate the bloodstream, leading to a spread of inflammation, which can reach remote organs and thus cause extraintestinal manifestations.

3.2 Extraintestinal Manifestations (EIMs)

The EIMs of IBD are widespread and include the brain and the inner ear [168,169] (Fig. 2). The IBD-related EIMs occur in approximately 50% of patients [170]. The therapy of IBD and associated EIMs is primarily concerned with the dietary modifications and systemic anti-bacterial and immunosuppressive agents (antibiotics, sulfasalazine, corticosteroids, azathioprine, and dapsone) [171,172]. IBD likely results in low-grade systemic inflammatory responses, which can spill over to the extraintestinal organs. Although the cause of EIMs is unknown, they have been linked to IB hyperpermeability [25]. Both IBD [173] and CeD [174] have been associated with gut dysbiosis and significantly increased levels of bacterial plasma components such as LPS [12–14]. Remarkably, after eliminating gluten from the diet in celiac patients, LPS levels decrease [174], and the IB regains its integrity. Therefore, it can be postulated that, as the pathogens infiltrate the circulation, they breach the natural barriers of immune-privileged organs, allowing pathogens in and causing localised inflammatory reactions.

Despite the general hypothesis that EIMs of IBD are related to immune reactions [175–179], their pathogenesis is not fully understood. There is increasing evidence that IBD results from a malfunction of the immune system and autoimmunity. Being diagnosed with IBD also increases the likelihood of developing other autoimmune diseases [180]. Due to shared epitopes, the “leaky intestine” of the damaged GIT mucosa may trigger immune responses at various extraintestinal sites [175,178]. Resultant from IB hyperpermeability, commensal bacteria metabolites and pathogens in the bloodstream may trigger autoimmune reactions due to the similarity between the bacterial and host epitopes [169,175,178].

Not all IBD and CeD patients develop EIMs. Genetic factors play a significant role in presenting IBD EIMs [181], with a concordance rate of 70% of parent-child pairs and 84% of sibling pairs [182]. Studies investigating the relationships between EIMs and major histocompatibility complex loci have shown that UC and CD do not share HLA genotypes [181,183,184]. CD patients are more likely to express HLA-A2, HLA-DR1, and HLA-DQw5 genotypes, whereas UC patients tend to express HLA-DR103, -B27, and -B58 genotypes [181,183]. It appears that the specific HLA genotypes are related to different EIMs [181,184,185]. For example, HLA-DR3 is associated with the increased risk of primary sclerosing cholangitis in UC, HLA-B27 and HLA-B58 are associated with EIMs related to skin and eyes, and HLA-B27 to ankylosing spondylitis in 90% of IBD patients [183,184,186].
co-localizes with amyloid plaques, neurons, and oligodendrocytes in the AD brain and may cause neuronal injury via TLR4-Cd14/Tlr2 pathways.

It appears that CeD, IBD, and mental disorders (autism, schizophrenia) share mechanisms involving microbial-derived metabolites that can cause neuroinflammation and damage in different brain regions [16,215–217]. The process starts with gut dysbiosis and leads to neurodegeneration and cognitive deficits via inflammatory pathways [16,214–218]. It has been established that gut dysbiosis induced by ageing, diet, obesity, alcohol abuse, and antibiotics could underpin the dysfunctional gut-brain axis [189], leading to inflammatory processes in the brain. Early antibiotic use is also a risk factor in developing autism and other neurological conditions [219].

