Chapter

Autoimmune Diseases of the GI Tract Part II: Emergence of Diagnostic Tools and Treatments

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Abstract

Autoimmune diseases (AD) have emerged as a pandemic in our modern societies, especially after the World War II. In part I, we have reviewed five main diseases and shed light on different aspects from introducing the concept of autoimmunity, the description of the disease's pathogenesis and the diagnosis, the role of antibodies as markers for the prediction of the disease, 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 this chapter, we review 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, autoantibodies, artificial intelligence, machine learning, immunological nutrition

1. Introduction

Autoimmune diseases can be defined as the inability of the human system to distinguish its own bodies from foreign bodies [1, 2]. The diagnosis of autoimmune diseases is not easy. However, with the emergence of the serological tool and our progress in understanding the science of the immunology, antibodies provide an excellent role in the prediction of GI autoimmune diseases. They serve as markers for the prediction or confirming the presence of an autoimmune disease. The emergence of artificial intelligence (AI) and the integration of machine learning (ML) algorithms in many applications and their incorporation into the health sector as well open the gate for improved diagnosis and management of the diseases. In ADs, they could be great asset as many of the diagnostic tests depend on imaging techniques that their interpretations could vary from one clinician to another. The treatment of GI autoimmune

diseases could be variable from the need for elimination diets to surgical interventions depending on the case and the disease.

In the previous chapter, we provided an introductory background on autoimmune diseases, definition of pathophysiology and etiology of autoimmune diseases, a review of the five most common GI autoimmune diseases, the role of psychological association with GI Tract autoimmunity, and microbiome and AD: The Gut–Brain Axis. In this chapter, which is a continuation of the second chapter we discuss other aspects that include shading the light and in-depth review of the fascinating roles of antibodies as predictors for the GI autoimmune diseases, the role of dietary and nutritional implications, the use of artificial intelligence in diagnosis of GI autoimmune diseases, and the treatment of GI autoimmune diseases.

2. Antibodies as predictors of the GI autoimmune diseases

The presence of autoantibodies in patient's serum has been considered a common symbol of autoimmune diseases. Autoantibodies are produced by pathogenic B cells, to target individual's own tissues. Many have considered them a clinical marker of diseases that can diagnose and predict prognosis of the disease. However, one GI disease can have more than one autoantibody, and many other diseases share the same autoantibodies. Some autoantibodies are specific to specific diseases, and some are not [3, 4]. This section is intended to give an overview of the most common and important autoantibodies in GI autoimmune diseases.

2.1 Anti-parietal cell antibody (APCA)

Anti-parietal cell (APCA) is an autoantibody that targets H+/K+ ATPase, a heterodimer made of alpha- and beta-subunits. This enzyme is a proton pump located on parietal cells, that is involved in the production and release of high amount of hydrochloric acid [5]. Studies have shown that the isotypes of APCA immunoglobulins ate A, M, and G isotypes [6]. Many studies have associated APCA with autoimmune GI diseases, such as atrophic gastritis and Helicobacter pylori-associated atrophic gastritis. For example, H+/K+ ATPase has been considered a major antigen in H. pylori-associated antigastric autoimmunity [7]. Antibodies against this antigen are believed to have a crucial role in H. pylori-associated atrophic gastritis too. This was concluded by Ito et al., as the levels of APCA were significantly higher in patients with severe atrophy than in patients with mild atrophy ($P = 0.01$) [8]. Furthermore, H+/K+ ATPase is also a major antigen in autoimmune gastritis [9]. It is important to note that chronic gastritis, most commonly autoimmune gastritis and H. pylori gastritis, can result in atrophic gastritis [10]. To help identify atrophy, Claeys et al. state that APCA, which are closely associated with classical autoimmune gastritis, can be used as useful indicators for the atrophy of body mucosa in chronic H. pylori gastritis [7, 11].

Moreover, APCA can also predict one's risk for developing atrophic gastritis and its severity. For instance, Zhang et al. detected an overall APCA prevalence of 19.5%. They discovered that APCA prevalence was strongly associated with an approximately fourfold increased risk of chronic atrophic gastritis (CAG) (46.2% vs. 18.0%, adjusted OR = 3.8; 95% CI: 3.1–4.7). This striking association was even more increased with raising severity of chronic autoimmune gastritis (CAG) defined by PGI levels. As a result, they concluded that examining APCA levels might be a useful marker to be added when screening patients for CAG [11]. De Block et al. also conclude that

individuals with positive anti-gastric parietal cell are at a higher risk for atrophic gastritis [12]. To summarize, occurrence of APCA can help predict the development of atrophic gastritis in the future.

2.2 Intrinsic factor antibodies (IFA)

Intrinsic factor antibodies are IgG autoantibodies that attack a 60-Kd intrinsic factor glycoprotein secreted by parietal cells that bind to vitamin B-12 and allow for its absorption. There are two types of those autoantibodies, the first is called Type I, which targets cobalamin binding sites and prevents the combination of IF and vitamin B-12. The other type is called Type 2, which targets ileal mucosa receptor and prevents IF-vitamin B-12 complex attachment to it [13, 14]. In addition to H+/K+ ATPase, intrinsic factor (IF) is also a crucial autoantigen in pernicious anemia [15]. IFA have been detected in 13 to 60% of patients with pernicious anemia [16–19] Type I IFA is found to be the predominant type in those cases. While Type II is only found in about half of those cases, Type II IFA is rarely detected in the absence of Type I IFA [14]. IFA has also been associated with autoimmune body gastritis. For instance, Lahner states that intrinsic factor autoantibodies are 100% specific for biopsy-proven autoimmune body gastritis. Moreover, they detected IFA in 27% of patients with ABG and none in healthy controls. Finally, Lahner et al. concluded that testing patients for IFA along with APCA can significantly increase the diagnostic accuracy for atrophic body gastritis and pernicious anemia [20].

