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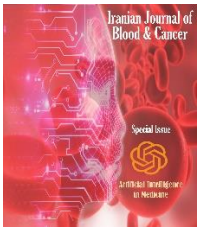

Review

Application of Artificial Intelligence in Celiac Disease: from diagnosis to patient follow-up

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Abstract

Celiac disease (CD) is an autoimmune digestive condition that is distinguished by inflammation of the small intestine as a result of gluten ingestion. Its worldwide prevalence is approximately 1%. Despite progress in understanding CD, challenges in pathogenesis, diagnosis, treatment, and management persist. Genetic and environmental factors, such as HLA and non-HLA genes, gluten, gut microbiota imbalance, and immune responses involving CD4+ T cells, influence CD. Diagnostic challenges arise due to diverse clinical presentations and overlap with other gastrointestinal disorders. Following a gluten-free diet (GFD) strictly is the primary treatment for CD, but this diet presents social, psychological, and financial hurdles. Artificial intelligence (AI) has emerged as a potent instrument in CD management. Techniques like machine learning (ML), deep learning (DL), natural language processing (NLP), and computer-aided algorithms have shown promise in CD diagnosis by improving microbiome analysis, disease prediction, interpretation of medical records and endoscopy images. AI-based decision-support systems can aid in diagnosis. AI-driven personalized nutrition and gluten contamination monitoring techniques offer potential improvements for treatment. Overall, AI has potential in addressing CD challenges and enhancing patient outcomes.

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1. Introduction

Celiac disease (CD) is an autoimmune digestive condition that occurs in genetically predisposed individuals upon exposure to gluten, causing chronic inflammation in the proximal small intestine, which leads to nutrient malabsorption. This condition is characterized by damage to the mucosal of the small intestine, which is caused by gluten-specific CD4+ T-cell autoimmune responses. The worldwide prevalence rate of CD is approximately 1% [1-3]. Despite significant advancements in understanding CD, ambiguities persist regarding its pathogenesis, diagnosis, treatment, management, and potential treatments, keeping this disease in a challenging position [4-7].

CD is a complex autoimmune condition that arises due to a combination of genetic factors (HLA and non-HLA genes), environmental triggers (gluten and imbalanced gut microbiota), epigenetic factors such as DNA methylation, and immune responses involving the activation of CD4+ T cells specific to gluten. [6, 8-10]. Although HLA genes have a powerful genetic linkage to the disease, they can only account for half of the observed susceptibility. It is evident that non-HLA genes, which have not been identified yet completely, contribute to the development of CD [11, 12]. Furthermore, the molecular pathways that cause the initiation and potentiation of inflammatory signaling in CD are not fully understood [13]. Indeed, despite extensive research efforts, the precise underlying cause and pathogenesis of CD continue to remain a mystery [5]. Furthermore, the advancement and progression of CD may be influenced by alteration in the gut microbiome's composition and function. CD is distinguished by an elevation in the quantity of gram-negative bacteria along with increased number of gram-positive bacteria. However, it is still uncertain whether dysbiosis is a primary cause or a secondary consequence of CD [14, 15].

CD can exhibit various manifestations, including intestinal symptoms like chronic diarrhea, abdominal pain, malabsorption, steatorrhea and weight loss. Additionally, extra-intestinal symptoms such as growth retardation, muscle weakness, psychiatric disorders, iron deficiency anemia, mouth ulcers, and fatigue may occur. However, CD can also be asymptomatic [16]. CD can be categorized into diverse groups according to its wide variety of clinical presentations, including classic (intestinal), non-classic (extraintestinal), subclinical, refractory (RCD), and seronegative CD. Given the extensive array of clinical presentations associated with this disease, the process of diagnosing it commonly entails significant delays [17]. Early diagnosis of CD is incredibly essential in order to avoid potential long-term complications [18]. CD diagnosis is based on determined through comprehensive evaluation of clinical symptoms and serological tests, followed by upper gastrointestinal endoscopy accompanied by duodenal biopsy, which is considered the gold standard for distinguishing this disease [19, 20]. Additionally, in cases where the results of serological and duodenal biopsy examinations contradict each other, genetic methods are employed to examine specific genes associated with CD (HLA DQ2/DQ8) [21]. Diagnostic errors can manifest in various stages of the diagnostic process, either singly or in combination [21]. For instance, certain conditions, like not consuming enough gluten, having protein-losing enteropathy, taking immunosuppressive medications, or being under 2 years old, can accompanied with incorrect negative results in tissue transglutaminase (tTG) tests that subsequently lead to delayed diagnosis of CD [18]. Furthermore, the lack of awareness among some physicians regarding CD as

