Chapter

Autoimmune Diseases of the GI Tract Part I: Etiology and Pathophysiology

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Abstract

Autoimmune diseases have emerged as a pandemic in our modern societies, especially after World War II. There are currently more than 80 autoimmune diseases that compromise the lives of millions of patients around the world. There is a variety of factors that are involved in the pathogenesis of autoimmune diseases that vary from environmental factors to genetic susceptibility. The GI tract is one of the most susceptible sub-systems in human bodies for autoimmune organ-specific diseases. There are five autoimmune GI tract diseases that are most common. This review consists of two chapters. In part I, we shed the light on introducing the concept of autoimmunity, the description of the disease's pathogenesis and the diagnosis, the link between the gut and brain through what is known as the gut-brain axis, and the relationship of this axis in GI autoimmune diseases. In part II, we will shed light on the role of antibodies as markers for the prediction of the disease, artificial intelligence in GI autoimmune diseases, the nutritional role and implications in the five GI autoimmune diseases, and finally the treatment of those diseases.

Keywords: achalasia, atrophic autoimmune gastritis, celiac disease, eosinophilic esophagitis, inflammatory bowel diseases, Crohn disease, ulcerative colitis, immunological continuum, epithelial barrier dysfunction, gut-brain axis

1. Introduction

Autoimmune diseases (ADs) can be classified as the inability of the human systems to distinguish their own bodies from foreign bodies [1, 2]. There have been more than 80 autoimmune diseases reported to date [3]. The immune system remains one of the most poorly understood systems in the human body. The COVID-19 pandemic has re-shed light on the immune system once again [4, 5]. ADs can be triggered in humans due to multiple factors such as environmental factors and genetic predisposition factors. The pathogenesis of the diseases can be hugely variable but the involvement of T and B lymphocytes from the adaptive immunity remains a hallmark for this umbrella of disease [6]. The increase in the detection and classification of ADs can be owed to

the development of serological tools to detect antibodies [7]. Autoimmune diseases can be classified as systematic and organ-specific diseases.

The Gastrointestinal Tract (GI tract) is a part of the digestive system in humans, and it is composed of six components: mouth, esophagus, stomach, small intestine, large intestine, and anus. The GI tract is prone to diseases, and it is affected by multiple factors in the pathogenesis of the disease and multiple manifestations of other systematic diseases appear in the GI tract. There are five common autoimmune diseases in the GI tract: (1) achalasia, (2) atrophic autoimmune gastritis (AAG), (3) celiac disease (CD), (4) eosinophilic esophagitis (EoE), and (5) inflammatory bowel diseases (IBD) which includes Crohn disease and ulcerative colitis (UC). The manifestation of other autoimmune diseases in the GI tract could be due to: (1) systematic mastocytosis, (2) systematic sclerosis and CREST syndrome, (3) autoimmune enteropathy, (4) autoimmune hepatitis, (5) autoimmune pancretitis, (6) mixed connective tissues disease, (7) primary sclerosing cholangitis and autoimmune sclerosing cholangitis, and (8) systemic lupus erythematosus (SLE). The review of the manifestation in the GI tract is beyond the scope of this chapter. This chapter covers the definition and etiology of autoimmune diseases, the relationship between autoinflammation and autoimmunity, an overview of the five diseases, the common antibodies that are used as a predictor factor for the disease, the role of gut-brain axis, and the psychological link in the GI tract autoimmune diseases, the role of nutrition in GI autoimmune diseases, and the treatment available for the diseases.

2. Definition, pathophysiology, and etiology of autoimmune diseases

ADs are a cluster of heterogenous pathological events with an increasing number of registered cases worldwide and a prevalence of around 10% in the western populations, according to thorough epidemiological studies [8]. The hallmark of AD is the tissue injury and consequent malfunction resulting from a system or organ-specific inflammatory reaction due to the failure of self-antigen tolerance [9, 10]. Shaping the classification of AD advanced and these diseases were re-defined over the years: autoimmune inflammatory diseases used to be typically divided into autoimmune diseases and autoinflammatory diseases [11]; this separation is based on the involvement of either the innate or the adaptive immune systems and the detection of increased titer of autoantibodies [11]. So according to this definition set, ADs are distinguished by the involvement of the adaptive immune system represented by T and B lymphocytes and the presence of autoantibodies [11]. Over a decade ago, McGonagle and McDermott suggested the "continuum model" in immunology, in which a spectrum of diseases is established including the autoinflammatory and AD in both extremities of the created spectrum [12]. Moreover, the authors suggested criteria to set the boundaries for diseases to be considered clinically autoinflammatory or autoimmune, based on the genetic mutations that occur in each type of disease [12]. Thus, margins of ADs are set by mutations linked to monogenic autoimmune diseases which exhibit predisposed to the adaptive immune system and the existence of autoantibodies. On the contrary, the margins are set for autoinflammatory diseases by mutations in elements that take place in the innate immune system mutations specifically in tissues that are prone to pathological events onset, where no evidence of the involvement of autoimmune mechanisms [12–14]. In the last few years, the concept of autoinflammation and autoimmune diseases kept being refined as several monogenic and polygenic common and novel disorders have been recognized, feeding into the updating of

knowledge of the pathophysiology of autoinflammatory and ADs [15, 16]. Thorough investigations associated with convincing pathophysiological hypotheses in model diseases from any extremity of the continuum reveal the intimate relationship between the mechanisms of innate and adaptive systems [17]. Advanced modern approaches including molecular imaging technologies, genome-wide association studies, and the characterization of tissue-associated factors in some diseases supported the idea of the interplay between innate and adaptive immune mechanisms in specific ADs [9, 13]. Eventually, these techniques also helped in the verification of the continuum model that was suggested by McGonagle and co-workers.

3. Inflammation to autoinflammation and epithelial barrier dysfunction: a brief look into the developmental stage

The most challenging aspect in immunological diseases such as autoinflammatory and autoimmunity diseases is to identify the early events that trigger immune dysregulation [18]. Autoinflammatory and autoimmunity are closely correlated and are sometimes confused by mistake. Although there are similarities and perhaps a continuum between them, but they nevertheless do not refer to the same thing. The biggest distinction line that can be drawn between autoinflammatory and autoimmune disease is that the autoinflammatory diseases is that autoinflammatory was referred to the dysregulations related to adaptive immunity while autoimmunity was defined due to the dysregulation in innate immunity [9, 19]. This definition is not entirely accurate and a little bit outdated as we will preview in this section how the innate and adaptive immunity are involved in both autoinflammation and autoimmunity and what are the links between them. The pathological nature of the two process that are self-destructive and systematic that include monogenic and polygenic diseases [20]. A chronic activation of the immune system happens in both processes that lead to tissue inflammation or damage.

3.1 The role of innate and adaptive immunity

Immunologic defenses in vertebrates consist of two immunologic subsystems—innate and adaptive immunities. Innate is the natural immunity by birth while the adaptive immunity is the acquired immunity [21].

