The Underlying Effects of Celiac Disease and Subsequent Implications on Deployment in the United States Army

CDT Grayson Seidel[*]; 2LT Halle Kotchman*[†]; MAJ Erin Milner, PhD*[*,‡]; Dr. Kevin J. O'Donovan*[*]

ABSTRACT

Introduction:
The purpose of this review is to provide an overview of the etiology, pathology, and treatments for celiac disease (CD), as well as to provide context as to how CD impacts the U.S. military.

Materials and Methods:
To conduct this review, the authors surveyed recent epidemiology and immunology literature in order to provide a detailed summary of the current understanding of CD, its diagnosis, and the real-world impacts within the Department of Defense (DoD).

Results:
We described the gluten proteins and both the immune response in CD. We further describe the underlying genetic risk factors and diagnosis and pathogenesis of the disease and conclude the review with a discussion of how current DoD regulations impact U.S. military readiness.

Conclusion:
Celiac disease (CD) is an autoimmune disorder that results in damage to the small intestine. Ingestion of gluten in a CD patient is usually followed by villous atrophy in the small intestine, often along with other gastrointestinal symptoms. Around 1% of patients diagnosed with CD can experience complications if gluten-free diet is not followed, including intestinal lymphoma and hyposplenism. Therefore, a patient showing possible symptoms should discuss the diagnostic process with their healthcare providers to ensure adequate understanding of serological and genetic tests along with the histological examination of intestinal biopsy. Patients should seek consults with registered dietitians to structure their diets appropriately. Considering the prevalence and incidence of CD and gluten intolerances are increasing, the military should consider providing gluten-free Meals Ready-to-Eat as an option for all service members. Given the retention of service members with CD, subsequent admission of personnel with mild CD that does not affect the duties will allow the DoD access to a growing population of fully capable service members with critical technical skills who are eager to serve the USA.

INTRODUCTION

Wheat is a major crop that is grown, traded, and consumed worldwide. A wheat kernel contains 8–15% protein, of which 85–90% is classified as gluten.[1] Gluten proteins are the precipitating factors for celiac disease (CD), an autoimmune disorder that results in inflammation of the small intestine.[2] Celiac disease (CD) is characterized by villous atrophy in the small intestine, leading to malnutrition and other gastrointestinal (GI) symptoms such as abdominal discomfort, bloating, loose bowel movements, and nausea.[2] Symptoms may range in severity from asymptomatic to a severe reaction from ingestion of food containing limited quantities of gluten. Individuals experiencing CD are recommended to adhere to a strict gluten-free diet.[3]

A recent comprehensive meta-analysis estimated that in the 21st century, the worldwide female incidence of CD was found to be 17.4 per 100,000 person-years, while male incidence was 7.8.[4] Furthermore, CD incidence has increased by more than 7% per year over the last several decades.[4] Patients with CD have three key elements: a genetic predisposition, a precipitating factor from the ingestion of gluten, and specific autoantibodies in response to the enzyme transglutaminase (TG2).[3] Two genetic factors in CD, the human leukocyte antigen (HLA) class II heterodimers, DQ2 and DQ8, and the autoantigen TG2 contribute to what can be a robust autoimmune response.[5]

Celiac disease (CD) can be problematic for the military because the rations, Meals Ready-to-Eat (MREs),[6] do not have a gluten-free choice nor do dining facilities typically offer or highlight gluten-free choices. Service members deployed in austere environments must often eat gluten, resulting in a range of possible problems for individuals with CD. Correct diagnosis and understanding of CD is important to the military because it affects admission of personnel into

[*]Department of Chemistry and Life Science, United States Military Academy, West Point, NY 10996, USA

[†]Case Western Reserve University School of Medicine, Cleveland, OH 44106, USA

[‡]Department of Medicine, Uniformed Services University of the Health Sciences, Bethesda, MD 20814, USA

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the Department of Defense (DoD), but CD could also manifest after one is already a service member, impacting soldier readiness and the health of those individuals. Celiac disease (CD) also exhibits a range of severities that do not necessarily fit within a single definition, which should be considered in the context of the DoD. The goal of this review is to summarize the current understanding of CD pathogenesis, tracing gluten as it elicits an immune response in the small intestine and results in a variety of symptoms, and to examine this condition in the larger scope of U.S. military personnel readiness.