2.3 Anti-transglutaminase (TGA)

Anti-transglutaminase (TGA) are autoantibodies targeting tissue transglutaminase (tTG) or transglutaminase 2, which is a 76-kD calcium-dependent ubiquitous enzyme released during inflammation that catalyzes the post-translational modification of proteins [21]. This ubiquitously expressed enzyme also plays a role as a GTPase, ATPase, and protein kinase [22]. This enzyme has been considered a specific marker for celiac disease (CD). Dieterich et al. were one of the first scientists to determine the role of tTG in CD [23]. Sabatino et al., further explain that tTG has at least two roles in CD one is being a deamidating enzyme to enhance the immunostimulatory effect of gluten, and the other as a target autoantigen in the immune response [21]. In a systematic review done by Ghatti et al., 11 studies detected intestinal transglutaminase 2 Immunoglobin A (IgA) deposits in 100% of adults with overt CD, while the prevalence in children ranged between 73.2 and 100% [24]. Similarly, in a study examining children, Borrelli et al. detected anti-TG2 IgA deposits in all 53 patients with confirmed CD and three out of three potential patients with CD. As a result, Borrelli et al. concluded that intestinal deposits of anti-TG2 appear early in the course of the disease and are of constant presence in patients with CD [25]. Furthermore, other studies detected TGA presence in serum of patients with CD. For example, Miller et al. detected TGA presence in 46 patients with untreated CD (sensitivity 100%) [26]. Moreover, in a study testing 37 patients with biopsy-confirmed CD, Damoiseaux et al. found that 86.5% have IgA antirecombinant human tissue transglutaminase antibodies (rh-tTGA) [27]. In addition, Tola et al. found significantly high levels of TGA in patients with CD [28]. TGA can be even found in the serum of asymptomatic individuals who later in life develop CD [29], which further emphasizes its importance in detecting CD. In fact, Rubio-Tapia et al. have found that elevated IgA anti-TGA has been associated with an increased mortality rate

among men aged 50 years old. They also concluded that IgA anti-TGA could be used as a nonspecific marker of serious disease in older men [30]. There are few studies documenting IgA anti-TGA in Crohn's disease; however, there are other conflicting reports about anti-TGA IgG presence [31, 32]. Tola et al. have found significantly low positive values in IBD (Crohn's disease and ulcerative colitis (UC)). In addition, Tursi et al. also detected antitransglutaminase (anti-tTG) in 5 out of 27 (18.52%) patients with Crohn's disease [33]. While Shor et al. also detected positive IgG tTG in 4 out of 26 patients with UC, and 2 out of 194 in healthy controls (11.1% versus 1%; P = 0.018) [28]. As a result, TGA was not found to be useful in IBD; therefore, serological screening testing was only recommended if there is a relevant clinical suspicion of Crohn's [34]. While in IBD, Watanabe et al. detected significantly higher levels of antibodies against tissue transglutaminase in patients, which also correlated with disease severity [35]. IgA against the autoantigen tissue transglutaminase (tTG) is frequently associated with untreated Crohn's disease but disappears with gluten exclusion [23]. TGA has also been associated with Crohn's disease and its severity.

Moreover, Fevre et al. also detected anti-tissue transglutaminase antibodies (TTG Ab) in 23% of patients diagnosed with eosinophilic esophagitis (EoE) during the study. Shor et al. also detected positive IgG tTG in 4 out of 26 patients with ulcerative colitis, and 2 out of 194 in healthy controls (11.1% vs. 1%; P = 0.018) [28].

2.4 Anti-gliadin antibodies (AGA)

Anti-gliadin antibodies are antibodies that are targeted toward Gliadin, a protein found in Bread wheat, rye, and barley [36]. AGA IgA antibodies have been shown to be one of the hallmarks of CD. For instance, Jassim et al. tested AGA-IgA and AGA-IgG in 58 patients with celiac disease and 27 healthy control and found that both antibodies were significantly higher in the CD patients than in control [3]. In addition, Damoiseaux et al. found that 73% of 37 patients with biopsy-confirmed CD have IgA AGA in their serum [27]. Moreover, Lindqvist et al. have found that patients with psoriatic arthritis have an increased prevalence of high serum IgA AGA and of CD [37]. In fact, CD was commonly found in patients with isolated positive AGA; therefore, Taylor et al. recommended that all those patients should be referred to gastroscopy (OGD) and D2 biopsy to undergo further investigation [38]. Both AGA and anti-tTG antibodies are considered good serologic indicators of CD, and they can be even found in the serum of asymptomatic individuals who later in life develop CD [29, 39]. The sensitivities detected for tTG, AGA IgA, and AGA IgG are 90 to 98%, 80 to 90%, and 75 to 85%, respectively. While the specificities were found to be 95 to 97%, 85 to 95%, and 75 to 90%, respectively [40, 41]. Moving to Crohn's disease, Tursi et al. detected AGA in 8 out of the 27 patients with Crohn's disease (29.63%) [33]. Furthermore, Shor et al. detected high levels of AGA IgG in 17 out of 83 patients with Crohn's disease, and 20 out of 194 in healthy controls (20.5% vs. 10.3%; P = 0.023) [28].

2.5 Anti-endomysial antibodies (EMA)

The endomysium is a perivascular connective tissue that separates smooth muscle fibers from each other [42]. Dieterich et al. stated that tissue transglutaminase is the target antigen in endomysium in CD [23]. Detection of anti-endomysial antibodies (EMA) in blood has been used as the most specific test to diagnose CD. However, EMA lacks sensitivity, particularly in the earlier stages of disease exhibiting mild villous atrophy [38, 43]. On the other hand, Farrell et al. state that sensitivity of EMA

IgA is equal to or exceeds 90%, while the specificity approaches 100% in untreated patients with CD. Kanthi et al., similarly, mention that the sensitivity and specificity of IgA EMAs are found to be 85–98% and 97–100%, respectively. As a result of that, blood EMA testing is estimated to have a high positive predictive value [44]. Another characteristic of EMA includes that the antibodies' levels fall after following a gluten-free diet [45]. Similar to IgA AGA, IgA EMA antibody will also not be detected in IgA deficient CD patients [46]. As for using it, Keren et al. recommended testing for EMA to help select patients who would be qualified for a biopsy [47]. While others used it for screening and estimating the prevalence of CD [48]. Kanthi et al. stated that EMA IgG_1 have been used for diagnosing celiac disease, especially in IgA-deficient patients [44]. EMA has also been detected in other diseases. For example, Damoiseaux et al. detected IgA EMA presence in 86.5% of 37 patients with biopsy-confirmed CD [27]. Moving on to Crohn's disease, Tursi et al. only found anti-endomysial antibody (EMA) in 4 out of 27 patients with Crohn's disease (14.81%) [33].