3.1.1 Innate immunity

The innate immune system constitutes the first line of defense in an individual's immune system. As a result, it detects pathogens as well as other harmful triggers that may cause inflammation and trigger adaptive immunity [22]. Among the effector cells of innate immunity are macrophages, dendritic cells, and antigen-presenting cells (APCs) [23]. Innate immunity identifies and recognizes the molecular patterns expressed by pathogens (pathogen associated molecular patterns, PAMPs) or by damaged cells (damage associated molecular patterns, DAMPs) [24]. There are three types of pattern recognition receptors (PRR): TLRs (Toll-like receptors), RLRs (RIG-I-like receptors), and NLRs (nucleotide-binding oligomerization domain-like receptors) [25]. It is thought that upon recognition of foreign molecules, intracellular signal transduction pathways are induced, which induces the expression of interferon alpha (IFN) sequences, IFN-α sequences, TNF sequences, and interleukin 1 (IL-1)

sequences. Both autoinflammatory and autoimmune diseases can be caused by the dysregulation of these receptors, which mostly involves excessive or prolonged activation [11, 26]. The activation of the inflammasome is crucial to host defense against pathogens. Several inflammasomes are implicated in the immunological process of diseases, including NALP1 and NALP3, or cryopyrin inflammasomes. By activating pro-caspase-1, the inflammasome mediates the conversion of pro-IL-1ß and IL-18 into the active forms. Genetic mutations in either pyrin, cryopyrin, or TNF receptor super-family genes have been associated with autoinflammatory diseases [27]. It is unclear how inflammasomes contribute to autoimmunity. Nevertheless, its role is still yet to be discovered as NLRI and IL-1ß as a primary suspect to look at. The upregulation of IL-2 receptor that leads to B cell proliferation and enhanced antibody production is caused by the crucial role of IL-1ß, which affects both B and T cells, thereby prolonging T cell survival [28]. Furthermore, they drive differentiation of the Th17 cells as well. Therefore, IL-1ß stimulates T and B cells and may play a crucial role in linking the NLR activation with adaptive immunity response [20].

3.1.2 Adaptive immunity

For adaptive immunity to mature, it requires between three and five days. B cells, T cells, and cytotoxic T cells are involved in adaptive immunity [19]. Antigens are recognized by specific antigen receptors, primarily B and T cell receptors (BCR and TCR), which are highly specific. As such, innate immunity provides a first line of defense against damage and infection. Adaptive immunity, however, provides a more effective but slower resistance.

A significant role is played by adaptive immunity in the development and maintenance of autoimmune diseases. Despite this, different mechanisms contribute to the disease by the innate immune system. The autoimmune process is divided into two phases: During the initiation phase (phase 1), self-nucleic acids released by apoptotic cells are recognized and internalized by dendritic cells (DC) through TLR, causing IFN-α, production. The IFN- α stimulates the maturation of dendritic cells, the presentation of autoantigens, the recruitment of B and T cells, and the production of autoantibodies. After entering a second phase, (self-sustaining amplification) plasmocytoid dendritic cells internalize autoantibodies and nucleic acids through Fcy-receptors (FcyRs). DC and T cells are stimulated and activated by IFN- α, resulting in self-perpetuation of antibody production and inflammation [6, 29].

3.2 The immunological disease continuum

IL-1 1β and type I interferon (IFN) are also polarized cytokines that are related to innate immunity, with IFN being more associated with autoimmune diseases, specifically Systemic Lupus Erythematosus (SLE), while IL-1β is associated with pure innate immunity. The importance of recognizing Type I IFN dysregulation driving autoimmunity, as well as NLR dysfunction driving classical autoinflammatory diseases without autoantibody formation, has led to a polarization in the classification of immune diseases. From the original recognition of autoinflammatory diseases being linked to NLR cytoplasmic resident innate immune receptors (NLRP3 in particular). There have been several reports linking innate immune-mediated pathologies to inflammasomes, including NLRC4. It is remarkable that NLR family members show consistent association with both monogenic and polygenic autoinflammatory disease, whereas TLRs do not, possibly attributable to functional redundancy in TLRs.

3.3 The epithelial barrier dysfunction: leaky gut as a third element of pathogenesis

The epithelium of the gastrointestinal tract or commonly known as the epithelial barrier is the largest mucosal lining that forms an interface between a mammalian host and the external environment [30]. Protecting the body from pathogens and foreign substances is the primary function of the epithelial barrier [31]. It is through the anatomical structure of the GI that processes such as digestion, absorption, and neuroendocrine network, as well as immune function balance, take place. Trillions of microbial inhabitants inhabit the lumen of the gut. These microbes play an important role in digestion and modulate the immune system [32]. The regulation of molecular trafficking between the intestinal lumen and the submucosa via the paracellular space maintains the capability of the intestinal permeability which interacts continuously with various bodies such as foodborne pathogens and antigens. Paracellular space is estimated to measure between 10 and 15 Å. Physiologically, solutes with a molecular radius of over 15 Å (~3.5 kDa) are not susceptible to uptake through this pathway [33]. The intestinal permeability is the property that allows solutes and fluids to pass between the lumen and tissues. Additionally, intestinal barrier function is determined by how well mucus and other extracellular components, such as mucus, prevent this exchange [32].

Transfers of macromolecules are largely affected by the paracellular permeability of epithelium, which is influenced by the intercellular tight junctions (TJs) [34]. The TJs are highly dynamic structures that serve a variety of functions both physiologically and pathologically in the intestinal epithelium [35]. The Zonulin protein appears to modulate intercellular TJs, and it has been shown that Zonulin expression is elevated in conditions associated with dysfunction of TJs, such as celiac disease [36–40]. An impaired epithelial barrier is associated with a wide range of chronic diseases, including allergies, autoimmune diseases, and metabolic disorders [41]. Changes in the permeability of the GI tract's epithelial lining facilitate a passage for commensal bacteria and their products from the lumen into the bloodstream creating what is known as a "leaky gut". There has been a growing interest over the past decade in the role of leaky gut's association with autoimmune diseases. There have been some suggestions that the leakage of pathogens into the body system results in autoimmunity making the leaky gut a third source of pathogenesis besides environmental triggers and genetic predisposition [42]. A dysbiosis which is a perturbation of the structural dynamics of the microbial community in the intestinal tract causes leaky gut condition and it is closely entangled with autoimmune diseases. As discussed here, the microbiota and particularly the intestinal microbes are important in the immune system and their disturbance can be associated with autoimmune diseases.

There are various immune cells such as T and B cells as well as macrophages and dendritic cells which are found beneath the layer of lamina propria of the intestinal epithelium. These cells are crucial for the maintenance of hemostasis in the intestinal epithelium. Epithelial cells suppress inflammation by generating regulatory dendritic cells, regulatory T and B cells, as well as anti-inflammatory cytokines [43]. In the event of a leaky gut and damage to the epithelial barrier, some pathogens such as *Staphylococcus aureus* may colonize areas such as leaky barrier areas [41]. In turn, dysbiotic microbiota moves to the interepithelial and subepithelial spaces, activating a local or systemic inflammatory response suspected to contribute to many immune-mediated diseases. There then follows a series of events that lead to chronic periepithelial inflammation with leaky epithelial barriers. It is not understood that

the autoimmune response occurs before the epithelial barrier insult or post the insult. The causes of the epithelial barrier's insults could be variable and include but are not limited to genetic predisposition such as filaggrins and TJ polymorphisms, environmental factors such as microplastics and food emulsifiers [44, 45], allergens such as house dust [46], microbiota's flora, surfactants, and dietary factors [47]. For a detailed review, we refer the reader to [41].