GLUTEN: FROM MOUTH TO INTESTINE

The average gluten intake in a typical Western diet ranges from 5 g/day to 20 g/day.[1] For those trying to avoid gluten-containing products, the term "gluten-free" lacks a universal standard. For example, Food Standards Australia New Zealand defines gluten-free as having less than 5 parts per million (ppm), while the Food and Drug Administration in the USA defines it as less than 20 ppm.[1] A safe quantity of gluten for individuals with CD can vary from 10 mg/day to 100 mg/day.[1] Nevertheless, once an individual with CD ingests gluten, the digestive system mounts an aberrant T-cell response to specific proteins in gluten.

Wheat gluten has two main constituents, gliadin in the soluble fraction and glutenin in the insoluble fraction.[7] Gliadin can be further subdivided into α, γ, and ω gliadins, which are composed of various amino acids.[7] All gluten proteins contain proline- and glutamine-rich repetitive sequences[7] that give gluten its unique properties.[8] The most widely studied repeats are three motifs present in glutenin: the hexapeptide PGQGQQ, the nonapeptide GYYPTSP/LQQ, and the tripeptide GQQ.[7] There are other repeat sequences that are less conserved, but all share a high number of proline and glutamine residues. These repetitive sequences are thought to be responsible for the unique solubility properties of gluten proteins, due to hydrogen bonds formed among glutamine repeats.[7] Notably, both glutenins and gliadins harbor antigenic epitopes, all of which are contained within the repetitive domains.[7] They fall into the following categories: immunogenic peptides, antigenic peptides, T-cell epitopes, CD-eliciting epitopes, or toxic peptides.[2] Immunogenic peptides induce a cellular response, while antigenic peptides are recognized by specific antibodies. Immunogenic peptides are a smaller subset of antigenic peptides since all immunogenic substances are antigenic.[9] The most immunodominant epitope for celiac comes from α gliadin, but sequences in γ and ω gliadins, in some glutenins, are also known to initiate CD.[1]

Gluten peptide fragments containing 15–20 residues survive in the small intestine and contain T-cell epitopes.[8] These specific CD-eliciting epitopes are highly resistant to gastric, pancreatic, and intestinal proteolytic digestion along the GI tract, with resistance due to the proline and glutamine repeats.[1] The intact gliadin fragments interact with chemokine receptor 3 on the apical side of epithelium in the small intestine, inducing the release of zonulin.[5] Zonulin is an endogenous modulatory protein that can cause disassembly of epithelial cell tight junctions, resulting in increased gut permeability.[5] Consequently, gluten peptides can traffic across the intestinal epithelium from the lumen into the underlying basement membrane, where the immune response may be induced.[3]

IMMUNE RESPONSE

The immune system can be divided into two broad categories, the innate (nonspecific) response and the adaptive (specific) response.[10] Each has a distinct impact on the pathogenesis of CD. The innate response plays a critical role as cytokines such as Interleukin (IL)-15 and Interferon (IFN)-α help initiate inflammation that can lead to enteropathy.[5] Importantly, phagocytic action of the innate response leads to mobilization of antigen-presenting cells (APCs) that help initiate an adaptive response,[10] which can render CD as an autoimmune disorder. Adaptive immunity is different from innate immunity in that it has the capacity for memory. The cells that carry out the adaptive response are antigen-specific T cells, forming the cell-mediated immune response, and B cells, which form the humoral or antibody-mediated immune response.[10] The T-cell receptors (TCRs) on a T-cell respond to antigen peptides that are proteolytically processed and subsequently presented on APCs.[11] Antigen-presenting cells (APCs) express proteins known as the major histocompatibility complex (MHC) and are categorized into class I (found on all nucleated cells) and class II (found only on certain cells of the immune system).[10] In humans, the MHC is referred to as HLA and class II HLAs are subdivided into DM, DO, DP, DQ, and DR, and present extracellular peptides to cells and are important in the etiology of CD.[10] An activated TCR will cause T cells to differentiate into cytotoxic T cells involved in the destruction of cells, or T helper (Th) cells, which are involved in maximizing the immune response.[10] There are several Th cell responses, with Th1 being associated with certain autoimmune diseases, but all induce cytokine release thus enhancing the immune response.[10] The Th1 response that occurs in CD leads to atrophy of intestinal villi and crypt hyperplasia—the most common manifestations observed in CD.[12] The Th1 response deviates from normal when Th cells in a CD patient recognize gliadin peptides that are presented by disease-associated HLA-DQ molecules, which does not occur in healthy individuals.[8] A Th2 response also occurs frequently, in which cytokines IL-4, IL-5, and IL-13 are released and involved in developing B cells and recruiting mast cells and eosinophils.[10] The interaction between gluten-specific T-cell epitopes and HLA molecules may underlie a genetic predisposition for CD.