2.6 Anti-Saccharomyces cerevisiae antibodies (ASCA)

Anti-S. cerevisiae antibodies (ASCA) are autoantibodies targeted toward the mannose residues on unicellular fungus *S. cerevisiae* (S. cerevisiae) [49]. Several studies associated those antibodies with GI autoimmune diseases. For instance, Shor et al. detected high levels of IgA ASCA in 16 out 83 patients with Crohn's disease patients, while only 2 of the 198 healthy controls had positive ASCA titers (19.3% vs. 1%; P = 0.000). In addition to IgA ASCA, the high titers of IgG ASCA were detected in 23 out of 83 patients with Crohn's disease, while only one healthy control of the 194 had a positive IgG ASCA titers (27.7% versus 0.5%; P = 0.000) [28]. Even in a pediatric population, El-Matary et al. detected a correlation between both ASCA IgA and IgG titers and clinical Crohn's disease activity [50]. Furthermore, Smids et al. detected IgA ASCA in 23% of Crohn's disease patients and only 3% of UC patients [51]. However, ASCA is not a specific marker for Crohn's disease, since it was also detected in patients with CD. Kotze et al. tested patients with Crohn's disease, and 3 groups of CD patients, including those at time of diagnosis, patients that follow gluten-free diet, and lastly, others who admit transgression in their gluten-free diet. Kotze et al. found statistically significant levels of ASCA IgA in patients with Crohn's disease, in addition to patients with CD at diagnosis and others that admit transgression in their gluten-free diet. Furthermore, ASCA IgG was also positive in Crohn's disease and in all groups of CD. They concluded in their study that ASCA detection is associated with the inflammation of small intestine [52]. Moreover, it was also detected in CD. For example, Damoiseaux et al. detected ASCA presence in 16 of 37 patients with biopsy-confirmed CD [27]. Also, Granito et al. detected IgA and/or IgG ASCA in 59% of 105 subjects with CD at the time of diagnosis. In their study, they did not find any significant correlation between ASCA positivity and severity of small intestinal mucosal damage. Furthermore, they tested 93% of revaluated coeliac patients again after they had followed a gluten-free diet and did not detect IgA ASCA. Instead, 83% of the subjects maintained their IgG ASCA reactivity [53]. ASCA can even help in predicting the development of CD in patients before they present with symptoms [53, 54]. Granito et al. called them the "potential/silent" CD and suggested diagnosing them with CD in case of positive serological markers (EmA and tTG) and typical HLA predisposing genotype (DQ8 or DQ2) [55]. In a study involving a Korean cohort, Choi et al. detected a positive rate of ASCA in 44.35% of patients with intestinal Behcet disease, compared to 8.8% in

healthy control subjects [56]. Furthermore, Cheng et al. concluded in a metanalysis of 9 studies, that there is a strong correlation between ASCA and gastrointestinal Behcet disease, specially ASCA-IgG (OR = 5.50 (95% CI 2.58 to 11.55), p = 0.000) and ASCA-IgG + IgA (OR = 5.36 (95% CI 1.40 to 20.45), p = 0.014). The study also found that in gastrointestinal Behcet disease the positivity rate of ASCA was higher significantly than that in UC: IgA (OR = 2.13 (95% CI 1.30 to 3.50), p = 0.003); IgG + IgA (OR = 2.19 (95% CI 1.03 to 4.66), p = 0.042); IgG/IgA ((=2.03 (95% CI 1.30 to 3.17), p = 0.002). Moreover, the frequency of ASCA-IgG was found to be significantly higher in patients with Crohn's disease than in those with gastrointestinal Behcet disease (OR = 0.48 (95% CI 0.28 to 0.83), p = 0.009, [57]. This shows that ASCA plays a significant role in pathogenesis of autoimmune gastrointestinal diseases. ASCA have also been detected in other diseases. Shor et al. also detected IgG ASCA in Crohn's disease, Graves' disease, SLE, vasculitis, and cryoglobulinemia patients [28].

2.7 Perinuclear anti-neutrophil cytoplasmic antibodies p-ANCA

Perinuclear anti-neutrophil cytoplasmic antibodies (p-ANCA) are a subset of anti-neutrophil cytoplasmic antibodies (ANCA) that target the heterogeneous collection of antigens, such as myeloperoxidase (MPO), cathepsin-G, elastase, lactoferrin, and bactericidal/permeability-increasing protein. p-ANCA mostly recognizes MPO, followed by neutrophil elastase, lactoferrin, and other antigens [58]. Atypical p-ANCA binds to those antigens in neutrophil granules leading to the staining of rim of the neutrophil nuclei and intranuclear foci [19]. p-ANCA is thought to be more dominant in UC than in Crohn's patients. For instance, p-ANCA has been detected in 40–80% of patients with ulcerative colitis compared to 5–25% of patients with Crohn's disease [58]. In addition, Smids et al. detected p-ANCA in 45% of UC patients, and only 5% of Crohn's patients [51]. Moreover, Ruemmele et al. state that p-ANCA are 92% specific for detecting ulcerative colitis, as those autoantibodies were absent in all non-IBD controls [59]. Smids also confirms p-ANCA specificity to UC (p = 0.0001) [51]. In addition to IBD, Freeman states that p-ANCA can also be present in patients with histologically-defined celiac disease with or without concomitant lymphocytic colitis [60]. Damoiseaux et al. also confirm the presence of p-ANCA in celiac disease patients as they detected its presence in 8 of 37 patients with celiac disease (21.6%) [27].

2.8 Autoantibodies against epithelial cell adhesion molecules

In a study examining eosinophilic esophagitis (EoE) patients, Dellon detected higher levels of anti-DSG3 IgG4 in EoE patients' serum compared to healthy controls (p = 0.02). In addition to that marker, he also detected very high levels of Anti-NC16A IgG4 EoE patient's serum when compared with healthy controls (p < .001), which then led him to conclude that this marker is useful for diagnostic utility as a serum-based EoE biomarker [61].