Accordingly, the expression of the peroxisome proliferator-activated receptor-gamma (PPARγ) gene is significantly reduced in CeD [95,220–222] and UC [223]. PPARγ is an essential anti-inflammatory [224] and probiotic gene [225]. PPARγ downregulation is associated with a shift in the microbiome, causing expansion of Enterobacteriaceae (phylum Proteobacteria) and decrease in otherwise abundant obligate anaerobic bacteria [225]. In macaque monkeys with CeD, downregulation of intestinal TJ proteins zona occludens-1 (ZO1) and claudin-1 with reduced or even absent occludin was observed [226,227]. TJ proteins maintain the integrity of the blood-brain barrier [227] and blood-labyrinth barrier [228]. These studies suggest that the downregulation of the PPARγ gene and TJ proteins may promote gut dysbiosis, intestinal inflammation, and EIMs associated with neurodegeneration [227]. Furthermore, Mohan et al. [227] have suggested that LPS can cross the BBB, activate microglia, and initiate neurodegeneration via micro-RNA (miRNA) mechanisms targeting genes associated with the innate immune system and TJs.

Micro-RNAs are small RNA molecules (~20–23 nucleotide long), which regulate gene expression post-transcription by binding to homologous sequences on the 3’ untranslated regions (UTRs; homologous base pairings between miRNA seed nucleotides 2 to 7 and the 3’ UTR) [227]. Micro-RNAs control most cellular processes such as cell proliferation, differentiation, apoptosis, cell signalling, immune and inflammatory responses [227]. Biopsies of intestinal tissue of celiac patients showed downregulation of miRNAs: miR-192-5p, miR-31-5p, miR-338-3p, and miR-197 and upregulation of chemokine C-X-C motif ligand 2 (CXC2L2) and nucleotide oligomerisation domain-2 (NOD2) at mRNA and protein expression levels [229]. These miRNAs play a significant role in innate immune responses. For example, miR-192-5p, a critical player in intestinal homeostasis, is downregulated in UC [230] and CeD [229,231]. Moreover, miR-449a, responsible for negative regulation of Notch receptor 1 (Notch1) and krüppel like factor 4 (KLF4) that regulate goblet cell proliferation and differentiation, are upregulated in pediatric CeD
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| 2005 | Akbayir et al. [233]            | Sensorineural hearing loss in patients with inflammatory bowel disease: a subclinical extraintestinal manifestation | Clinical study involving 39 patients with IBD (21 Crohn’s disease, 18 ulcerative colitis) and 25 healthy age- and sex-matched controls. To assess auditory function, otoscopy, tympanometry, and pure tone audiometry were carried out. | o  Il patients and control subjects had normal otoscopy findings, and tympanometry was unremarkable, excluding middle ear disease and conductive hearing loss.  
   o  The average hearing thresholds were raised significantly in the IBD group at higher frequencies (2, 4, and 8 kHz).  
   o  There is a significant threshold increase for the UC group at frequencies 2, 4, and 8 kHz and for the CD group only at 4 kHz.  
   o  A trend of SNHL worsening with the patient age and extent of ulcerative colitis was observed.  
   o  No significant correlation between SNHL and sex, involvement site in GI tract, medication history for IBD, and coexistence of other EIMs. | “(…) it was demonstrated that a subclinical SNHL may be associated with UC and somewhat with CD, affecting mainly the high frequencies. In light of this finding, it may be advisable to investigate labyrinth functions as well as other extraintestinal manifestations in patients with IBD.” |
| 2009 | Karmody et al. [240]            | Sensorineural hearing loss in patients with inflammatory bowel disease | A clinical study was conducted over 11 years. Medical and audiometric documentation of 38 patients with a diagnosis of IBD (ulcerative colitis and Crohn’s disease) was reviewed. | O  Of 38 patients with a history of IBD, 58% (n = 22) recorded SNHL.  
    O  19 patients with SNHL had no other identifiable aetiology for their inner ear dysfunction.  
    O  14 patients with SNHL had been diagnosed with UC, and 5 had CD.  
    O  16 had bilateral SNHL, and 3 patients had unilateral SNHL.  
    O  70% developed hearing loss before the age of 50 years.  