The intestinal commensal is exposed to the host's immune system in various organs due to epithelial intestinal barrier leakage and autoimmune diseases. It has been observed that few of the GI intestinal epithelial cells (IECs) are essential for maintaining intestinal homeostasis and in the function of the intestinal epithelium, as well as participating in IBD pathogenesis [48]. There is collective evidence about the role of the epithelial barrier in EoE. It is reported that EoE–linked calpain 14 is an IL-13–induced protease that mediates esophageal epithelial barrier impairment [49]. There is also a reported role of TGF-β1 in the alterial esophageal epithelial barrier function by attenuation of claudin-7 in EoE [50]. The role of epithelial barrier dysfunction is well established in EoE and we refer the reader for in-depth scope review [51]. In ADs, there is an association between leaky gut and the development of AD. For instance, in CD, an increase in the number of apoptotic IEC in the peritoneal mucosa is reported as well as impaired epithelial barrier function [52]. It is reported that epithelial barrier is dysfunctional through TJs defects [52]. This is a growing area of research and by shedding the light more on the relationship between epithelial barrier dysfunction and what is known as leaky gut syndrome, the association between it and GI autoimmune diseases if confirmed can provide a therapeutic route in the treatment and prevention of GI autoimmune diseases.

4. The 5 common GI autoimmune diseases

4.1 Achalasia

Achalasia is a rare autoimmune motility disorder that is caused by the degeneration of the myenteric neuronal esophageal plexus that consequently results in an aperistalsis and impaired incomplete relaxation of the lower esophageal sphincter (LES) and ineffective contractions in the esophageal body [53]. In the distal esophagus and the lower esophageal sphincter, achalasia is characterized by a functional loss of myenteric plexus ganglion cells or chronic ganglionitis [54]. Since there is no known cause for the initial loss of inhibitory neurons in individuals suffering from achalasia, it could be considered an idiopathic disorder [55]. Nevertheless, the onset of neuronal degeneration may be caused by an indolent viral infection such as herpes simplex virus 1 (HSV-1), measles, and human papillomavirus have been proposed as potential antigens. Evidence indicates that HSV-1 DNA has been detected in esophageal tissue, and that isolated T cells from achalasia are monoclonal in nature and that they proliferate and release cytokines upon exposure to HSV-1 antigens [56, 57]. It is possible that this is since HSV-1 is a neurotropic virus with a predilection for squamous epithelium, which causes selection loss of enteric neurons in the esophagus. Nevertheless, this theory is not entirely accurate, as HSV-1 DNA was also frequently detected in control individuals' esophagus [58]. Thus, it might be argued that HSV-1 only triggers persistent immune activation and subsequent loss of enteric neurons in individuals with genetically suspected hosts [59]. In patients who have an immunogenetic variation, viral infection may trigger a disordered immune reaction. Achalasia

may also be caused by muscular eosinophilia in some cases. It has been demonstrated that such inflammatory processes decrease, gradually destroy, or eventually eliminate the esophageal myenteric plexus (MP) [60]. It has been found that achalasia is associated with several genes and immunological markers including Interleukin-10 promoter polymorphism [61] and Interleukin 23 receptor [62], HLA class II gene polymorphisms [63], KIT (KIT proto-oncogene, receptor tyrosine kinase) [64, 65], and vasoactive intestinal peptide receptor 1 [66, 67], among others.

Achalasia is reported to have an annual incidence of 1 per 100,000 individuals worldwide [68]. There is an equal frequency of achalasia in men and women when they are adults [69] and among different ethnicities [70]. Other autoimmune diseases are prevalent in achalasia patients such as diabetes. Progressive dysphagia to both solids and liquids is the hallmark symptom associated with a diagnosis of achalasia [71]. In addition, regurgitation of undigested food, respiratory symptoms such as nocturnal coughs, recurrent respiratory infections, pneumonia, chest pains, and loss of weight may occur [58, 72, 73]. According to conventional manometry, the characteristics of achalasia are as follows: (1) absence of peristalsis, sometimes with increased intra-esophageal pressure associated with the stasis of food and saliva, (2) The LOS remains partially relaxed on deglutition (residual pressure > 10 mm Hg), and (3) the LOS often exhibits a raised resting tone.

4.2 Atrophic autoimmune gastritis (AAG)

Atrophic autoimmune gastritis (AAG) is an immune-mediated disorder characterized by nonspecific symptoms [74–76]. A diagnosis of AAG is confirmed by the presence of circulating antibodies against the adenosine triphosphate enzyme H/K (parietal cell antibodies, PCA); the same antibodies are also found against anti intrinsic factor (anti-IF) [77]. In AAG, the native gastric glands within the mucosa gradually disappear or shrink over time [78]. Consequently, mucosal atrophy occurs sparing the antrum and extensive pseudopyloric or intestinal metaplasia occurs [79]. There may be involvement of both the antrum and corpus, but the corpus only has apparent functional and clinical consequences [80]. Multiple modifications may precede atrophy, including focal atrophy, lymphoplasmacytic infiltrate in the lamina propria, parietal cells pseudohypertrophy, and enterochromaffin-like (ECL) cell hyperplasia. It has long been recognized that AAG, as well as other autoimmune disorders, tend to cluster in families, which could reinforce the genetic component of disease. Through using mouse models, it has been possible to discover AAG susceptibility genes (Gasa 1, 2, 3, and 4) on chromosomes 4 and 6 and H2 region, three of which are located on the same locus as non-obese diabetic mouse diabetes mellitus susceptibility genes [12, 13]. The prevalence of autoimmune atrophic gastritis is relatively low. It may be attributed at least in part to the underdiagnosis of *Helicobacter pylori*-induced gastritis in many cases, and the absence of clinical manifestations in the early stages of the disease [81]. The incidence of AAG is three times higher in women than in men [82]. There is an age-dependent increase in the prevalence of AAG of 2% [83]. AAG occurs in 25 out of every 100,000 people each year. Patients with AAG have 3–5 higher risks of developing other autoimmune diseases, such as oral erosive lichen [84], myasthenia gravis [85], vitiligo [86], diabetes mellitus (DM) [87], autoimmune thyroid disease [88], and Addison's disease [89]. Patients are usually diagnosed in advanced stages when the disease is irreversible or threatening symptoms have occurred, including abnormalities such as pernicious anemia, and neurological or gastric oncological complications [90–92]. The symptoms of AAG appear slowly and may

remain asymptomatic for a long period of time. Symptoms of the disease range from mild weakness to severe psychological manifestations such as paranoia (megaloblastic madness). Pernicious anemia is the main clinical manifestation of AAG. A common symptom of iron deficiency is fatigue, restless legs, brittle nails, hair loss, impaired immune function, and poor wound healing. Iron deficiency is independent of and precedes anemia. Shortness of breath, dizziness, tachycardia, and lightheadedness are some of the symptoms of anemia (regardless of the cause) [93]. The presence of AAG can be asymptomatic or cause symptoms, depending on the level of atrophy that affects the absorption of vitamin B12 or other substances, such as folate and iron. Deficiency in vitamin D can develop over a long period of time, and patients may not show symptoms until reserves are exhausted. The diagnosis of AAG can be done through serological tests, endoscopy, and histopathology biopsy. Antibodies that are used for serological tests such as APCA, anti-ID antibodies, and anti-*H. pylori* antibodies (anti-HP-IgM and anti-HP-IgG). AAG patients who have oxyntic gland atrophy often have elevated levels of gastrin (including Gastrin-17) and it is measured in many cases to confirm the diagnosis. Endoscopy has been often used in the diagnosis, although it has many limitations such as low sensitivity and specificity. There is, however, a golden rule when it comes to diagnosing AAG through endoscopy, which is the absence of normal capillaries resembling honeycombs and collecting venules in regular shape and appearance. Biopsy histology is the most reliable method. Before oxyntic mucosa is lost completely, AAG appears as a series of features: (1) infiltrated lymphocytes and plasma cells in lamina propria, (2) focal atrophy of oxyntic mucosa along with SPEM or IM, (3) pseudohypertrophy of parietal cells and (4) hyperplasia of the ECL [93].