well as in the public population, due to the vast range of symptoms and atypical disease presentation and overlap of symptoms with other gastrointestinal disorder like irritable bowel syndrome (IBS) leads to high rates of misdiagnosis and delay in diagnosis [22-24].

Following a strict gluten-free diet (GFD) is considered as the main treatment for CD, but it brings about a multitude of challenges for patients, particularly teenagers [25, 26]. These challenges encompass the need for long-term commitment to the dietary restrictions, the expensive nature of gluten-free products, and their limited availability [25, 27]. Following this diet may give rise to various social and psychological pressures, especially among adolescents. The extensive presence of gluten in food sources and insufficient information provided on food labels are obstacles that affect eating out or traveling and also impact social relationships of patients [25, 28, 29]. As a result, individuals who adhere to the diet feel different and experience rejection from society. These challenges can significantly discourage individuals from strictly adhere to the diet [25]. Non-adherence to the GFD can have serious consequences for patients [30], and may increase their chances of developing other autoimmune diseases [31, 32]. Hence, the successful implementation and maintenance of a GFD necessitates the assistance of a trained nutrition expert and psychologist to provide guidance and support throughout the entire process [33-36].

Moreover, due to the various challenges in patients that undergo treatment, it is crucial for patients with CD to be regularly followed up from the time of diagnosis. It allows clinicians to thoroughly examine all factors that may negatively impact their quality of life (QoL) and to ensure correct following a GFD. Follow-up examinations enable healthcare professionals to evaluate the potential presence of additional immune disorders along with CD and facilitate the early detection of autoimmune comorbidities [37]. In addition, it is highly recommended to regularly screen individuals at high risk, such as those with a genetic predisposition or first-degree relatives of patients, as it can help in the early identification of CD in these individuals [38-40].

2. Artificial intelligence

Artificial intelligence (AI) is an extensive field of computer science focused on the creation of intelligent machines capable of acquiring knowledge and comprehending intricate concepts. In the realm of healthcare, AI plays a vital role across various stages such as screening tools, diagnosis, the formulation of novel therapeutic agents, proposing appropriate management plans, as well as identifying prognostic indicators. Its applications extend to disease predictions, aiding researchers in the development of efficient healthcare policies, and designing models for preventing various types of illnesses. The extensive utilization of AI is helping overcome obstacles and improving the overall efficiency of healthcare practices [41, 42].

3. Pathophysiology of Celiac Disease

The onset of CD is triggered by the translocation of gluten peptides into the lamina propria, despite their resistance to gastrointestinal breakdown. Once these undigested peptides reach the lamina propria, they interact with gluten-reactive T cells, igniting a strong immune response. Upon entering the lamina propria, gliadin peptides undergo deamidation facilitated by the tTG enzyme. These deamidated gliadin peptides are then recognized by HLA-DQ2 or -DQ8 molecules on antigen-presenting cells (APCs). Subsequently, the APCs present these gliadin peptides to CD4+ T cells, leading to activation. This activation triggers the production of pro-inflammatory cytokines like interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), resulting in an increase in the number of IELs. Additionally, activated CD4+ T cells play a

pivotal role in driving the activation and clonal expansion of B cells. Consequently, B cells differentiate into plasma cells, which produce antibodies specifically targeting gliadin and tTG. This cascade of inflammatory reactions ultimately leads to the characteristic villous atrophy and crypt hyperplasia in celiac disease. (**Figure 1**) [43-45].