    O  Only one SNHL patient had a lasting response to medical treatment. | “(…) this study demonstrates a correlation between SNHL and IBD, but a larger controlled investigation is needed. If IBD is an autoimmune disorder, the inner ear could be affected by the underlying systemic immune dysfunction. Unravelling the pathophysiology of IBD should explain the mechanism of its association with dysfunction of the inner ear.” |
| 2014 | Wengrover et al. [241]          | Hearing loss in patients with inflammatory bowel disease             | A prospective blinded comparative study was conducted over 3 years.                                                                 | O  21% (n = 16) of the IBD patients complained of hearing loss since the first IBD diagnosis; 13% had hearing deficits.  
    O  Audiometric examination showed hearing loss (mild to severe) in 23 (30%) of the IBD patients, matched with 3 (10%) of the controls. | “Sensorineural hearing loss may be another EIM of IBD. It is found in 30% of IBD patients and in up to 43% of patients with other EIMs. Early hearing evaluation should be recommended to IBD patients who have other EIMs.” |
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| 2016 | Wengrower et al. [9]     | Hearing loss in patients with inflammatory bowel disease             | A prospective blinded comparative study was conducted over three years. 76 IBD patients and 29 controls underwent a complete otorhinolaryngological examination and audiometry test.                                      | o  Hearing loss (mild to severe) was found in 29 (38%) of the IBD patients, and 4 (14%) of the control group.  
  o  Moderate to severe hearing loss was found in 7/33 (21%) in the EIM-positive group compared to 4/43 (9%) in the EIM-negative group.  
  o  Out of 11 patients over 40 with other EIMs, all (100%) had hearing loss compared to 8/12 (66%) of patients over 40 without other EIMs.       | “Hearing loss may be another EIM of IBD. It is found in 38% of IBD patients and up to 52% of patients with other EIMs; hearing loss increases over the age of 40. Early hearing evaluation should be recommended to these high-risk IBD patients.” |
| 2020 | Polat et al. [242]       | Assessment of hearing function in children with inflammatory bowel disease | The clinical study involved 32 pediatric patients with IBD and 31 age-matched controls. Examinations involved detailed ENT examination, pure tone audiometry (PTA), high-frequency audiometry (HFA), signal-to-noise ratio (SNR) and distortion product (DP) otoacoustic emissions testing. | o  No differences in age and gender and PTA thresholds at low frequencies between controls and children with IBD.  
  o  The mean PTA responses at 1,000; 8,000; 10,000; 12,500; 16,000; SNR1400; SNR2000; SNR2800; and SNR4000Hz of the IBD group were significantly higher than those of the controls (p < 0.05 for all). | “(…) SNHL in pediatric patients with IBD was seen at the high frequencies. It could represent a potential early indicator of SNHL in this population. We recommend hearing function tests twice a year for early diagnosis. HFA and DPOAE can be used safely in this population for monitoring the hearing loss.” |
| 2021 | Yozgat et al. [243]      | Ulcerative colitis may be a risk factor for sensorineural hearing loss | The clinical study involved 53 patients with IBD and 20 matched controls within period of 4 months. Examinations involved tympanometry, otoscopy and audiometry.                                      | o  No significant difference in terms of gender and age between the IBD and control groups.  
  o  No significant difference in air and bone conduction in both ears in patients with CD.  
  o  A significant difference in both air and bone conduction in ulcerative colitis (p = 0.0001 in the left ear, p = 0.004 in the right ear).  
  o  SNHL was detected in 45.2% (n = 14) of UC patients and 13.6% (n = 3) of CD patients using audiometry.  
  o  Three UC patients had moderate, one had moderate to severe, and one had profound hearing loss.                       | “SNHL has been detected in a significant number of UC patients. Also, the hearing function deteriorated significantly as the age of the patients and the duration of the disease increases. It should be recommended to evaluate UC patients over 40 years of age and with the long-term disease for SNHL.” |
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<td>2011</td>
<td>Hizli et al.</td>
<td>Sensoryneural hearing loss in pediatric celiac patients</td>