4.3 Celiac disease

Celiac disease (CD) is a multisystem disorder characterized by enteropathy [94]. Genetically predisposed individuals develop CD when the immune system reacts inappropriately to a T cell-mediated immune response [95]. Almost any organ system can be affected by celiac disease, approximately half to two-thirds of patients suffer from extra-intestinal symptoms; some studies claim that they may be more common than gastrointestinal symptoms [96]. CD patients can be classified into two categories symptomatic and asymptomatic. Asymptomatic CD patients are those who at the time of their initial diagnosis of CD do not exhibit any symptoms even if they are directly questioned about their condition. The term symptomatic CD refers to those individuals who demonstrate clinically visible gastrointestinal and/or extraintestinal symptoms related to gluten consumption [97, 98]. Symptomatic celiac disease can be further divided into classical and nonclassical celiac disease. Some genes have been involved in CD. It is often considered that CD can be viewed as a polygenic disorder that involves both major histocompatibility complex MHC (human leukocyte antigen [HLA]) and non-MHC genes [99]. Currently, it is well-established that six MHC and 39 non-MHC loci, as well as several independent genetic variants, contribute to disease risk. The genetic variants are responsible for roughly 31% of CD heritability, and the MHC is responsible for 25% [100]. In CD, HLA-DQ2 and -DQ8 are key genetic markers, and an autoantigen is involved (tissue transglutaminase 2: tTG2). Approximately 25–35% of the general population has HLA-DQ2/DQ8 with only 3% of these individuals developing CD [101]. Globally, CD affects between 0.6% and 1% of the population [102]. CD affects both children and adults. The mean age at the diagnosis is 38, but 20% of the patients are diagnosed over the age of 60 [103]. Women however are diagnosed

at an earlier age and present more often with constipation, bloating, and anemia of iron deficiency than men [104, 105]. Gluten is the main etiology of CD. Gluten is a mixture of proteins found in grains of wheat (including gliadins and glutenins). CD can be caused by the presence of proteins from barley (hordeins) and rye (secalins). Among these, the gliadin peptides are the most immunogenic for CD [106]. Any case with malabsorption is defined as a classical disease and all other cases as nonclassical. Neoclassic CD manifests with largely extraintestinal symptoms, often monosymptomatic (e.g. iron deficiency anemia, premature metabolic bone disease, infertility, elevated transaminase levels) in the absence of clinical malabsorption. Over time, diarrhea has become less common at presentation, but it remains the most common gastrointestinal symptom [104]. Potential CD is a clinical term to describe suspected CD patients. Potential CD is characterized by normal small intestinal mucosa with positive CD serologic findings [107]. The diagnosis of CD remains challenging as it is estimated that currently only 20% of patients who have CD have been diagnosed [108]. CD cannot be diagnosed with one tool only. There is always a need for a combination of clinical features, serology, and histology are needed together to confirm the diagnosis [109]. In serological tests, patients should be on gluten-containing diets. Positivity in tests for Serum immunoglobulin A (IgA) anti-tissue transglutaminase antibody (anti-tTG-IgA) is widely accepted for the diagnosis but has low specificity. Serum immunoglobulin A (IgA) anti-tissue transglutaminase antibody (anti-tTG-IgA) are 100% specific but less sensitive [110–116]. Deamidated gliadin peptide (DGP) antibodies of the IgG class are advantageous for younger children [117]. All patients with suspected CD should undergo a duodenal biopsy. Regardless of CD serology results, duodenal biopsies should be performed in high-risk symptomatic patients [118]. There is a four out of five rule that is common in the diagnosis of CD. According to this rule, four of the following criteria are sufficient to establish CD diagnosis: (1) apparent and typical signs and symptoms of diarrhea and malabsorption, (2) positive serological tests of antibodies, (3) a patient with HLA-DQ2 or HLA-DQ8 positivity, (4) damage to the intestines, such as villous atrophy and lesions and (5) the response of the patient to GFD. This rule is important in the diagnosis of the diseases as many CD subtypes can be classified naming the non-classical CD which has no malabsorption or diarrhea, seronegative CD patients who do not show responses to serological antibodies, and a potential CD which has no damage to the intestines, and non-responsive CD who show no responses to GFD [109].

4.4 Eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is an immune-mediated condition in which eosinophils infiltrate into the esophageal mucosa and lead to symptoms of esophageal dysfunction [119]. In the absence of secondary causes, the disease is considered to belong to the spectrum of eosinophilic gastrointestinal disorders [120]. In the absence of treatment, EoE can lead to esophageal fibrosis, the formation of strictures, and esophageal narrowing leading to esophageal dysfunction [119, 121]. Throughout the world, the health care systems are burdened by EoE, a major factor in upper gastrointestinal morbidity [122, 123]. The US healthcare system is estimated to spend $350 to $947 million burden annually on EoE [122]. It has been found that the EoE disease prevalence has been associated with Single Nucleotide Polymorphisms (SNP) in the Thymic stromal lymphopoietin (TSLP) and TSLP-Rwhich is correlated with increase in the TSLP levels [124]. There are several environmental allergens implicated. One of these allergens is food. Food allergens trigger EoE and the disease can be put into

remission by removal of specific foods, either via elimination diets or hypoallergenic elemental formulas [125–127]. It is commonly accepted that EoE, is due to a Th2 inflammation driven by TSLP secreted by esophageal epithelial cells and is under the influence of genetic predisposition [124, 128–130]. EoE Th2 inflammation with a non-IgE-mediated trigger has been found to be triggered by certain foods [131]. It was reported that food that causes vomiting and abdominal pain is soy, wheat, egg, and milk [132, 133]. An elimination diet known as the six-food elimination diet (SFED) refers to the removal from the diet of EoE patients of wheat, milk, eggs, nuts, soy, fish, and shellfish that are considered to be allergens [134]. Th2 cytokines result in an increased Th2 response from T cells, basophils, Invariant natural killer T iNKTs, and mast cells in EoE. Th2 cytokines also enhance eosinophil survival and activation, thus resulting in fibrotic modification [135]. It has been reported that IL-4 enhances eotaxin-3 secretion by epithelial cells, which is responsible for the increased migration of eosinophils. IL-4 also causes fibroblasts to release periostin, collagen, and B-actin, promoting local fibrosis [136]. Eosinophils are mainly differentiated, recruited, and survived by cytokine IL-5 [137]. The cytokine TSLP is primarily produced by epithelial cells at barrier surfaces such as skin, gut, and lungs because of danger signals, infectious agents, cytokines produced by atopic cytokines (IL-4, IL-13, TNFα), and environmental allergens [138]. The Th2 inflammation observed in EoE is most likely caused by TSLP. EoE prevalence estimates vary with location. The highest incidence occurs in western countries where EoE is more easily diagnosed and has an estimated prevalence of 56 per 100,000 people [139] in some statistics. However, several estimates place the prevalence of EoE at between 0.5 and 1 case per 1000 individuals, yet the disease is detected in between 2.4% and 6.6% of patients undergoing endoscopy for any reason [140–144]. The primary symptoms of EoE in adolescents and adults is dysphagia, which affects 60–100% of patients, food impaction can affect more than 25%, and 30–60% of patients report heartburn and 44% report noncardiac chest pain [145–150]. Diagnostic criteria must include both clinical and histological features: symptoms of esophageal dysfunction, the presence of at least 15 eosinophils in a high-power field, and exclusion of alternative causes of eosinophilia in the esophagus [119, 151].