4. Application of AI in the management of celiac disease

The complexity of CD manifestations, as well as the fact that some patients have an incomplete response to a GFD, necessitates ongoing monitoring and repetitive testing. Additionally, the lifelong nature of the disease emphasizes the need for innovative diagnostic approaches and therapeutic interventions. AI can contribute to improved diagnosis and management of this disease.

4.1. AI and diagnosis of CD

AI is an extensive field of computer science that was first described in 1950. It focuses on using computers and technology to imitate human intelligence, including the abilities to think critically and exhibit intelligent behavior [46-48]. The introduction of AI has completely transformed the healthcare industry, causing significant changes that include improved diagnostic abilities [49, 50]. For instance, AI is fundamentally transforming the field of microbiome research by facilitating the efficient analysis of extensive datasets and yielding valuable understandings about the composition and activity of microbial populations. By utilizing AI-driven predictive algorithms, scientists are now capable of studying the influence of diet on microbial communities and predicting the likelihood of developing certain illnesses based on the composition of gut bacteria. Additionally, AI greatly assists in identifying microbial biomarkers linked to particular health conditions, aiding in early disease detection and the development of targeted treatments [51]. For example, a prediction model built upon fecal microbiome data using AI technique, can accurately identify patients with IBS [52]. Given the significant association of CD with changes in gut microbiota, AI can provide us with valuable insights into the dysbiosis and finding novel microbial biomarkers in patients with CD [53].

Moreover, physicians can utilize AI technology to take notes, evaluate their interactions with patients, and subsequently input requisite data directly into electronic medical record (EMR) systems [54]. EMRs can be characterized as an extensive and perpetually expanding repository of health-related data. This substantial database can prove invaluable in assisting physicians with diagnosis, management, as well as providing personalized recommendations [48]. AI techniques can analyze CD patients' EMRs collected from various healthcare centers [48, 55]. This analysis may help identify patterns and biomarkers associated with CD and enable modeling and predicting the likelihood of CD in susceptible individuals.

Machine learning (ML), deep learning (DL), and natural language processing (NLP) stand out as the top three prevailing AI techniques in use [56]. ML, a cutting-edge AI technique, operates on the basis of mapping inputs to outputs through an algorithmically trained function derived from an extensive complex of examples. This approach is increasingly utilized in medicine and healthcare to create models that can predict diseases based on patient symptoms [48]. It is a field that concentrates on enabling computers to learn autonomously from provided data, recognizing resemblances or recurring patterns, and making disease predictions without relying on human input or explicit programming instructions [57]. Carreras et al. utilized multiple ML and artificial neural network analyses to predict and model CD based on gene expression data. This approach led to the identification of several potential