GLUTEN T-CELL EPITOPES AND GENETIC FACTORS

The HLA-DQ2 or HLA-DQ8 alleles appear frequently in the general population (25–30%)[5] and have been linked to multiple autoimmune diseases including lupus, type I diabetes, Graves' disease, dermatitis herpetiformis, and autoimmune

hepatitis.[13,14] In CD, the class II MHC molecules HLA-DQ2 and HLA-DQ8 bind to gluten antigens and initiate the inflammatory T-cell reaction.[3] Although nearly all CD patients express these HLA subtypes, only 3% of these individuals will develop the disease,[5] providing evidence that these alleles are necessary but not the only factor required for development of CD.[8] The HLA-DQ2 haplotypes can be further separated into HLA-DQ2.2 and HLA-DQ2.5, and indeed the homozygous HLA-DQ2.5:HLA-DQ2.5 variant is most strongly associated with CD, although the HLA-DQ8 and HLA-DQ2.2 haplotypes have also been linked to CD.[8] The behavior of gluten-reactive T cells may depend on the HLA molecule association, but DQ2.5 is the most prevalent and offers the clearest relation.[8] The level of HLA-DQ2 expression also correlates with the risk of CD and the strength of the T-cell response.[12] For example, gluten peptide presentation by homozygous HLA-DQ2.5 APCs will result in a T-cell response that is five times stronger than that of heterozygous HLA-DQ2.5/DQX, and HLA-DQ2.2 presentation for most epitopes is less efficient than that of HLA-DQ2.5.[12] In summation, homozygous HLA-DQ2.5 is associated with the strongest celiac response due to a higher percentage of the possible alleles expressing the most CD-eliciting protein (DQ2.5), followed by heterozygous HLA-DQ2.5 and then by HLA-DQ8 and HLA-DQ2.2. This points to a more complicated understanding than just the "classic" CD. Biologically, CD contains a range of genetic makeups and differing responses.

Gluten T-cell epitopes, after surviving proteolytic degradation in the GI tract, are affected by the specificity of TG2 and HLA binding.[8] Normally, gluten peptides bind poorly to MHC class II molecules, but CD-associated HLA-DQ molecules, along with the presence of the enzyme TG2, promote the selective binding of HLA to gluten.[8] Gluten-reactive T cells recognize these antigenic peptides better when TG2 converts specific glutamine residues to glutamate via deamidation.[8] In contrast to glutamine, glutamate is negatively charged and binds with higher affinity to HLA-DQ2.5 and HLA-DQ8 at anchor sites.[8] The key concept is the formation of a stable peptide–MHC complex, resulting in a robust anti-gluten T-cell response.[8]

DIAGNOSIS

Patients often present exhibiting common symptoms in reaction to ingesting gluten with subsequent diagnoses derived from a combination of tests that require four out of five results: (1) typical symptoms of CD, (2) antibody positivity, (3) HLA-DQ2 and/or HLA-DQ8 positivity, (4) intestinal damage, and (5) clinical response to a gluten-free diet.[3,5]

A combination of clinical evaluation, serologic assays, genetic tests, and histologic analysis[15] of intestinal biopsy remain the gold standard for diagnosis of CD.[16] Preliminary serological diagnostic testing in the past focused on deamidated gluten peptide (DGP) antibodies, along with anti-gliadin immunoglobulin G (IgG) antibodies (AGAs),[5] but use has decreased due to its low positive predictive value for detecting CD (around 70%).[3] Anti-DGP assays are more accurate than AGA assays, especially in the IgG class, and can be employed for patients with selective immunoglobulin A (IgA) deficiency. Anti-gliadin IgG antibody (AGA) screening for CD does permit improved selection of patients for duodenal biopsy and adds specificity to the histologic diagnosis.