<td>A sample of 32 biopsies and serologically proven newly diagnosed pediatric celiac patients and matched healthy subjects (control group) were involved in this study. Pure-tone audiometry at frequencies 250–8000 Hz was performed in all subjects. Slight/mild SNHL was defined as a loss of sound detection within the 16–40 dB range. The mean age of the patient and control group was 11.9 and 11.3, respectively (p &gt; 0.05).</td>
<td>SNHL was found in 40.6% (n = 13) celiac pediatric patients (6 unilateral and 7 bilateral), and 3.1% (n = 1) control group.</td>
<td>“(...) a higher prevalence of SNHL in pediatric celiac patients than in controls, suggesting an association between CeD and SNHL. The findings of this study suggest that hearing impairment should be investigated in newly diagnosed pediatric CeD patients. Further longitudinal investigations on a larger sample size will be necessary to confirm the present data and to search the immunological processes which could be the basis of the association between CD and SNHL.”</td>
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<td>2011</td>
<td>Karabulut et al.</td>
<td>Audiological findings in celiac disease</td>
<td>41 pediatric celiac patients and 31 controls were included in the study. Both groups were evaluated with audiometry, tympanometry, transiently evoked otoacoustic emission (TEOAE), distortion product otoacoustic emission (DPOAE), and contralateral suppression of the TEOAE.</td>
<td>The average PTA thresholds at 250 Hz of the CeD patients were significantly higher (p &lt; 0.05) in CeD compared to the control group.</td>
<td>“(...)CeD seems to have an important impact on the auditory system and results in an elevation of the PTA thresholds at 250 Hz and a decrease in the amplitudes of DPOAE and linear TEOAE at 1 kHz in children.”</td>
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<td>2012</td>
<td>Solmaz et al.</td>
<td>Celiac disease and sensoryneural hearing loss in children</td>
<td>25 pediatric patients with biopsy-proven celiac disease were diagnosed in the pediatric gastroenterology department, and 25 healthy control subjects were included in the study. All subjects underwent tympanometry and pure tone audiometry at frequencies 250–8000 Hz.</td>
<td>Tympanometry showed normal peak compliance, gradient, peak pressure, ear canal volume, and acoustic reflexes in the patients and controls.</td>
<td>Sensorineural hearing loss (SNHL) and celiac disease (CeD) may be observed coincidentally. Children with clinical signs of hearing deficiency of unknown aetiology should be assessed for CeD.</td>
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| 2012 | Leggio *et al.*    | *Coeliac disease and hearing loss: Preliminary data on a new possible association* | Twenty-four adult celiac patients and 24 healthy subjects matched for gender, age, smoking and drinking habits were enrolled in the study. Among the celiac patients, 6 were newly diagnosed, and 18 patients were on a gluten-free diet for at least one year. | • A hearing loss was found in 47.1% (n = 10) of celiac patients and 9.1% (n = 2) controls.  
• All celiac patients with hearing impairment developed SNHL.  
• The prevalence of SNHL was not significantly different between untreated (33.3%) and treated (44.4%) celiac patients. | “Despite the low number of subjects evaluated, the present study showed a higher prevalence of hearing loss in celiac patients than in healthy controls, suggesting an association between CeD and hearing loss. Immunological processes such as ear-specific and non-specific autoantibodies and vasculitis could be the basis of this association. Further longitudinal investigations on a larger sample size will be necessary to confirm the present data.” |
| 2015 | Urganci *et al.*    | *Sensorineural hearing loss in pediatric patients with celiac disease* | Otoscopy, tympanometry and pure tone audiometry were performed in 44 pediatric patients with celiac disease and 20 matched controls. | • SNHL was detected in only 6.8% (n = 3) patients within 1–3 years after diagnosing CeD.  
• None of the patients or controls had symptoms such as hearing loss, tinnitus or balance disturbance.  
• All group members had normal otoscopy and tympanometry, excluding middle ear disease and conductive hearing loss. Pure tone audiometry showed no abnormality. | “(...) subclinical sensorineural hearing loss was demonstrated in adult patients with CeD; therefore, we recommend to perform audiometric examinations in pediatric patients for recognising hearing loss early during the course of the disease.” |