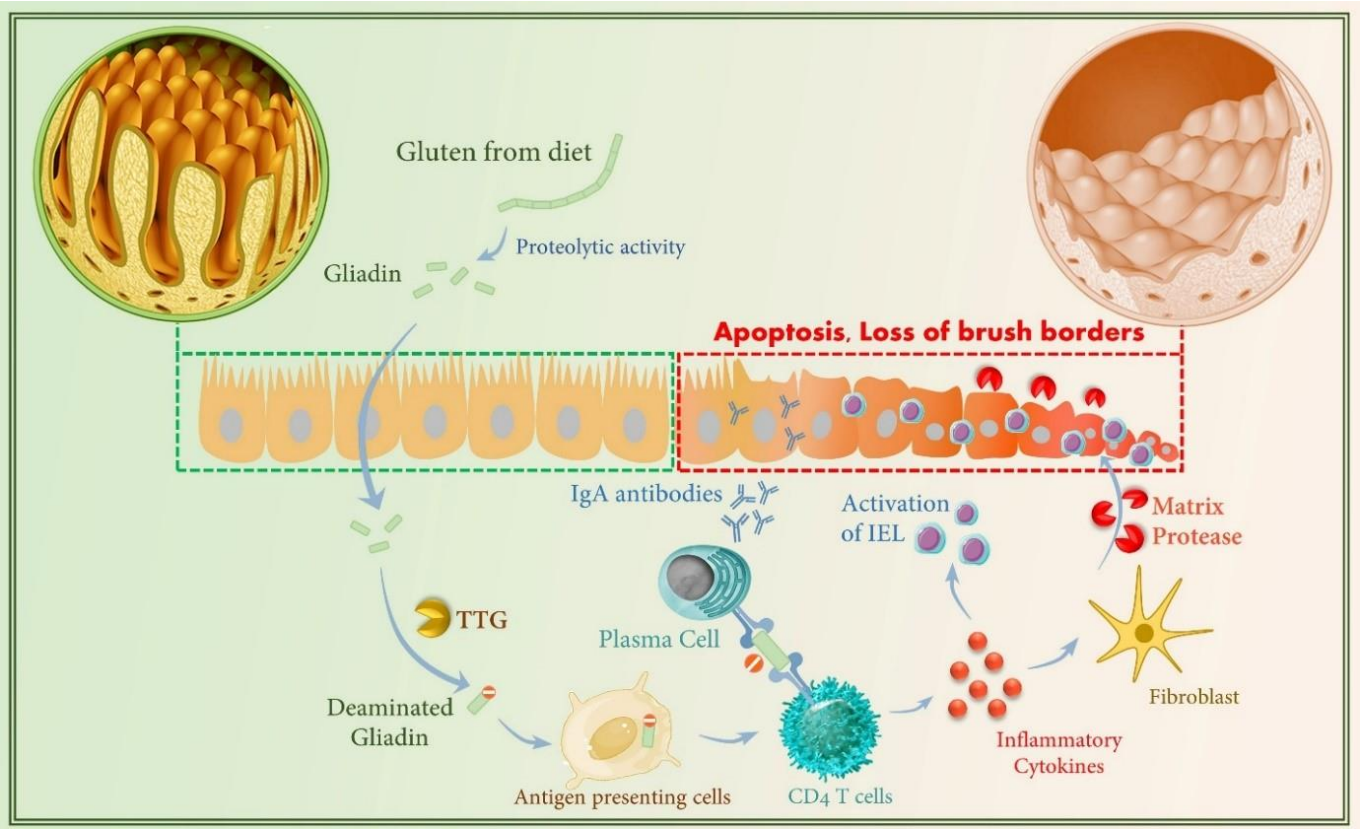

Figure 1. **Pathophysiology of platelet disease.** The ingestion of food that contains gluten leads to the release of tissue transglutaminase (TTG). This enzyme modifies gliadin, a component of gluten proteins. As a result, pathogenic T cells respond to and become activated by the modified gliadin. The activated T cells subsequently initiate persistent inflammation within the intestines, resulting in harm to the epithelial lining via a pathway mediated by intraepithelial lymphocytes and fibroblasts. This damage leads to villous atrophy, crypt hyperplasia, and loss of the brush border.

pathogenic candidates. The research found that CD is characterized by elevated levels of BTLA (B and T lymphocyte attenuator) expression in inflammatory cells of the lamina propria. Notably, the study further validated the presence of BTLA at the protein level through immunohistochemistry in an autonomous set of experiments. Overall, these findings demonstrate the effectiveness of AI models in providing insights into the likelihood of an individual having CD by utilizing an autoimmune discovery gene panel. Moreover, AI has the capability to identify specific genes and pathogenic markers that contribute to the development of CD [58]. ML models efficiently analyze EMR data to identify potential candidates for clinical trials. This not only saves time but also provides physicians with a list of suitable candidates within a matter of minutes to hours, alleviating the tedious and tiresome process of recruiting participants [48].