The enzyme TG2 was established as the autoantigen for endomysial antibody (EmA) in CD, allowing better understanding of the specific immune response.[12] The IgA anti-tissue transglutaminase (IgA anti-tTG) antibody is widely utilized for serologic diagnosis of CD based upon >95% sensitivity and >96% specificity for CD.[17,18]

The EmA acts against the smooth muscle inter-myofiber bundles (endomysium).[19] Sensitivity and specificity for detecting CD from an EmA test are reported to be greater than 95%.[20] However, once TG2 was shown to be responsible for EmA positivity, an ELISA for TG2 was developed as an alternative that is less operator-dependent and more quantitative than the immunofluorescence-based technique used to test for EmA.[12] Transglutaminase 2 (TG2) is a calcium-dependent enzyme that executes several physiological functions including the covalent crosslinking of glutamine residues to inter- or intramolecular to lysine e-amino groups, the transamidation of primary amines into proteins, and, at low pH, the deamidation of glutamine to glutamate.[12] With respect to CD, both crosslinking[21] and deamidation of glutamine enhance gluten epitope affinity to HLA molecules. TG2 has shown a high specificity for wheat gliadin as a substrate because 30–40% of its glutamine residues are accessible to modification.[12] These functions of TG2 offer two roles that this enzyme can play in the pathogenesis of CD.

A typical diagnostic process (Fig. 1) would start with symptom assessment, followed by laboratory analyses involving a combination of serological and genetic tests.[5] A common serological approach includes both IgA anti-tTG and IgG anti-DGP assays, which yields greater sensitivity then a single test with increased specificity. It should be noted that a related ailment, non-celiac gluten sensitivity (NCGS), commonly presents with the same symptoms as CD and can produce similar results in the laboratory.[2] An increase in AGAs and IFN-γ expression in patients with NCGS has been shown to occur, as well as villi blunting in the duodenal biopsy although not to the extent usually seen in CD.[2] However, NCGS can be differentiated from CD using anti-TG2 and anti-EmA, which are usually absent in NCGS individuals.[2]

A genetic HLA test for DQ2/8 is not always performed because it is not specifically correlated to disease, but absence of these haplotypes may rule out CD.[5] Histological diagnosis[22] of a duodenal biopsy is often performed to detect intestinal damage such as increased intraepithelial lymphocytes (IELs) and a broad range of morphologic changes in intestinal mucosa. The CD-related lesions can be stratified into the five stages of the Marsh classification, with higher-level types giving an increased probability of CD.[5] Celiac disease (CD)