4.5 Inflammatory bowel diseases

Inflammatory bowel diseases (IBDs) refer to both ulcerative colitis (UC) and Crohn's disease, as well as other non-infectious inflammations of the bowel that are symptomatic of relapsing chronic disorders of the bowel [152]. There has been an increasing incidence of inflammatory bowel disease (IBD) globally. It has been commonly agreed that genetic susceptibility, external environment, microbial flora of the intestine, and immune responses are all components of IBD pathogenesis [153, 154]. Globally, IBD affects 4.2 million people, including 1.5 million Americans, and 2.2 million Europeans [154, 155]. First-degree relatives are five times more likely to develop IBD than those without IBD. There is a possibility that some genes are shared by both diseases since Crohn's Disease and UC can occur within the same family. In both diseases, environmental factor leads to triggering events [156]. In recent studies, 163 IBD-associated gene loci have been identified, of which 110 are associated with both diseases, 30 with Crohn and 23 with UC. Genetic analyses have revealed the essential role of autophagy in immune responses to IBD and identified two autophagy-related genes, ATG16L1 and IRGM [157–159]. Autophagy plays an important role in intracellular homeostasis, working to degrade cytosolic contents

and organelles and resist infection, and eliminate microbes inside the cell. The coding mutation T300A is associated with an increased risk of Crohn since ATG16L1 is essential for all forms of autophagy [160]. Recent studies have demonstrated a link between IBD and IL23R (a coder for pro-inflammatory IL23 cytokine) [161]. IL23 is involved in Th17 cells [162]. IBD is well established to be caused by the Th17 and IL-23 pathway, with susceptibility loci for UC and Crohn, identified in IL23R, IL12B, JAK2, and STAT3 [163, 164]. The incidence and prevalence of IBD are increasing worldwide but are highest in westernized areas. In Europe, the highest prevalence values have been reported (ulcerative colitis 505 per 100,000 in Norway; Crohn's disease 322 per 100,000 in Germany). Several countries in Europe and North America have a prevalence of inflammatory bowel disease that exceeds 0.3%. Caucasians are prone to IBD more than Africans and Asians. Crohn is slightly more likely than UC to have a family history of the disorder, although both disorders are polygenic [165, 166]. The peak incidence for UC and Crohn is in the second to fourth decade, and no significance influence on prevalence by gender [167]. IBD patients compared to that in healthy control have unstable gut microbiota and it is often considered one of the triggering factors of IBD [168, 169]. There is a reduction in the diversity of microbiota in IBD, possibly making the host more vulnerable to pathogens or pathobionts colonizing it [170]. A high level of NO2 and SO2 correlate with an increased risk of IBD with elevated levels of air pollution. This is related to an increase in circulating polymorphonuclear leukocytes and plasma cytokines in IBD [171–173]. Environmental priming with triggering events is involved in manifestation of both diseases. Several triggers exist, including geography, social stress, a fast-paced lifestyle, smoking, diet, and drugs [174]. It has also been correlated that low vitamin is associated with IBD [175]. Stress has been commonly associated with IBD patients and it has been labeled as a trigger cause through multiple immunopathogenic pathways [176]. Persistent diarrhea with blood and mucous is a common symptom of IBD patients. The results of laboratory tests could be valuable in diagnosing IBD. Among the initial tests to be performed are complete blood count (CBC), renal function tests, liver enzyme tests, stools cultures, and C difficile toxin [156, 177].

4.5.1 Crohn disease

Crohn's disease is an inflammatory bowel disease characterized by skip lesions and transmural inflammation, leading to inflammation throughout the entire gastrointestinal tract, from the mouth to the anus [178] There are three major locations of Crohn's disease, involving the terminal ileum, the colon, and the small bowel in about 55% of patients, and the colon in about 20% of cases. In 25% of patients, fissures and fistulas may develop, as well as upper gastrointestinal disease or extraintestinal manifestations. In 10% of patients, isolated perianal complaints may develop [179]. Although Crohn's etiology is not completely understood, genetics, immunology, and environment contribute to the onset and progression of this disease [180]. The annual incidence of Crohn is approximately 3 to 20 cases per 100,000 people [154]. Incidence of Crohn is highest among patients younger than 30 years of age, although it is increasing in older individuals [181]. North America and Western Europe are the most common places where individuals experience Crohn's disease, but Asia and Latin America are experiencing it in an increasingly more often manner as well [174, 182]. In general, the gender ratio of CD is almost similar with slightly higher prevalence in women. In western countries, there is no sex difference is apparent in incidence, whereas in Asian populations, Crohn is slightly more prevalent in men than in women. It was identified

that more than 200 loci were associated with Crohn's risk [183]. The coding variation in the intracellular pattern recognition receptor gene NOD2 (also known as CARD15), is selectively associated with Crohn's risk. There is considerable variance at a few loci that are associated with aggregate heritable risk, including IL23R, the IL-2 receptor gene, and NOD2 [184, 185]. Being homozygous at NOD2 increases the risk of developing Crohn's by 20–40 times while being heterozygous increases it by 2–4 times [186]. Crohn's pathogenesis is linked to NOD2 c.3019-3020insC and ATG16L1p.Thr300Ala, respectively as has been shown by novel immunopathogenesis study [187]. It has been shown that patients with early onset of Crohn have mutations in IL-10 receptor genes [188]. Crohn can be divided into three phenotypic subtypes: inflammatory, structuring, and fistulizing. The inflammatory Crohn phenotype is characterized by inflammation of the gastrointestinal tract with no evidence of stricturing or fistulizing. Over time, this inflammation may result in fibrosis and luminal narrowing, resulting in stricturing disease. The fibrosis is reversible and there would be a need for surgical intervention. Transmural inflammation can also result in the development of a fistulous tract or sinus in patients with fistulizing Crohn. The bowel can develop a fistula with any adjacent organ (such as the bladder, vagina, or other parts of the bowel) [189]. Crohn typically manifests as weight loss, diarrhea with blood, iron deficiency, chronic and postprandial abdominal pain, fever, lack of rectal urgency, and nighttime awakenings [190]. C-reactive protein levels, sedimentation rates, or other acute phase reactants (e.g. ferritin and platelets) are commonly elevated in Crohn patients. Low B12 levels are also common. Family histories of IBD also significantly influence Crohn patients [178]. Just like other GI autoimmune diseases, some tests are used together to confirm the diagnosis such as serological tests, endoscopy, and histological tests for biopsies. Crohn is diagnosed by autoantibodies, such as anti- Saccharomyces cerevisiae antibodies (ASCAs), anti-outer membrane porin C antibodies, anti-Pseudomonas fluorescens-associated sequence I2 antibodies, and anti-CBir1 antibodies. Additionally, perinuclear antineutrophil cytoplasmic antibodies (pANCAs), antimannobioside carbohydrate antibodies, anti-laminaribioside carbohydrate antibodies, anti-chitobioside carbohydrate antibodies, as well as anti-laminarin antibodies [191–193]. In endoscopy findings for a diagnosis of Crohn are often characterized by a patchy distribution of inflammation and skip lesions. It might be apparent in endoscopy the presence of aphthous erosions or longitudinal ulcers.