NLP is an exciting field of ML that allows computers to process and analyze free text data. It involves developing algorithms and techniques that empower machines to understand and make sense of human language [59]. Computerized EMR-based NLP algorithms have the potential to effectively identify individuals at a heightened risk of developing CD. These algorithms can contribute to healthcare by prompting physicians to conduct

CD tests for patients exhibiting clinical and laboratory data indicating a high risk of CD [60]. DL, an enhanced iteration of ML, employs multi-purposes. Notably, in the realm of image analysis, particularly within the field of endoscopy the Deep convolutional neural networks (CNN or DCNN) has emerged as the dominant learning algorithm [61]. During intestinal endoscopy, it is necessary for clinicians to take multiple biopsies to accurately diagnose CD and assess small intestinal damage in CD patients. It is hypothesized that these AI methods have the potential to reduce the risks related with endoscopy by eliminating the requirement for biopsies.The application of AI, specifically CNNs, has proven to be effective in classifying endoscopic images for diagnosing CD. In a study by Wimmer et al. techniques like the modified immersion technique (MIT), as a CNN technique, are employed to differentiate healthy mucosa and CD-affected mucosa by analyzing the endoscopic images. They achieved an impressive accuracy of 90.5%. Their work implies that even though the gold standard for diagnosing CD is still endoscopy, AI might be helpful in situations where it's challenging to acquire biopsies [62, 63]. Vècsei et al. created an automated method for classifying the severity of CD in pediatric patients using endoscopic images. Different AI methodologies were compared using a restricted dataset of 612 image patches. The technique achieved an 88% accuracy in distinguishing between disease and no disease, however, it exhibited a comparatively lower accuracy of 63.7% in categorizing the severity of the disease. Although not yet applicable, their research emphasized that AI possesses the ability to distinguish between diseased and non-diseased conditions (**Figure 2**) [62, 64, 65].

Video capsule endoscopy (VCE), a highly evaluated wireless technology procedure, has become essential in diagnosing and monitoring various gastrointestinal disorders. It is now recognized as a valuable tool for visually confirming suspected villous atrophy in cases of CD. Unlike conventional endoscopy, VCE is a noninvasive technique that efficiently detects subtle abnormalities throughout the entire small intestine. Currently, physicians manually analyze video clips to evaluate mucosal images from VCE. However, this process is time-consuming and monotonous. Consequently, the suggestion of utilizing computer-aided algorithms to assist in CD diagnosis has emerged [66, 67]. By incorporating AI-based tools, the utilization of VCEs can potentially enable computer-assisted interpretation. This means that machine learning algorithms (MLAs) could be employed to automatically diagnose CD and assess the severity of the disease burden [68]. Ciaccio et al. theorized that using automatic analysis on VCE images could effectively detect the characteristic small intestinal villous atrophy associated with CD. By examining VCE images of nine patients with confirmed CD through biopsies and seven healthy control individuals, the researchers determined that the AI algorithm achieved an overall accuracy of 88.1%, specificity of 92.9%, and sensitivity of 83.9%. [62, 69]. The study conducted by SC Zammit et al. indicated that applying MLAs to VCE can offer a highly detailed evaluation of the extent and severity of injury to the small intestine mucosal lining, potentially facilitating automated diagnosis and assessment of disease burden in individuals with CD. These findings indicate that the integration of these technologies in the future could pave the way for automated diagnosis, evaluation, and referral of CD patients, especially in healthcare centers lacking expertise in the field [68].