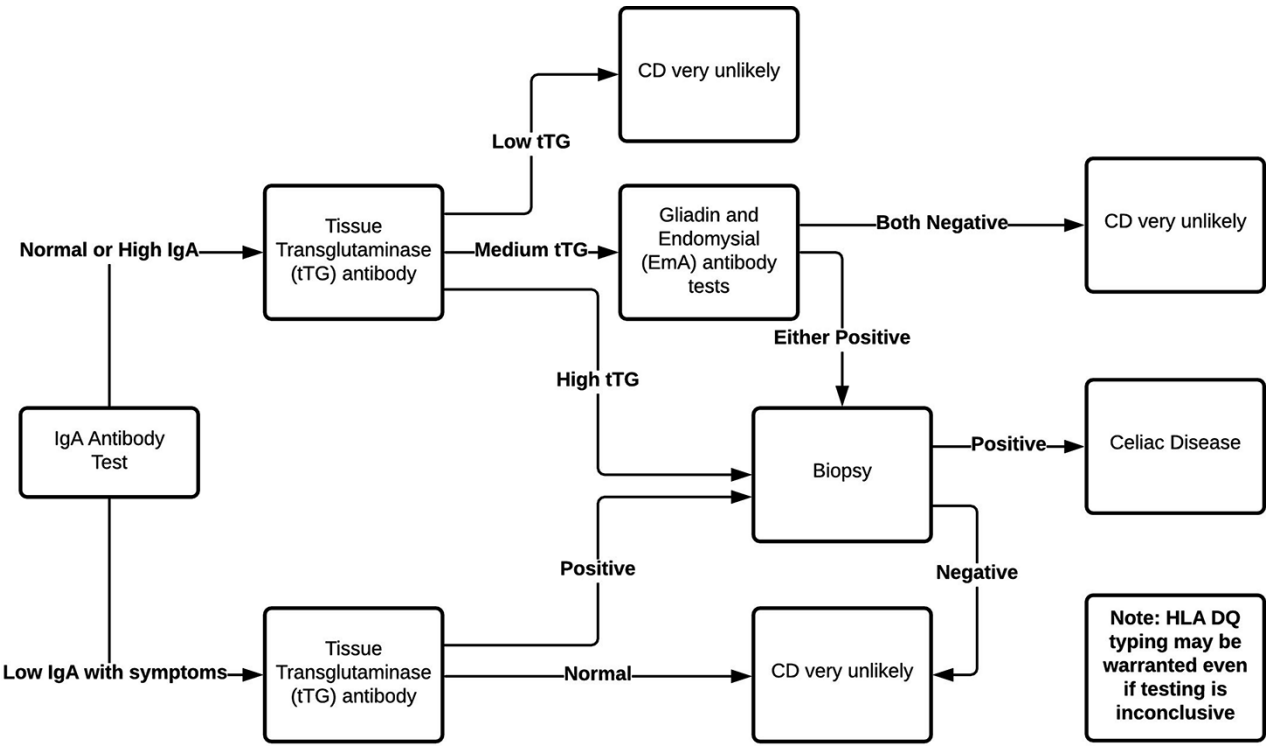

FIGURE 1. Celiac Disease Diagnostic Algorithm. The schematic depicts a flowchart (left to right) for a basic diagnostic algorithm for celiac disease. Abbreviations: Immunoglobulin (Ig), celiac disease (CD), human leukocyte antigen (HLA), and DQ refers to a subdivision of HLA D genetic locus.

is treated with a strict gluten-free diet, calling for patients to refrain from ingesting foods containing wheat, rye, barley, and spelt.[3] Seventy percentage of patients with classic symptoms have improved symptoms within 2 weeks of initiating a gluten-free diet, and the serological features of CD normalize in 3–12 months.[3]

PATHOGENESIS

Gluten's components, the immune system's innate and adaptive responses, HLA molecules' specificity to gluten T-cell epitopes, and the TG2 enzyme combine to help explain the pathogenesis of CD. When undigested gluten peptides pass through the epithelial barrier of the small intestine, TG2 deamidates the fragments, converting glutamine to glutamate.[2] This potentiates antigen-presenting dendritic cells to present gluten peptides to Th cells in the context of HLA-DQ2 or HLA-DQ8 molecules.[12] This is the first mechanism TG2 can use to affect mucosal damage—the activated Th cells produce high levels of proinflammatory cytokines, beginning a Th1 cascade.[12] In a Th1 response, IFN-γ is produced, activating macrophages and enhancing immunity to viral and other pathogens.[10] In addition, Th1-derived cytokines promote inflammatory effects that include increased IELs and natural killer T cells, leading to the death of enterocytes and the creation of the characteristic CD lesion.[12] The proinflammatory cytokines along with keratinocyte growth factor contribute to the villous atrophy and crypt hyperplasia.[5] Activated Th cells can also generate Th2 cytokines that induce expansion and differentiation of B cells into plasma cells for secretion of anti-gliadin, anti-TG2, and anti-EmA antibodies that are key characteristics of CD.[2] This inhibits normal TG2 function and leads to decreased matrix stabilization and wound repair, resulting in mucosal damage.[12]

MILITARY APPLICATION

As mentioned above, the current worldwide incidence of gluten is estimated to be 17.4 per 100,000 person-years for females and is 7.8 for males.[4] We recently utilized the Defense Medical Epidemiology Database, a subset of data within the Defense Medical Surveillance System that includes disease and injury rates within active component military populations. It contains information on demographics, military service, military rank, and total populations. The database was queried from January 2016 to December 2019 to provide a 4-year cross-section of disease incidence. We selected all cases from 2016 to 2019 containing ICD10 code K90.0 (celiac disease) and only cases marked as first occurrence were counted to prevent the inclusion of duplicate encounters for celiac presentations from the same patient. Demographic information was divided based on service member's gender, age, race, branch, and rank. Age, race, military branch, and rank were classified as indicated in Table I. The total numbers of active service members in each category were recorded under the same demographic categories. Incidence rates were calculated per 100,000 persons for each demographic- and military-specific category as well as total numbers for each year.