2.9 IgE/IgG to food antigens

It has been shown that EoE patients' serum exhibited various IgE against food antigens. For instance, Roy-Ghanta et al. found that 82% of 23 patients with biopsy-proven EoE exhibited serum IgE targeting one or more food-associated

allergens. Most common food allergens were onion, wheat, carrot, and tomato [62, 63]. Moreover, Erwin et al. have also concluded that EoE-sensitized patients have higher IgE titers in comparison to nonsensitized patients (median, 150 vs. 13 IU/mL; $P < .001$) [64]. It is also common for EoE patients to have IgE targeting some milk proteins. For example, using ImmunoCAP assays for specific milk allergens, Erwin et al. have detected positive IgE antibodies in 31 out of 34 EoE patients. He then detected a strong correlation between IgE antibodies targeting Bos d 4 (α-lactalbumin) and Bos d 5 (β-lactoglobulin) and milk extract ($R = 0.89$ and $R = 0.76$ respectively; $p < 0.001$) [65]. In another example, Schuyler et al. also confirm the prevalence of antibodies against milk proteins in EoE patients. He found that 79% of 67 children diagnosed with EoE had cow milk (CM) sensitization (sIgE ≥0.10 IU/mL) compared with unselected controls, where only 22% of 101 had CM sensitization. When comparing specific IgG4 and total IgG4, both were significantly detected in EoE patients in comparison to unselected controls ($p < 0.001$ vs. $p < 0.01$, respectively). Just like Erwin et al., Schuyler et al. also found significantly high titer of antibodies against alpha-lactalbumin; however, the antibody was sIgG4, when compared to control ($p < 0.001$). He also detected another targeted protein in milk which was caseins ($p < 0.001$) [66]. Clayton also reports the presence of IgG4 targeting food in EoE patient's serum [67].

2.10 Aeroallergen-specific IgE

There can be a difference in aeroallergen-specific IgE serum levels between age groups in EoE patients. For instance, Erwin et al. have noticed that children have higher aeroallergen-specific IgE serum levels than adults. Regarding specificities, Erwin et al. have shown that prevalence of sensitization to one or more aeroallergen specificities was higher than that in children (93% vs. 65%), while the sensitization to each individual aeroallergens ranged from 12 to 61% [65].

2.11 Circulating antimyenteric autoantibodies (CAA)

CAA are circulating antibodies that target the myenteric neurons located in the GI tract. Several studies have associated those autoantibodies with the pathogenesis of achalasia disease. For instance, Storch et al. have detected IgG antibodies directed at Auerbach's plexus, also named myenteric plexus, in patients with achalasia with varying duration and stages of diseases (specificity 93%, sensitivity 64%, $p < 0.0001$) [68]. Furthermore, Verne et al. also detected them in 7 out of 18 achalasia patients. Those autoantibodies were found to stain most of the neurons found within plexi in the intestinal and esophageal sections, even nitric oxide synthase positive and negative neurons. While none of the controls exhibited neuronal staining [69]. Moreover, Ruiz-de-León et al. also confirmed CAA association with achalasia, as he found CAA in 54.3% of patients with achalasia and only 7.5% of healthy individuals ($P < 0.001$) [70]. When examining nuclear or cytoplasmic fluorescence patterns, Kallel-Sellami et al. found significantly high titers of CAA in patients with achalasia, in comparison to healthy controls (33% vs. 12%, $P = 0.03$ and 48% vs. 23%, $P = 0.001$ respectively) [71]. On the other hand, Kraichely et al. did not detect any specific myenteric neuronal antibody in all the 70 patients with primary achalasia he examined. Instead, they found significantly high levels of GAD65 autoantibody in patients with achalasia, which is an autoantibody found in other autoimmune diseases such as type 1 diabetes mellitus ($P < 0.0001$) [72].

3. Artificial intelligence (AI) in the diagnosis of GI autoimmune diseases

Artificial intelligence is a study of methods capable of imitating intelligent human behavior (e.g., making decisions under uncertain conditions) [73]. Machine learning (ML) is a subset of AI. The introduction of machine learning (ML) has revolutionized the image processing and analysis field in medicine. ML in computer science can be defined as the process by which computers can learn without being explicitly programmed. Machine learning is intended to assist in learning from data. There are many datasets available today, leading to an increase in ML demand [74]. The information extracted from the data can sometimes be difficult to interpret after viewing it. The use of ML can make machines more efficient at handling data. There are two famous models in ML which are unsupervised and supervised machines [75]. Supervised learning is an optimum choice for smaller volumes of data and clearly labeled data [76]. For large datasets, unsupervised learning generally results in better performance and results. If a large dataset is readily available and labeled, deep learning techniques are optimum for use [77]. The application of AI and ML in healthcare has a promising potential in providing medical solutions for the healthcare sector. One of the aspects that could be a valuable addition to the healthcare sector is the incorporation of AI into the diagnosis. In this section, we aim to shed the light on some of the recent applications of AI in GI autoimmune diseases.

3.1 AI in achalasia diagnostics

AI has not explored much of achalasia diagnosis. One of the scarce examples is the work of Carlson et al. where they used functional luminal imaging probe panometry as a method to detect achalasia subtypes using ML. Manometry was performed on 180 patients with achalasia's 3 subtypes. FLIP is a technique that is used to measure distensive pressures and distension-induced esophageal contractions. Correlation analysis, single tree, and random forest were adopted to develop classification trees to identify achalasia subtypes. Their decision tree model accurately identified spastic (type III) versus nonspastic (types I and II) achalasia with 90% and 78% accuracy, respectively. The train and test cohorts correctly identified achalasia subtypes I, II, and III with 71% and 55% accuracy, respectively [78]. In a recent conference proceeding, Jiang et al. reported an automated real-time esophagus achalasia detection method for esophagoscopy assistance through the use of convolutional neural network (CNN) to detect all achalasia frames in esophagoscopy videos. Since it is hard to distinguish achalasia features, they further introduced dense pooling connections and dilated convolutions in the CNN to better extract features from esophagoscopy frames. They reported a real-time achalasia detection system that achieved 0.872 accuracy and 0.943 AUC score on their dataset [79].