4.5.2 Ulcerative colitis

UC is a chronic inflammatory disease of the colon characterized by a continuous mucosal inflammation extending from the rectum to the proximal colon with a variation in the degree of extent [194]. Colitis of the colon and rectum is characterized by continuous areas of inflammation and ulceration, without any segments of normal tissue present. It typically affects only the innermost lining [195]. Tenesmus and bloody diarrhea are hallmark symptoms of UC. The patients also report mild tenderness, lower abdominal cramping as well as fatigue due to the blood loss. Even though the etiology of UC remains unclear, increasing evidence suggests it may be an autoimmune condition [196]. The disease can develop at any age but is most commonly diagnosed before the age of 30 [197]. It has been reported that the prevalence of UC varies globally between 2.42 and 298.5/100,000, with the highest incidence occurring in North America and Northern Europe [154]. UC affects both sexes equally, and it affects all ethnicity with 3–6 more prevalence in Jewish people [198]. A "Western diet," left-handedness, and depression may increase risk for UC [199–203]. As part of

the diagnosis of UC, it was recommended to test for CBC to check for intestinal blood loss and anemia [195]. Additionally, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fecal lactoferrin, and fecal calprotectin levels are used to assess inflammation [198]. Nutritional status and deficiencies are assessed using serum albumin, iron studies, and vitamin B12 levels. UC is usually confirmed by sigmoidoscopy or colonoscopy if it has not been ruled out. It has a hallmark of the presence of continuous colonic inflammation characterized by erythema, loss of normal vascular pattern, granularity, erosions, friability, bleeding, and ulcerations, with a clear distinct demarcation between inflamed and non-inflamed bowel (**Table 1**) [198].

5. The role of psychological association with GI tract autoimmunity

Stress occurs when a demand of the environment exceeds an individual's ability to adapt [204]. Described by Selye in 1936, stress is defined as an organism attempting to maintain homoeostasis that faces either an actual threat (physical) or a perceived threat (psychological) for which it must adapt its behavior to survive [205]. Stress is not necessarily a negative effect as sometimes it can be a positive aspect for people to motivate them and enhance their performance in life in general and in this case, it's

	Disease description	Etiology	Prevalence (%)	Clinical manifestation
Achalasia	Damage at the lower end of the esophagus prevents food from entering the stomach	Nerve damage	0.001	Dysphagia, regurgitation of undigested food, nocturnal coughs, pneumonia
AAG	The parietal cells of the stomach's corpus and fundus are destroyed	Pernicious anemia is caused by a lack of vitamin B12	0.025	Variable symptoms depend on level of atrophy but mainly iron deficiency symptoms
CD	An enteropathy-associated multisystem disorder	Gluten intolerance	0.6–1	Asymptomatic; symptomatic includes constipation, bloating, diarrhea, malabsorption, and iron deficiency anemia
EoE	An immune-mediated condition that causes esophageal dysfunction when eosinophils invade the esophageal mucosa	Environmental allergens	0.05–1	Dysphagia, food impaction, heartburn, chest pain
Crohn disease	The entire GI tract exhibits skip lesions and transmural inflammation	Genetics, immunological, and environmental factors	0.02	Weight loss, diarrhea with blood, iron deficiency, abdominal pain, lack of rectal urgency, nighttime awakening
UC	A continuous mucosal inflammation from the rectum to the proximal colon with varying degrees of extent	Genetics, immunological, and environmental factors	0.002–0.3	Tenesmus and bloody diarrhea, abdominal cramps, and fatigue

Table 1.
Summary of the 5 GI autoimmune diseases.

called eustress [206]. Trauma and significant life stressors, such as a loss of a loved one or a natural disaster, occur to almost all people at some point in their lives [207]. A decrease in an individual's ability to adapt to environmental factors can lead to events that are negative and cause distress [208]. There are different kinds of stressors that can cause a disturbance: acute (lasting for minutes), brief (for a short duration), or chronic (lasting for a long time) [209]. As a result of their exposure to these stresses, a considerable number of people will develop serious psychiatric reactions, including posttraumatic stress disorder (PTSD). In addition, the acute stress reaction may be best defined as a reaction triggered by a life event that causes great stress or a change in life that triggers an acute stress reaction. Hence, it is apparent that stress and psychiatric disorder can cause physiologic changes. It is possible that the hypothalamic-pituitary-adrenal axis and the autonomic nervous system are disrupted, impairing immune function, and making people more susceptible to physical diseases. Many autoimmune diseases have unknown etiology. It has been speculated that there is a huge influence on the psychiatric reactions to life stressors and their influence in relation to autoimmune diseases. Many animal studies have suggested a close link between them [210]. Nevertheless, human studies are limited [211, 212].

5.1 Pathways for stress and related disorders

Stress causes activation of endocrine processes that provides a key pathway for further effects on health. Two main endocrine systems are involved: hypothalamic-pituitary-adrenocortical (HPA) and sympathetic-adrenal-medullary (SAM) axes. Cortisol is the main culprit controlling several physiological processes due to HPA activation like anti-inflammatory processes, metabolism of fats, carbohydrates, proteins, and gluconeogenesis. In a similar way, catecholamine released because of SAM activation regulates several functions like cardiovascular, pulmonary, hepatic, skeletal muscles, and immune system in collaboration with autonomic nervous system. Exposure to stressors causes activation of these endocrine systems. Prolonged activation of HPA and SAM causes an impaired control of physiological systems responsible for physical and psychiatric illness.

5.2 Stress as a trigger for autoimmune diseases

Stress was shown to lead glandular disturbance including autoimmune endocrine disorders [213]. In autoimmune diseases, there is a close link between stress and major stress hormones as an etiological factor [214]. Immune dysregulation could lead to atopic autoimmune diseases due to the infiltration of cytokine production and increased host defense. The repetition and the duration of stress could lead to an acute phase response that results in a chronic inflammatory process [215]. The inflammatory response is contained within the stress response, implying that stress can affect the innate immune system and causing an inflammatory response [216]. There is an association between some sort of psychological stress especially PTSD with elevated T cells that can lead to hyperreactive immune responses, higher igM, and lower dehydroepiandrosterone levels which is found in many cardiovascular and autoimmune diseases [217].

5.3 Phycological associations with the GI autoimmune diseases

Many of the patients who have GI autoimmune diseases suffer from psychiatric comorbidities such as anxiety, stress, and depression. The link between them could

be bi-directional as anxiety, stress, and depression could be an etiology as well as comorbidities due to autoimmune diseases.