A creation of a decision-support system (CDSS), functioning as a computer program, specifically aims to assist healthcare providers in their clinical decision-making processes. By employing statistical

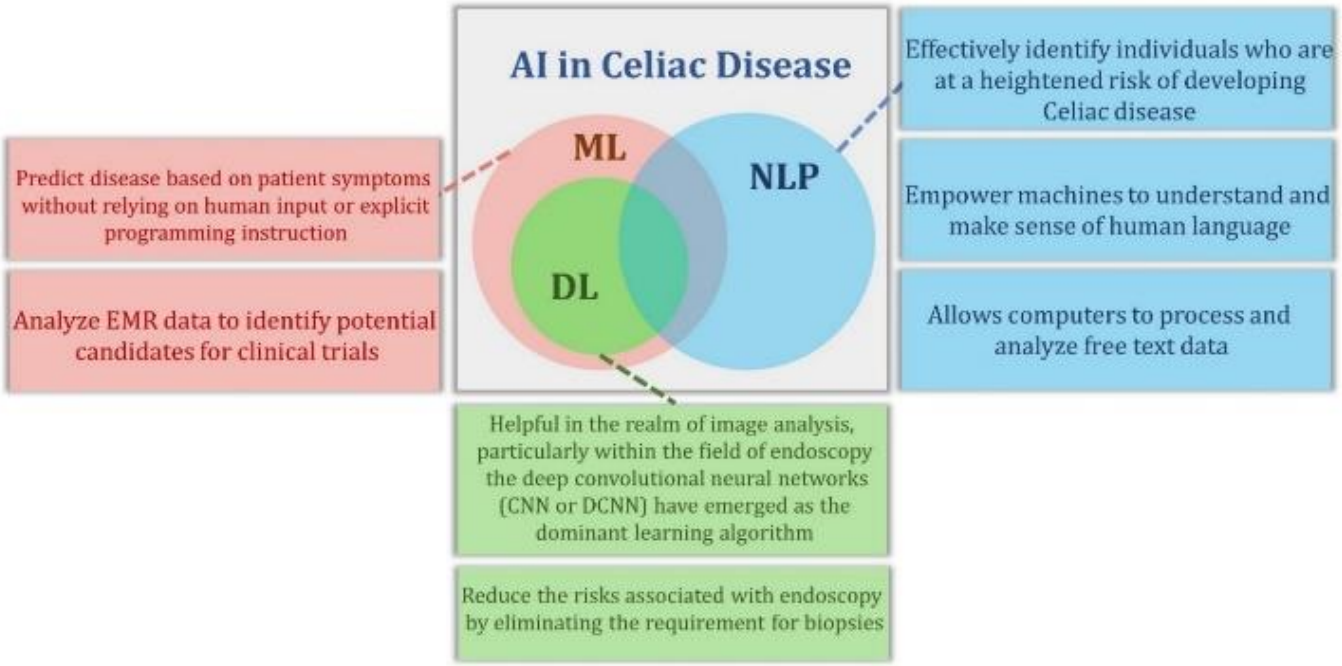

Figure 2. **AI techniques application in CD management. AI:** Artificial intelligence; **CD:** Celiac disease; **ML:** Machine learning, **DL:** Deep learning; **NLP:** Natural language processing, **EMR:** Electronic medical record.

methodologies, a CDSS can furnish pertinent information, thereby bolstering diagnostic and management decision-making and effectively bridging the disparity between evidence and clinical practice during patient care [70]. Due to the considerable diagnostic challenges of CD, employing CDSS as an AI technique is advantageous for aiding in the decisive identification of the disease.

4.2. AI and treatment of CD

Following a special diet plays a decisive role in managing several diseases, including CD. The cornerstone of managing this condition revolves around adhering to a GFD, as it efficiently alleviates symptoms and enhances the overall well-being of affected individuals [71, 72]. AI-driven software applications for personalized nutrition have attracted growing interest lately [73]. AI systems hold the potential to revolutionize nutrition assessments by gathering and analyzing data related to an individual's dietary intake. Additionally, AI devices have the potential to generate valuable and accurate feedback, playing a pivotal role in clinical nutrition [56]. The emergence of AI has provided clinicians with a valuable opportunity to elevate the quality of their decision-making pertaining to patients' nutritional needs [74].