3.2 AI in AAG diagnostics

The atrophic gastritis can benefit from the applications of AI in the diagnosis as well. It is often hard to distinguish between the different types of gastritis. One of the most promising applications is the recent report by Franklin et al. that utilized a CNN machine learning model that can distinguish between cases of HPG and autoimmune gastritis with accuracy equal to GI pathologists [80]. This could be beneficial particularly in AAG since it is hard to diagnose pathologically depending on the expertise of the clinician.

3.3 AI in celiac disease diagnostics

Diagnosis of celiac disease (CD) is difficult because its symptoms are shared with many other diseases. However, AI can be used to further facilitate the diagnosis of CD. Joceli et al. proposed a web-based Clinical Decision-Support System (CDSS) using ML algorithms to identify CD. The database used for testing and training the algorithms consisted of clinical data of patients with 35 attributes of CD-related symptoms recorded per case. For the training set, a total of 178 cases were recorded out of which 46% were diagnosed with CD. For the testing set, a total of 38 cases were recorded out of which 37% were CD positive. The study used different variations of 13 algorithms equating the total number of models to 270. The algorithms were trained on the training set, and the best variation of each algorithm was used on the testing set. The selection criteria were the area under the curve of the receiver operating curve (AUC ROC). The results were compared with clinical diagnosis and the golden standard, and the results showed that the best algorithm was able to diagnose the CD cases with great accuracy. This preliminary work shows the prospective of using AI can be used to aid physicians in their diagnosis of diseases like CD [81].

3.4 AI in EoE diagnostics

The applications of AI in EoE have been on rise. One of the most recent applications by Guimarães et al. is the utilization of CNN networks in endoscopic images of EoE. Their study examined 484 real-world endoscopic images taken from 134 subjects within three distinct categories (normal, EoE, and candidiasis). In their results, they found that global accuracy (0.915 [95% confidence interval (CI) 0.880–0.940]), specificity (0.936 [95%CI 0.910–0.955]), and sensitivity (0.871 [95%CI 0.819–0.910) were all higher than for the endoscopists on the test set. The global area under the receiver operating characteristic curve was 0.966 [95%CI 0.954–0.975] [82]. One study by Dnaiel et al. applied machine learning to EoE biopsies and created a dataset for training a multilabel segmentation deep network. Their model was able to segment intact and notintact eosinophils with a mean intersection over union (mIoU) value of 0.93. This segmentation was able to quantify intact eosinophils with a mean absolute error of 0.611 eosinophils and to classify EoE disease activity with an accuracy of 98.5%. Their model achieved 94.8% accuracy, 94.3% sensitivity, and 95.14% specificity in detecting EoE disease activity when using whole slide images from the validation cohort [83]. EoE diagnosis could be flourished with the introduction of AI as more already ongoing research on it in the literature [84–87].

3.5 AI in IBD diagnostics

AI has also been explored widely in IBD diagnosis. The need for AI in identifying IBD and correctly identifying the type of Crohn's disease and ulcerative colitis has been pointed out by Suandram et al. The problem with diagnosing IBD through endoscopy is the subjectivity of the endoscopist in interpreting the results rather than the endoscopic result visualization. To aid in the decision-making, making AI-based applications exist, such as computer-aided diagnosis (CADx). The works reviewed by Suneha et al. have shown great accuracy in detecting and differentiating IBM diseases. Mossotto, 2017 was able to classify UC and Crohn's disease with an accuracy of 83.3% using pediatric data involving endoscopic images and histology [88]. Barash,

Study	Disease	Classification Technique	Predicting Classes	Accuracy (%)	Sensitivity (%)	Specificity (%)
(Carlson et al. 2021)	Achalasia	Decision Trees	Type I	55	9	86
			Type II		72	23
			Type III		64	97
(J. Zhang et al. 2021)	Atrophic Gastritis	Improve-DenseNet	AG/ Non-AG	98.63	95.42	93.87
(Y. Zhang et al. 2020)		DenseNet 121	Mild, Moderate, and Severe	94.24	94.58	94.01
(Tenório et al. 2011)	Celiac Disease	Bayesian Classifier (AODE-F1)	CD/ Non-CD	80	78	80
(Manandhar et al. 2021)	Inflammatory Bowl Diseases*	Decision Trees	IBD/ Non-IBD	0.72 ± 0.02	0.81 ± 0.04	0.63 ± 0.04
		Elastic Net		0.69 ± 0.02	0.77 ± 0.05	0.62 ± 0.06
		Neural Networks		0.63 ± 0.04	0.80 ± 0.22	0.46 ± 0.18
		Random Forrest		0.74 ± 0.02	0.84 ± 0.03	0.64 ± 0.04
		Support Vector Machines		0.67 ± 0.02	0.77 ± 0.06	0.58 ± 0.06
	Inflammatory Bowl Diseases*	Random Forrest	Crohn's/UC	0.83 ± 0.03	0.85 ± 0.04	0.80 ± 0.06

Table 1.
AI applications summary in GI tract autoimmune diseases.

2021 was able to diagnose CD ulcer severity with great accuracy based on capsule endoscopy images [89]. On the other hand, Gottlieb, 2020 used an endoscopy video to the grade the UC severity [90]. Takenaka, 2020 predicted the UC remission with 90% accuracy using endoscopic images and histology [91]. For detailed reviewing of AI in IBD, we refer the reader to in-scope reviews (**Table 1**) [92–101].

4. The role of dietary in GI autoimmune diseases: Nutritional implications

The value of the nutrition in the treatment and the prevention of the diseases has been known for thousands of years before the current modern medicine. The growing interest in the value of nutrition made it clearer that many of the diseases that have boomed in the modernism era are entangled with the poor nutrition and the lifestyle of the individuals. In this section, we aim to explore the role of the nutrition in the GI autoimmune diseases.

4.1 Role of dietary interventions in achalasia

Nutrition in patients with achalasia has often been overlooked. Achalasia is initially characterized by dysphagia when eating solid and liquid foods. Solid food tends to cause more dysphagia than liquids. Most patients modify their eating habits to ease

the progress of the food bolus: eating more slowly or using certain maneuvers, such as raising the arms or arching the back [102].