5.3.1 Psychological association with achalasia

It was noted that achalasia can occur after a long episode of chronic stress. Since achalasia is a rare disorder, not so many studies try to research the relationship between stress and anxiety and achalasia. In 2020, Kalantari et al. conducted a study that maps the experience of achalasia patients from initial symptoms to management of symptoms. In their findings, they found that people who had achalasia before the diagnosis had anxiety due to the uncertainty about their diagnosis [218]. According to a study from Germany, after the diagnosis of achalasia, patients were more likely to develop depression at significantly higher rates than those without the condition. Regardless of other comorbidities and the clinical characteristics of the patients, achalasia is associated with an increased incidence of depression according to their study [219]. The question whether stress, anxiety, or depression are a contributor or trigger for achalasia, or they are a secondary outcome of achalasia yet needs to be further studied.

5.3.2 AAG

It was also reported that acute stress can be a cause for AAG [220]. There is more evidence that AAG may lead to vitamin B12 deficiency, which may manifest as neuropsychiatric disorders, such as emotional instability, cognitive deficits, depression, and personality change [221]. In 2015, Tenca et al. found that the psychopathological profile has a role in symptoms occurrence in AAG [222]. It was also reported that those with AG have a significantly higher risk of experiencing psychological distress, with younger females (<50 years) displaying the highest risk, regardless of whether they have an infection with *H. pylori* (HP) [223]. Zhao et al. found that chronic atrophic gastritis patients were 54.5% likely to experience depression, as the regression analysis indicated that interpersonal sensitivity correlated positively with depression [224].

5.3.3 Celiac disease

In CD, there is a clear relationship that associates celiac diseases with stress, anxiety, and depression. Just like the other autoimmune GI diseases, the debate is not yet settled. However, it is suggested that CD has a role in these manifestations [225]. CD presents in many clinical presentations that are poorly understood such as changes in behavior are evident in cases of anxiety, depression, short-term memory loss, sleep disturbances, cognitive impairment, psychosis, and attention deficit disorder [226]. In CD, many patients have reported the symptoms of CD after stressful life events [227]. Addolorato et al. reported in a longitudinal study that 71% of people with celiac disease suffered from high levels of anxiety, the levels of anxiety were high in 24% of the control subjects, and 26% of the newly diagnosed celiac patients demonstrated anxiety [228]. In a Swedish study that evaluated patients with CD between 1973 and 2016, they concluded that children with CD have an increased risk of developing psychiatric disorders in adulthood [229]. According to Wahab et al., CD is associated with anxiety and oppositional defiant behavior when it is combined with HLA-DQ2 or HLA-DQ8 risk alleles [230] as a conclusion for their study on CD Autoimmunity and Emotional and Behavioral Problems in Childhood. Depression has been reported

in association with CD since 1951 [231]. Several studies have shown that people with CD are more likely to suffer from depression than people without CD [232–239].

Butwicka et al. found that children with CD had a 1.4-fold greater risk of developing mental disorders compared with the general population. Childhood CD was identified as a risk factor for mood disorders, anxiety disorders, eating disorders, behavioral disorders, ADHD, ASD, and intellectual disabilities in their study. Moreover, mood, eating, or behavioral disorders were more common before celiac disease diagnosis [240]. Individuals with CD have an increased risk of anxiety disorders, according to several studies [228, 241, 242]. These come in agreement with Clappison's systematic review and meta-analysis on the psychiatric disorders association with CD [243]. Psychological symptoms before diagnosis could be caused by the general health of the patient, or by hypoperfusion of the brain in certain regions, a result of vitamin deficiency due to malabsorption. Also, Hyperphomocysteiemia can damage the blood-brain barrier, exposing the neuronal tissue to neuro-irritative substances [226]. Additionally, they may be associated with Ads such as thyroid disease, a risk factor for depression, panic disorder, and type 1 diabetes. There is speculation that one of the possible explanations could be due to the cytokines that are produced by the immune reactions, which can affect the brain circuits that control mood [226].

5.4 EoE

There is some evidence that EoE and its treatments can significantly reduce psychological functioning, resulting in increased anxiety and depression [244]. Mental distress is a common problem among adult EoE patients, with an increased risk of significant anxiety among those younger than 35 years of age [245]. Mechanistically speaking, the protein Eotaxin-1/CCL11 which is involved in Eosinophil Recruitment could be the reason for the pathopsychological involvement in EoE patients. There has been evidence that eotaxin affects the central nervous system, and it was noted that eotaxin-1/CCL11 crosses the blood-brain barrier unaltered [246]. Eotaxin-1/CCL11 inhibits neural progenitor cell proliferation in isolated neurons and neurons derived from neurospheres, as well as in hippocampal slices without affecting their ability to form neurons or astrocytes in vitro [247]. Neurons were not directly affected by eotaxin-1/CCL11. However, related chemokines were able to promote microglial migration and activation, producing reactive oxygen species, which exacerbated glutamate-induced neurodegeneration [248]. The serum levels of 22 cytokines/chemokines, including eotaxin-1 and CCL11, were assessed in 49 patients with major depression, and 49 matched controls reported increased levels of the molecule in an inflammatory context [249].

5.5 Inflammatory bowel disease: celiac disease and UC

Stressors (i.e. environmental events) can affect the expression of symptoms in people with Crohn. It was suggested by Crohn himself, in his book Regional ileitisi in 1949 [250]. It has been reported that stressful life events cause the disease to manifest since 1960 [251–255]. UC has been shown to be psychosomatic disease since 1969 [256]. Psychological stress has been shown to promote systemic and mucosal proinflammatory responses, which could contribute to the exacerbation of UC in everyday life [257]. The UC patients exhibit hostility, somatization, anxiety, and depression even during remission, which is not surprising since the disease was entirely reversible [258]. In general, IBD exhibit more psychological disorder. IBD patients suffer

from high rates of psychological distress and comorbid conditions, including depression, anxiety disorders, and bipolar disorder according to a cohort study [259]. An analysis of 1078 patients with IBD, including 303 patients with Crohn's disease and 775 patients with ulcerative colitis, found that 75% of patients believed that psychologic stress caused an exacerbation of their symptoms [260].

5.5.1 The bidirectionality in IBD

According to a study that assessed perceptions of stress over time (2 years) in three subgroups, those with chronically active symptoms had the greatest perceptions of stress over time [261]. Over time, those with chronically inactive symptoms displayed the lowest levels of perceived stress [261]. Perceived stress scores were intermediate between those whose symptoms fluctuated from inactive to active over the 2-year period. In these studies, the directionality of the association between adverse mental health and active symptoms of disease could not be established [262]. They do indicate, however, that adverse mental health is a problem for those whose disease is symptomatic. Psychological comorbidity is three times more prevalent in people with IBD than in the general population [262, 263]. More than 25% of patients with IBD may suffer from depression and more than 30% from anxiety during their lifetime [262, 264, 265]. Study of the Manitoba IBD Cohort Study population that underwent the CIDI and comparison with the Canadian Community Health Survey population that did the CIDI revealed that people with IBD were twice as likely to have a lifetime history of mood disorders than controls both within 12 months of diagnosis and within a year following diagnosis [262, 264]. Nearly 80% of those with IBD and an anxiety disorder had their anxiety disorder diagnosed more than two years before their IBD diagnosis. It is estimated that more than 50% of those with mood disorders were diagnosed before they were diagnosed with IBD. Therefore, it seems that not just chronic disease symptoms can lead to an increased level of anxiety and depression, but the presence of these psychological diseases could also predispose a person to develop IBD [262].