Moreover, in some cases, even with diligent commitment to a GFD, symptoms may persist, raising concerns about the potential cross-contamination of gluten-free products with gluten [75, 76]. The Food Cross-contamination with gluten-rich grains during harvesting, transportation, and/or food processing stages can result in unintentional gluten presence in gluten-free food, thereby jeopardizing QoL for individuals with CD who are under-GFD. For this reason, it is of utmost importance to regularly oversee and control contamination in foods that are labeled as gluten-free [77, 78]. The ELISA-based technique is the most

commonly used method for evaluating gluten in food products, which is both time-consuming and requires laboratory equipment. However, there is a growing demand for a quick and equally efficient method to verify the presence of gluten contamination in food. Recently, AI-based indirect analysis methods have been proposed to evaluate the gluten content of food products [79]. In their study, Okeke et al. investigated the application of Fourier transform infrared (FTIR) spectroscopy combined with ML approaches for the identification and measurement of gluten contamination in grain-based foods. The findings of this study indicate that various ML algorithms demonstrate potential capabilities in detecting and quantifying cross-contamination between non-gluten and gluten-rich flours at different levels of contamination. This ongoing research holds the potential to enhance the application of AI in guaranteeing food safety and improving quality examination procedures [80].

AI algorithms, specifically ML and DL, have been effectively employed in conjunction with Near-Infrared Spectroscopy (NIRS) technology to address various challenges in the food industry. These applications primarily focus on the analysis and assessment of food samples. For instance, Jossa-Bastidas et al. developed an impressive and cost-effective Internet of Things (IoT) system that combines NIRS technology with ML and DL algorithms. This innovative system, developed to swiftly and accurately detect the presence or absence of gluten, can analyze three types of flour samples including rye, corn, and oat. Notably, it achieves accuracy rates of 94.52% (ML model) and 91.77% (DL model). This technological fusion represents an early progress in the development of solutions that can enrich the QoL for individuals dealing with food intolerances [79].

Moreover, DL using CNNs offers a fresh and creative approach to detect allergens, departing from the traditional methods. It can effectively differentiate between authentic and contaminated products by examining digital images [81]. For this purpose, Pradana-López et al. employed CNNs and transfer learning methods to quickly identify wheat (gluten) traces in lentil flour samples. By analyzing digital images captured using a basic reflex camera, the CNN models displayed exceptional performance in detecting and accurately quantifying adulterants in legumes. It is worth noting that the DL models achieved impressive accuracies of 99.1% and 96.4%. These findings emphasize the possibility of detection of food allergens by combining digital imaging and DL techniques [81]. This advancement is particularly advantageous for individuals with food intolerances as it can be easily accessed through a smartphone. By simply taking pictures of questionable food items and uploading them to cloud-based models, users can swiftly receive real-time outcomes and interpretations in a matter of seconds [81].

4.3. AI and follow-up of the patients

Providing thorough follow-up care for patients with CD necessitates a comprehensive approach and efficient referral processes, which can be quite demanding. The lack of extensive published data and absence of standardized evidence-based protocols further intensify the challenges [37]. Nevertheless, follow-up plays a crucial role in managing CD effectively. It helps in ensuring strict adherence to a GFD and effectively treating disease-related symptoms. Additionally, it plays a noteworthy role in averting potential complications [37, 82]. Moreover, regular follow-up becomes crucial to assess the likelihood of potential CD (PCD) patients progressing to the active form of the disorder [83]. Actually, individuals with PCD have a genetic predisposition and can be identified by the existence of serum anti-tissue-transglutaminase (anti-TG2)