The disease is extremely rare and has a high success rate in treatment. The clinicians usually recommend the patients to eat what they can tolerate and usually the patients resume the regular diet after the treatment. An adequate nutrition modification should be a part of the therapy. If the patient experiences swallowing difficulties, they may be advised to reduce their fiber intake as soluble fibers increase the viscosity of the bolus, decreasing its absorption, while insoluble fibers have a high water-binding capacity, increasing the bulk of the bolus. Low-fiber diets would be physiologically advantageous in situations where luminal narrowing is present, such as in achalasia due to high LES pressure. There is a possibility that some patients will have to switch to high-calorie/protein liquids if this is necessary for their condition. Patients with persistent vomiting might also benefit from supplementation with thiamine (and other vitamins and minerals). Achalasia patients who continue to have difficulty meeting their nutritional needs orally may need gastric access for enteral feeding, but this is rarely needed due to the effective treatment options available [103–105].

4.2 Role of dietary interventions in AAG

AAG patients are reported to have the malabsorption of food-bound vitamin B12 due to decreased IF production resulting in hematological, gastroenterological, and neuropsychiatric disorders. In addition, they are reported to have malabsorption of iron resulting in microcytic anemia. They are also reported to have a vitamin C deficiency that leads to decreased antioxidant defense, immunity, and protein synthesis. They are also reported to have calcium deficiency that could lead to osteopenia/osteoporosis. Furthermore, they are reported to have vitamin D deficiency that could lead to secondary hyperparathyroidism, osteopenia/osteoporosis, decreased immunity, and an increased risk of autoimmune disease development [106]. It is recommended that patients with AAG to follow an anti-inflammatory diet and avoid the food that causes inflammatory responses [107]. Some foods in particular such as garlic could be of beneficial use in the anti-inflammatory intake [108–111]. In addition, probiotics that can have positive influence on the gut microbiota have been shown to be good for the diet of AAG patients [112].

4.3 Role of dietary interventions in celiac disease (CD)

Gluten is considered an environmental trigger for CD. Unlike other autoimmune diseases, the progression and chronic dynamics of CD are reversible. The reconstruction of the mucosa is also achievable when accompanied by total gluten avoidance [113]. Hence, a strict gluten-free diet (GFD) results in intestinal and extraintestinal symptoms improvement, intestinal villi regrowth, and autoantibodies negativity. Furthermore, this diet reverses the complications of CD that includes malabsorption, osteopenia, osteoporosis, diarrhea, bloating, constipation, and abdominal pain [114]. Besides a GFD, lactose present in milk and most dairy products should be avoided at the early stages of treatment due to a brush border lactase deficiency that is a secondary result of the surface epithelial cells damage [113]. Another thing to consider is a diet low in fermentable, oligosaccharides, disaccharides, monosaccharides, and polyols (FODMAPs). Since irritable bowel syndrome (IBS) symptoms are prevalent in 38% of CD-treated patients, these symptoms

persist even when they are following a strict GFD [115]. Lactose-free milk/yogurt, feta, cheddar, mozzarella, parmesan, brie, butter, and plant-based milk/yogurt are good alternatives that have low lactose content. A variety of dairy products that are low in lactose could provide CD patients with sufficient calcium. However, when choosing nondairy, lactose-free products that are made from soy, rice, and nuts it is crucial to find products that are supported with calcium since plant-based products are poor in calcium. CD individuals should aim for 200 – 300 mg of calcium/250 ml per serving [116].

Oats, rice, corn/quinoa/millet bread, sourdough, starch, corn tortilla, potato, soba/rice sticks/kelp/brown rice noodles, sago, samp, wonton wrapper, rice-based products, quinoa-based products, and quinoa/chickpea/sourdough pasta are all good substitutes that are gluten-free and would help CD patients to have a varied and balanced diet.

4.4 Role of dietary interventions in eosinophilic esophagitis

In most cases, but not all, EoE is triggered by food antigens. Hence, the nutrition plays an important part in both the pathogenesis and the treatment of the disease [117]. In pediatric and adult populations, food antigens are clearly antigenic triggers for EoE induction and exacerbation [118]. In 1995, Kelly and Sampson proposed that acid persistent esophageal eosinophilia can be caused by food antigen exposure in children [117]. Ever since the direction toward studying the role of food allergens in the pathogenesis and the treatment of EoE has been established. Some of the therapies that have proven the efficacy are the empiric elimination diets, such as the famous 6 food elimination diets (6-FED). These six foods are wheat, milk, egg, nuts, soy, fish, and eggs [119]. In animal studies, it was shown that accumulation of eosinophils in the murine esophagus occurred after the introduction of peanuts and eggs [120, 121]. Statistics show that 77% of patients with EoE have at least one positive skin-prick test (SPT) for at least 1 food allergy and up to 50% of adults have at least 1 positive test for food allergy [122, 123].

Currently, there are diets approaches that are used for EoE patients: 1) A crystalline amino acid-based elemental diet (ELED), 2) 6-FED, 3) 4-FED, 4) 2-FED) 5) Cow's milk elimination diet [124–126]. The amino acid diet is useful as it can eliminate all possible allergens and it has shown improvement in the symptoms in many cases, and the diet can last for 6 weeks. Initially, the 6-FED was studied in pediatric patients from Chicago in 2006, in which six food groups responsible for most IgE-mediated food reactions were eliminated for 6 weeks [127]. All studies have consistently shown that nuts and fish/seafood rarely trigger EoE in response to a 6FED, but cow's milk is by far the most common cause of EoE, followed by wheat/gluten, egg, and, to a lesser extent, wheat/gluten [118, 127–132]. The 4-FED is based on the elimination of the most common food triggers in EoE (animal milk, gluten-containing cereals, eggs, and legumes). Cow's milk (85%), egg (35%), wheat (33%), and soy (19%) were the most common food triggers. The 2-FED is based on the elimination of milk and gluten [126]. After reintroduction of individual foods, cow's milk was found to be the only trigger food in 55% of pediatric responders [133]. Therefore, the 1-FED or the cow's milk elimination diet could be recommended for some patients. One of the clinical practices in the dietary therapy is that a clinician could start with a 1-FED diet, if no response is observed the clinician could upgrade to 2-FED, 4-FED, or 6-FED. Patients could have more than food allergens; therefore, 6-FED is considered the most efficient diet (**Figure 1**) [125].