6. Microbiome and autoimmune diseases: the gut-brain axis in GI autoimmune diseases

Mammalian microbiota consists of a variety of microorganisms, such as bacteria, archaea, fungi, and viruses. A symbiotic relationship exists between humans and bacteria, most of which are present in the gastrointestinal system [266]. An essential component of the host's health and well-being is the gut microbiota, the collection of intestinal microorganisms throughout the GI tract [267]. Assemblage of the gut microbiome begins during birth, primarily from the mother's vaginal and fecal microbiomes if naturally delivered, or from the skin and environmental microbes if delivered via cesarean section [268–270]. There are more than 100 trillion microorganisms living within the GI tract, which together form the microbiota, a complex biosystem. Microbiota are organisms belonging to all domains of life, including Eukaryotes, Bacteria, and Archaea. The main components that comprise this microuniverse belong to the bacterial group and are divided into four phyla: Actinobacteria, Proteobacteria, Bacteroidetes, and Firmicutes [271]. In terms of host health, microbes found in the gut are involved in nondigestible carbohydrates metabolism, immune system development, and drug metabolism. Human diseases linked to gut microbiota

include IBD, metabolic diseases, allergic diseases, and neurodevelopmental diseases [272, 273]. The microbiome of a newborn infant is affected by nutrition, physiochemicals, and biological properties of the body, as well as life events [274]. In this period of life, while breast milk is the primary source of nutrients, there are big shifts in bacterial taxa and much more variation between infants than between adults. Different immune responses to the microbes colonizing the host or other lifestyle factors could account for the large functional and phylogenetic variability [275]. The gut and brain developed from the same tissue, the neural crest, during embryogenesis and influence each other tightly [276].

As both are parts of the immune system, the gut, the brain, and multiple organs can all be affected by disturbances in this system. Communication between the gut and brain is known as gut-brain axis [277]. Communication between the brain and gut involves neural pathways, such as the enteric nervous system (ENS), vagus, sympathetic, and spinal nerves, as well as humoral pathways involving cytokines, hormones, and neuropeptides as signaling molecules [278]. The ENS controls the functions of the gut and includes blood flow absorption, motility, and secretion, and these four compromise the main function of the gut-brain axis [267]. The alteration of the gut microbiota by any factor can lead to signaling to ENS resulting in an alteration in the hormone secretion. Chemical signals from the intestinal epithelium, enteric endocrine system, and immune system are highly receptive to this area, and it provides input to sensory pathways that signal the emotional and cognitive centers of the brain. ENS also receives efferent information from the brain via autonomic neural connections (sympathetic and parasympathetic) and hormonal pathways that modulate digestive functions [279]. Food intake regulation, glucose metabolism, and modulation of the GI-associated immune system include digestive processes, GI tract synchronization of physical and emotional states are all part of brain-gut axis interactions [267]. The relationship between gut-brain axis and stress, depression, and anxiety is well established. These psychological conditions have biological mechanisms and manifestations. Allostasis is process in which the body's ability to restore homeostasis can result these psychological conditions. In allostasis, the hypothalamic-pituitary-adrenal (HPA) axis regulates the body's stress response systems, including neuroendocrine signaling and the glucocorticoids it produces, and BDNF it regulates, help with memory and learning [280]. Glucocorticoids is released from adrenal glands during stressful events, and it controls the homeostatic conditions. However, it can result anti-inflammatory responses [281]. It was shown that the gut microbiota helps to regulate the stress response as its absence results in an overproduction of Glucocorticoids after stressful events, particularly through Lactobacillus spp. in stress. In addition, it was shown that *Lactobacillus rhamnosus* reduces anxiety and Bifidobacterium spp. improves stress.

There is bidirectionality between gut and the microbiota in stress management. Through the release of cytokines and neurotransmitters, inflammation of the GI tract stresses the microbiome [282]. In conjunction with the increase in intestinal permeability, these molecules then travel systemically. Rogue molecules from the permeable gut (leaky gut) are amplified when blood levels of TNF-a and MCP (monocyte chemoattractant protein) are elevated [283, 284]. Anxiety, depression, and memory loss result from their release [285]. It was reported that there is a relationship between elevation of IL-5 and TNF-a with depression and anxiety that suggest that these pro-inflammatory cytokines are involved in the development of anxiety and

depression which is also manifested in chronic inflammation and altered immune cells in the peripheral blood [284]. The hypothalamicpituitary- adrenal (HPA) axis can be simulated with pro-inflammatory cytokines. The hypothalamus can release corticotropin releasing factors simulating the adenohypophysis to release adrenocorticotropic hormone (ACTH). The ACTH can induce the release of cortisol which is a stress hormone from the adrenal gland which acts as negative feedback in the pro-inflammatory signal transduction. Hyperactivity of the HPA axis is a major cause of psychological responses such as stress, anxiety, and depression [286].

The research focus on gut-brain axis is recent and it's not proceeding with the pace that it was expected to be. Nevertheless, it's a complicated area of research due to variety of factors that are involved in the process and the multiple pathways that could play a vital role in the processes. In addition, the components of the gut microbiota are huge. Several neural, hormonal, metabolic, immunological, and microbial signals drive gut-brain communication [287]. In autoimmune diseases, many patients have reported psychological comorbidities and it's not confirmed whether these comorbidities are due to quality of life with the disease, or they are one of the inducers that are involved in the pathogenesis of the disease. It could be bidirectional, nevertheless. There is an autoimmune component to major psychiatric disorders. In psychiatric disorders, disequilibrium of cellular processes in the GI tract is likely to contribute to immune dysfunction [288]. Symptoms of gastrointestinal diseases worsen psychological complaints and vice versa, suggesting a significant role for an imbalance in the gut-brain axis in both conditions. The gut is strongly implicated in a variety of neurological diseases via direct and indirect mechanisms, according to growing evidence. Intestinal microbes and their products (e.g., metabolites) as well as immune education in the mucosal immune system, including the release of proinflammatory cytokines, are key components. The intestinal epithelium regulates these processes by translating signals from bacteria and inflammation to the immune system and secreting hormones and peptides which are involved in the metabolic processing of dietary nutrients [289]. Some of GI autoimmune diseases mechanisms of gut-brain axis role and the clear direct relationship of stress, anxiety and depression are well established such as IBD [290, 291] and CD [292]. Since this is a growing area of the research, more investigations need to be done to cover the relationship between the involved components.

7. Conclusions

To conclude, GI autoimmune diseases can be compromising to the patients' life, and they can be due to multiple factors. Over the past few decades, the number of GI autoimmune diseases have increased exponentially. GI autoimmune diseases although they are organ specific. Nevertheless, there is a need for multidisciplinary approaches for diagnosing and understanding the pathogenesis of these diseases. Antibodies provide a current excellent predictor for those diseases. Nevertheless, the investment in biotechnology to develop more specific and sensitive tools for is needed. The understanding of the interwinding between the brain and gut as well as other etiological factors can provide better approach in preventive medicine in dealing with this disease as well as increase in the quality of the life of the patients beside the current available pharmacological and surgical available options.

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Conflict of interest

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