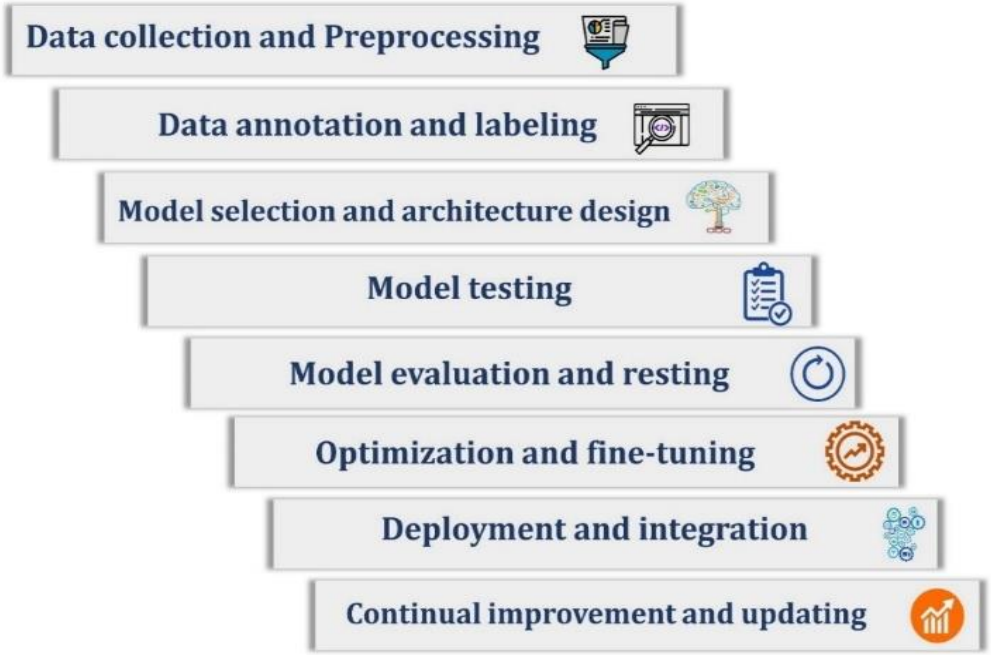

Figure 3. AI-Powered Celiac Disease Detection Workflow.

antibodies. Although the small bowel mucosa may not show any morphological changes, a small portion of them may still exhibit clinical symptoms. While most individuals with PCD do not undergo deterioration of the small intestinal mucosal damage, approximately one-third eventually develop damage in the small intestine over long-term follow-up. Identifying those at risk of tissue damage is essential to prevent the disease from advancing [84]. Piccialli et al. utilized ML techniques to effectively forecast the result of PCD. By analyzing a follow-up dataset, their aim was to identify crucial features that could accurately forecast the outcome of PCD. These characteristics, gathered during the time of diagnosis, have the capabilities to effectively differentiate between patients who will stay in the potential stage and those who will experience duodenal atrophy [84]. The researchers employed four ML methods: Logistic Regression, Extremely Randomized Trees, Boosted Trees, and Random Forests, to identify the influential features for predicting PCD's outcome. Remarkably, all four methods achieved an accuracy exceeding 75%. The Boosted Trees model, after optimization, demonstrated the highest efficiency, with a sensitivity of 58%, an accuracy of 80%, and a specificity of 84%. This accomplishment signifies a successful implementation of AI such as ML techniques, allowing for the categorization of PCD patients who have an increased susceptibility to developing overt CD (**Figure 3**) [84].

5. Conclusion

AI has the potential to address different aspects of CD. AI-driven decision-support systems and personalized nutrition assessment tools can assist healthcare providers in making clinical decisions and enhancing CD management. AI-driven software applications for personalized nutrition can aid in assessing dietary intake and providing valuable feedback. AI tools also show potential in detecting and quantifying gluten contamination in food products, enhancing food safety. It can help differentiate between patients who will remain in the potential stage and those who may experience further

progression, aiding in the prevention of the disease. Overall, the integration of AI in the treatment and follow-up of CD shows significant potential in improving the quality of care and enhancing the quality of life for individuals with CD. However, further research and validation are needed to ensure the effectiveness and integration of these AI applications in clinical practice. Ultimately, AI has the power to revolutionize CD management, resulting in improved patient care and outcomes.

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Competing interests

The authors declare no competing interests.

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