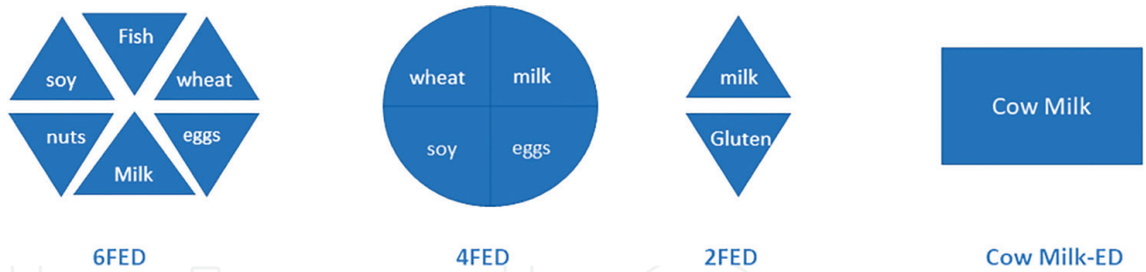

Figure 1.
The various types of food elimination diets.

4.5 Role of dietary interventions on inflammatory bowel disease (IBD)

The triggers of IBD include internal (enteric microflora) and external (food) triggers [134]. Overconsumption of sugar and refined carbohydrates was associated with the manifestation of Crohn's disease. Furthermore, excess intake of sugar over the years could alter the intestinal bacterial flora and general milieu, which could damage the mucosa or alter bile acid composition. These alterations could be the result of infective agents or sugar fermentation [135]. A balanced diet that includes fruits, vegetables, meat, olive oil, and fish (blue fish particularly) should be prescribed to IBD patients. Insoluble fiber might have negative effects in case of major intestinal stenosis coexisting with IBD. However, insoluble fiber intake should not be restricted in IBD patients. Moreover, dairy products are a crucial part of IBD nutrition intervention due to their calcium content. Products that contain lactose could be avoided if the patient had lactose intolerance and substituted with plant-based products that contain enough calcium. Supplementation with calcium and vitamin D3 might be required along with systemic steroids treatment as well as other treatments that have greater local effects such as budesonide or beclomethasone. Furthermore, iron and folic acid deficiencies should be closely monitored due to their huge prevalence in IBD patients. Deficiencies in iron or folic acid contribute to anemia in this population and could be easily treated orally or intravenously [134].

5. Treatments of GI autoimmune diseases

5.1 Achalasia

Esophagectomy is only necessary for 5% of patients with end-stage achalasia. Among the options for treating achalasia are botulinum toxin injection, pneumatic dilation, laparoscopic Heller myotomy, and peroral endoscopic myotomy (POEM). Botulinum toxin injections are one of the first-line treatment options in achalasia. The injection reduces the lower esophageal sphincter (LES) pressure by inhibiting the release of acetylcholine from nerve endings [136]. The injection is extremely safe and rarely causes any adverse reactions. The injection is, however, limited in its durability, which lasts only for a few months [137–143]. Another common treatment option is the pneumatic dilation. Under fluoroscopic guidance, the balloon dilates the LES fibers through intraluminal dilation and can be either 30, 35, or 40 mm in diameter. If no success is achieved, the clinician will go for a bigger balloon size. The success rate as per Eckardt score is achieved in 84% of the patients [144]. Another common treatment is the laparoscopic Heller myotomy. This treatment was based on surgical myotomy to disrupt the LES fibers through an incision but now it has been minimally

invasive laparoscopic myotomy with a partial fundoplication. Clinical success is not purely determined by Eckardt's scores. The primary outcome measure was improvement of dysphagia, which was treated as a dichotomous variable. Overall, 87.7% of studies reported improvement in dysphagia through this treatment [144]. POEM is the last common treatment in achalasia, and this treatment was only established 12 years ago [145]. The clinical success in POEM was 98% [144].

5.2 Autoimmune atrophic gastritis (AAG)

In the early stage of AAG, due to the reduced gastric acid secretion and intrinsic factors the clinician should focus on preventing the deficiency of B12, iron, and folate as the development of anemia could be prevented with supplementation of these nutritions. In case of the presence of pernicious anemia already, the clinician should consider B12 repletion, cyanocobalamin, and iron supplements to restore hemoglobin function. Also, clinician should note that AAG is usually associated with autoimmune diseases, such as autoimmune thyroid disease, type 1 diabetes mellitus, and Addison disease [146–156].

5.3 Celiac disease

A lifelong strict GFD can be considered the only treatment for celiac disease [157]. For patients who have refractory type celiac disease, they might need a pharmacological intervention besides the strict GFD diet. The use of drugs that work on proteolytic destruction of gluten peptides, inhibition of intestinal permeability to prevent gluten absorption, inhibition of TG2, or modulation of the immune response to gluten to prevent T cell activation is a promising option [158, 159]. Currently, the most promising treatment is the vaccine Nexvax2, which is an adjuvant-free mixture of tripeptides immunodominant epitopes for gluten-specific CD4-positive T cells. However, it is still in the preliminary stages [160–162].

5.4 EoE

Overall, EoE is treated with three main categories: drugs, diet, and dilation [163–165]. The diet therapy has been discussed in a previous section. Pharmacological treatment includes topical corticosteroids, such as fluticasone or budesonide, swallowed rather than inhaled, for an initial duration of 8 weeks. It has been shown that the patients' symptoms have improved as decreased esophageal eosinophilia was apparent, and were generally well-tolerated by patients [166–172]. Proton pump inhibitors (PPI) are usually given to the patients of EoE since the patients usually suffer from regurgitation and acid reflux. The response to PPI is hugely variable between 30 to 70% [173]. PPI-responsive and PPI-resistant EoE have yet to be identified. In patients with PPI-responsive EoE, expression of the potassium channel gene, KCNJ2, is lower. CYP2C19 rapid metabolizers and allergy patients are more likely to lose EoE control despite continued PPI treatment [174]. Since the long-term use of corticosteroids can result in harmful effects, immunomodulators, such as 6-mercaptopurine and azathioprine, are often used for the treatment of the patients. They might have a role in inducing and maintaining long-term clinical and histologic remission in EoE in limited cases but their side effects can be discouraging [175, 176]. Monoclonal antibodies have been investigated in the last few years against EoE including some famous drugs including mepolizumab (anti-IL-5), reslizumab (anti-IL-5), QAX576