| 2015 | Sahin *et al.*      | *Evaluation of hearing loss in pediatric celiac patients*            | The study included 110 pediatric patients with biopsy-confirmed celiac disease and 41 matched controls. The hearing was evaluated using tympanometry and pure tone audiometry (250–8000 Hz frequency). | • Audiometric bone conduction thresholds were significantly ($p < 0.05$) different between the celiac patients and the controls.  
• There were no significant differences in pure-tone averages for air conduction ($p > 0.05$). | “These results indicate that subclinical hearing loss may be present in children with CeD, which could precede more serious hearing impairments at older ages and later stages of the disease. Hearing screenings should be recommended for children with CeD in order to prevent the potentially unfavourable effects of hearing loss on the emotional, behavioural, cognitive, and sensorimotor development of these patients.” |
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<td>2019</td>
<td>Yazici et al. [246]</td>
<td>Does celiac disease cause autoimmune sensorineural hearing loss?</td>
<td>The prospective study included 103 adult celiac patients and 79 healthy controls between 2012 and 2018. Celiac patients were divided into two groups: remission or active, according to their gluten-free diet duration and serum levels of anti-tissue transglutaminase. They underwent pure-tone audiometry after detailed ear examination.</td>
<td>· When the results for celiac patients were analysed according to the duration of disease (≤36 months and &gt;36 months), a significant difference in bone conduction thresholds ($p &lt; 0.05$) was observed, with substantial increments at the later stages of the disease. However, this difference was insufficient to define clinical hearing loss, as the pure tone average thresholds remained below 20 dB. · Only 3.88% ($n = 4$) of celiac patients showed SNHL. · There was no statistically significant difference between the hearing levels of the celiac patients and the control group in air and bone conduction measurements. · The PTA thresholds comparing the remission and active celiac patients did not differ in air and bone conduction frequencies.</td>
<td>“In this study with a higher number of CeD patients when compared with the previous studies, it has been shown that CeD does not appear to cause autoimmune SNHL. In addition, patients in the remission of CeD did not show different PTA thresholds than the active cases.”</td>
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<td>2020</td>
<td>Yaprak et al. [239]</td>
<td>Hearing evaluation with ABR in pediatric patients with celiac disease</td>
<td>38 pediatric celiac patients were included in the study. The patients had confirmed diagnosis of Celiac disease through duodenal biopsies and transglutaminase antibody. The control group consisted of 18 children aged 3 to 17 years old who were all admitted to the pediatric gastroenterology department due to complaints of constipation and transglutaminase Ab. All children underwent Auditory-Brain-Stem-Evoked Responses (ABR).</td>
<td>· The results of the ABR examination did not show any difference between the patient group and control group as regards the latency of the waves I, III, V. · No difference was observed between the two groups in the interpeak latencies of the ABR waves I–III, I–V and III–V. None of the patients was observed to have clinical hearing loss.</td>
<td>“The exact pathogenesis of neurological damage observed in CeD is still unknown. Humoral immune mechanisms are the most frequently attributed cause. Although no significant difference was found in ABR responses between the study group and healthy control group, there is a need for further research on this subject.”</td>
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patients, thus explaining the reduced amount of goblet cells in CeD [232]. Another study demonstrated elevated miR-204 in rhesus macaques with CeD [226]. This miRNA directly targets the intestinal TJ protein claudin-1, reducing its expression [227]. The loss of TJ proteins can compromise the BBB, leading to the translocation of intestinal LPS to the brain, activation of microglia, and neuroinflammation [227].