(anti-IL-13), omalizumab (anti-immunoglobulin-E), and infliximab (anti-TNF-α) [177]. IL-5 produced by Th2 lymphocytes has a critical role in eosinophil activation. Animal studies have shown that overexpression of IL-5 can induce EoE [178, 179]. IL-5 receptors, which are mainly expressed on the surface of eosinophils, are blocked by mepolizumab, a monoclonal antibody against IL-5 [180]. The use of mepolizumab seems promising in decreasing the number of eosinophils and reducing the dependency on corticosteroids but more clinical studies need to be conducted [181–183]. Another humanized anti-IL-5 mAb called reslizumab prevents IL-5 from binding to its receptor. The available trials show an improvement in eosinophil count but not in the symptoms and the drug was generally safe [184–186]. In the pathogenesis of EoE, IL3 plays a multifunctional role. An anti-IL3 therapy could be efficient in EoE one of the most famous anti-IL13 drugs is QAX576. Patients tolerated QAX576 well. Patients decreased by 60.0% and sustained for 6 months on the QAX576, which is an anti-IL3 drug. Unfortunately, the primary endpoint was not reached. A trend for improved symptoms was observed particularly dysphagia. Six months after treatment, QAX576 helped to improve expression of esophageal transcripts related to EoE, such as eotaxin-3, periostin, and markers of mast cells and barrier function [187]. Since mast cells are involved in the pathogenesis of EoE, targeting them directly could be an efficient treatment for EoE. Malizumab is a monoclonal anti-IgE antibody that prevents mast cell activation by binding to IgE [188]. However, in most of the trials, the response was poor in patients or reoccurrence of symptoms presented after a short time [189–191]. TNF-α and IFN-γ are found in esophageal mucosal biopsy of the EoE patients. A potent inhibitor of TNF-α is infliximab that is a chimeric IgG1mAb. Infliximab was not shown to be of no benefit for EoE patients [192].

Dilation is also sometimes used in the treatment of EoE. The most common use of esophageal dilation is in adults with EoE and strictures. Conservatively applied, this approach is safe and has a low complication rate. Dilation treats structural alterations in EoE. Although esophageal dilation is well tolerated by patients and can provide long-term symptomatic relief, it does not improve histologic changes [193–195].

5.5 IBD

IBD can have a wide range of treatments. In Crohn's disease, treatments include immunomodulators, corticosteroids, and monoclonal antibodies. 5-aminosalicylates is the most commonly prescribed for symptoms management in mild and moderate disease [196]. Corticosteroids are efficient, prednisone can be efficient in the course of treatment [197]. Budesonide (Entocort EC) may be preferred for diseases affecting the ileum and/or proximal colon since it is delivered specifically to those areas [196]. Immunomodulators, such as thiopurines and methotrexate are the most effective immunomodulators used in Crohn's disease [198]. Anti-TNF agents, anti-integrin agents, and anti-interleukin-12/23p40 antibody therapy are considered the most efficient in treating Crohn's disease. The continuation of any of them in the treatment plan depends on the remission success [199]. In moderate- to high-risk patients, anti-TNF agents, such as certolizumab pegol (Cimzia) and adalimumab (Humira) induce and maintain remission, or patients with inadequate responses to corticosteroids or immunomodulators [200]. In anti-integrin agents, vedolizumab is the most favorable drug because of its specificity to leukocyte trafficking in the gut and has demonstrated effectiveness in achieving clinical response, remission, and corticosteroid-free remission [201]. In, anti-interleukin-12/23p40, ustekinumab is promising for Crohn's

Disease	Treatment
Achalasia	Esophagectomy for end-stage patients botulinum toxin injection, pneumatic dilation, laparoscopic Heller myotomy, and POEM
AAG	B12, Iron, and Folate nutritional supplementation therapy
CD	Gluten-Free Diet (GFD) Drugs that can destruct gluten peptides, inhibition of intestinal permeability to prevent gluten absorption, inhibition of TG2, or modulation of the immune response to gluten Nexvax2 vaccine
EoE	Diet: FED diets and amino acid formula diets Dilation Drugs: PPI, glucocorticoids, anti-IL5, Anti IgE, anti IL13, and anti-TNF-α
Crohn's Disease	Drugs: Glucocorticoids, ant-TNF, anti-integrin agents, and anti-IL12/23p40
UC	Does not differ much from Crohn's treatment

Table 2.
Common treatments for GI autoimmune.

disease as it was recently approved by FDA [202]. In Crohn's disease, 57% of the patients might need surgical intervention to treat fistulas, abscesses, perforation, obstruction, strictures, uncontrolled bleeding, dysplasia, malignancy, and perianal disease [196, 203].

In UC, the treatment options do not differ much from Crohn's Disease. The mainstay of therapy for mild-to-moderate UC is sulfasalazine and other 5-ASA agents [204]. Corticosteroids are also efficient in UC patients and it's usually given to the cases of severe symptoms. Prednisone is the most used corticosteroid. Immunomodulators are also used such as their usage in Crohn's Disease. Azathioprine and 6-mercaptopurine (6-MP) are purine analogs that are the commonly most used in the treatment [205]. Also, monoclonal antibodies used in UC such as infliximab has proven their efficiency [206]. In addition, vedolizumab has proven to be efficient as well in UC [207]. Surgical treatment is an option as well in UC. This is generally considered a last resort when all other options have failed. The most common type of surgery is a subtotal or total colectomy with a temporary stoma [208]. Also, laparoscopic surgeries are a safe option in UC (**Table 2**) [209].

6. Conclusions

To conclude, GI autoimmune diseases can be compromising the patient's life. Nevertheless, the exploration of more diagnostic options, such as the antibodies, the growing applications of artificial intelligence in autoimmune diseases diagnosis, understanding the interaction of nutrition whether in the pathogenesis or the management, and the efficient treatment plans can help for better diagnosis, management, and treatment of GI autoimmune diseases, which is a sub-category of autoimmune diseases that are considered a pandemic in our modern societies.

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Conflict of interest

The authors declare no conflict of interest.

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