3.4 Hearing Loss as an Extraintestinal Manifestation of CeD and IBD

EIMs of IBD and CeD include SNHL (Tables 1 and 2) [9,233–246]. Between 40–60% of pediatric CeD patients demonstrate at least unilateral SNHL [234,236,237]. Therefore, it was suggested that children presenting with idiopathic hearing loss should also be checked for CeD [236]. Correspondingly, if the child is diagnosed with CeD, the audiometric examination is warranted to identify early hearing deficits [237]. However, the pathophysiology of CeD-induced SNHL is still enigmatic. Several hypotheses have been put forward, including vasculitis, malnutrition, labyrinth infiltration by activated lymphocytes, anti-neuronal antibodies, and deposition of immune complexes [245]. The endolymphatic sac contains and recirculates IL-2-producing immunocompetent cells, which regulate immune responses [245]. IL-2 activation in endothelial cells of the spiral modiolar vein stimulates intercellular adhesion molecule-1 (ICAM-1) to attract more leukocytes to the target tissue and initiate immune and inflammatory reactions [245,247,248]. The autoimmune aetiology of IBD-induced SNHL was also proposed [10], even though the presentation of SNHL in IBD patients is more consistent with chronic inflammation, similar to the neuroinflammatory processes in the brain.

4. Blood-brain and Blood-labyrinth Barrier and Gut Dysbiosis

4.1 Hyperpermeability of the Blood-brain Barrier in CeD and IBD

The blood-brain barrier (BBB) is a critical anatomical and physiological structure protecting neural tissue. The BBB is formed by the blood vessels of the central nervous system (CNS). In the CNS, the blood vessels are not permissive, restricting the infiltration of pathogens into neural tissue [249–251]. The integrity of the BBB can be affected by multiple mechanisms, which, in turn, allow pathogens and inflammatory cells to infiltrate neural tissues [249,252]. This can result in neuroinflammatory disorders, such as multiple sclerosis [253,254], acute disseminated encephalomyelitis [255], or transverse myelitis [256]. Neuroinflammation can also be triggered by an injury, exposure to a neurotoxin, neurodegenerative disease, or ageing [257–259].

The leaky gut and resulting systemic inflammation can negatively impact the integrity of the BBB. As a result, the BBB’s ability to selectively restrict the passage of pathogens and neurotoxic agents to the brain is diminished. Inflammation and hypoxia can be classified as primary culprits [16], often by weakening the TJ of the BBB [16]. Han et al. [260] demonstrated that dextran sodium sulfate (DSS)-induced colitis in mice could provoke systemic inflammation leading to cortical brain inflammation via up-regulation of inflammatory cytokines in the serum. Other studies demonstrated that colitis induced by trinitrobenzene sulphonic acid (TNBS), which affects the IB permeability, can also disturb the integrity of the BBB [252,261]. In monkeys, the alteration of the gut microbiome by antibiotics can also increase BBB permeability [262] due to gut dysbiosis [260,263]. The permeability of the BBB can be increased by pro-inflammatory cytokines such as IL-1β, which can affect the BBB by breaking down and translocating TJ proteins [264].

Interestingly, germ-free (GF) mice show increased resistance to neuroinflammatory diseases [265]. However, Branieste et al. [204] reported an increase in the permeability of the BBB in GF mice. A possible explanation is that the normal gut microbiota also regulates the TJ structure and function within the BBB; thus, a lack of commensal bacteria may lead to an aberrant formation of TJs, such as occludin and claudin-5 [204].

In conclusion, there is strong evidence that “leaky gut” disorders can induce a variety of EIMs resulting from breached barriers of immune-privileged organs, such as the BBB.

4.2 Can IBD and CeD Increase Permeability of the BLB?

Despite the anatomical differences between the IB, BBB, and BLB, these barriers also have several commonalities [263,266]. Diseases associated with pathological alterations of gut microbiota (e.g., diabetes, obesity, IBD, CeD) also share an ability to affect the permeability of all three barriers. Therefore, we postulate that gut dysbiosis and leaky gut have a similar influence on both the BBB and BLB via a feedback loop driven by microbial solutes and the innate immune system.

One of the factors that consistently affects the permeability of the BLB is inflammation. Another potential mechanism that might affect the permeability of the BLB and the BBB in IBD and CeD is OS [11,15,267–269].

OS results from the overproduction of reactive oxygen species (ROS) [267,270,271]. Along with inflammation, it is considered one of the primary mechanisms in CeD. It was suggested that OS might predispose CeD patients to other autoimmune disorders [267]. Previous studies have shown that brain-derived microvascular endothelial cells of the BBB, when exposed to OS, express elevated matrix metalloproteinase 9 (MMP-9) activity that affects TJ protein occludin [264,272]. Similarly, elevated OS markers such as inducible nitric oxide synthase (iNOS) show that vascular endothelial cells of the BLB are also prone to ox-
Fig. 3. Leaky gut can cause systemic inflammation resulting in a breach of the blood-brain and blood-labyrinth barrier and local low-grade chronic inflammation in the brain and the cochlea. Abbreviations: BM, basement membrane; EC, endothelial cell; PVM/M, perivascular-resident macrophage-like melanocyte; TJ, tight junction; SV, stria vascularis; SL, spiral ligament; SG, spiral ganglion.

Idiopathic damage, triggering inflammatory pathways within the cochlea [273].

In mice, specific cytokines (IL-1, IL-6, and MIP-1α) enhance the permeability of the BLB, allowing ototoxic drugs to enter the cochlea [274]. LPS-induced low-grade endotoxemia can also increase BLB permeability via toll-like receptor 4 (TLR4) [275]. However, LPS is not sufficient to alter BBB permeability on its own [276,277], but it can induce inflammation and production of pro-inflammatory cytokines [274], which can disturb the BBB and the BLB (Fig. 3). In rodents, LPS can enter the brain by the lipoprotein-mediated transport mechanism and bind to its receptors CD14 and TLR4 [278]. Upon activation of these receptors, the regional pro-inflammatory cascade starts [208]. The cochlea houses both receptors - CD14 and TLR4, which can induce an ototoxic response to cisplatin [279–281]. TLR4 activation could also cause sensory cell degeneration and cochlear dysfunction after a noise-induced trauma [281].

CpG motifs can also activate innate and adaptive immune responses via TLR9 receptor-mediated MAPK and NF-κB pathways in immune and epithelial cells [282, 283]. The innate immune system then releases pro-inflammatory cytokine IL-18, followed by the recruitment of neutrophils and leukocytes to the sites of infection [37]. During cochlear inflammation, resident macrophages of the cochlea can additionally increase BLB permeability [284–286]. This, in turn, allows infiltrating macrophages from the systemic circulation to migrate to the inner ear to resolve the inflammation [287,288].

Cytokines and chemokines increase the permeability of the BBB by stripping off its protective glyocalyx [269]. The glyocalyx is an equivalent of the superficial unstirred mucus layer in the IB and forms both the BBB and the BLB [289]. As a result, the endothelial cells are exposed to inflammatory mediators, allowing for their erosion [269].

5. Conclusions

“Leaky gut” disorders, such as IBD and CeD, lead to an increase in IB permeability. The compromised IB allows pathogens and microbial metabolites to infiltrate the circulatory system and spread to distant organs. The immune-privileged organs (brain, cochlea) are protected by barriers with a similar structure; thus, these barriers are more likely to be compromised by the same type of stimuli. EIMs of CeD and IBD include dysfunctions of the blood-brain and the blood-labyrinth barrier (Fig. 3). Based on the current literature, we postulate that the breach of these bar-

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rriers causes neuroinflammation and inflammation-induced SNHL. We have coined the term gut-inner ear axis to describe the crosstalk between the gut and inner ear, analogous to the gut-brain axis.

**Author Contributions**

DK designed the study and performed the literature search, and SMV provided advice. DK analysed the literature and drafted the review. Both authors contributed to editorial changes in the manuscript. Both authors read and approved the final manuscript.

**Ethics Approval and Consent to Participate**

Not applicable.

**Acknowledgment**

We thank Mr. Corey Beran for proofreading this manuscript.

**Funding**

This study was funded by Eisdell Moore Centre (Auckland, New Zealand), grant number 3721994.

**Conflict of Interest**

The authors declare no conflicts of interest.

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