TABLE I. Celiac Disease Incidence from the Defense Medical Epidemiology Database, 2016–2019. We Selected First Occurrence Cases from 2016 to 2019 Containing ICD10 Code K90.0 (Celiac Disease) and Only Cases Marked as First Occurrence were Counted in Order to Prevent Recounting Duplicate Encounters for Celiac Presentations from the Same Patient. Demographic Information Divided Based on Service Member's Age, Military Branch, Race, and Gender were Classified as Indicated

	Total Incidence (per 100,000 persons)			
	Year			
	2016	2017	2018	2019
	29.95	18.62	16.12	17.34
Age				
<20	6.67	7.2	11.79	13.46
20–24	12.99	11.5	9.36	11.1
25–29	29.9	14.87	12.74	13.49
30–34	38.52	22.26	23.41	20.86
35–39	42.84	35.9	21.32	28.06
≥40	70.11	32.9	32.11	32.2
Service				
Army	29.08	20.65	14.34	17.17
Navy	24.46	10.98	11.42	16.62
Air Force	45.34	27.5	26.22	22.68
Marines	15.77	11.43	11.9	9.14
Race				
Black	6.74	7.67	4.51	6.66
White	38.04	22.71	20.34	20.36
Other	19.65	12.38	9.74	15.58
Gender				
Male	24.04	14.95	13.57	14.72
Female	61.48	37.66	29.09	30.26

Upon comparison to previously published data from a military population,[23] we note a robust increase in incidence of all categories consistent with reported increases in worldwide CD cases.[4] We further note an apparent age dependence as there are many more cases for those patients >30 years of age compared to those <30 years of age.

Currently, there are no estimates regarding the number of new recruits or service members with CD, who are not reporting symptoms or have been misdiagnosed. Given that service members have indicated self-diagnoses as well as attempts to mitigate their CD symptoms without medical treatment for fear of separation from the military,[24] there are currently no estimates regarding the number of new recruits or service members with CD who are not reporting symptoms or have been misdiagnosed. These regulations outline disqualifying medical conditions to ensure that service members are medically capable of completing training and duties and adaptable to the military environment without geographical limitations.[25] Celiac disease (CD) is mentioned specifically in section 5.12 as disqualifying if a recruit has a "history of intestinal malabsorption syndromes, including but not limited to celiac sprue."[25]

Given CD can manifest after a service member has commissioned or enlisted in the service, the administration of current service members is outlined within DoDI 6130.03 Volume 2 (September 4, 2020) Medical Standards for Military Service: Retention.[26] Celiac sprue is listed under malabsorption syndromes and it is noted that "conditions in this paragraph do not meet retention standards if associated with the inability to maintain normal weight or nutrition, require repeated procedures or surgery, or if the condition requires immunomodulating or immunosuppressant medications."[26] Although CD is a medically disqualifying condition for recruits without consideration of severity, for existing service members the condition must "persist despite appropriate treatment and impair function to preclude satisfactory performance of required military duties." The disparity between CD recruitment and retention standards is not addressed within DoDI 630.03.[26] Similarly, lactase enzyme deficiency does not meet the standard for disqualification, except if it is "of sufficient severity to interfere with military duties."[25] Medical professionals could develop a CD assessment analogous to lactase deficiency for recruits associated with gluten intolerance relative to health status and the ability to deploy within the context of specific Military Occupational Specialty or Area of Concentration. Authorizing healthcare providers increased flexibility to assess the severity of CD, relative to interference with military duties, which would promote accurate reporting and the proper management of CD.

The continued evaluation of service member performance by the military[27] would afford the opportunity to remove gluten from some MREs to avoid potential adverse effects while potentially improving athletic performance. Recent studies have highlighted the surge in non-CD athletes preferring a gluten-free diet to improve athletic performance.[28,29] Recognizing the importance of nutritional menu choices, the army has implemented the "Go for Green" program, which promotes healthier options such as lean proteins and vegetables, making it easier to eat gluten-free at DoD dining facilities.[30]

Meal Ready-to-Eat (MRE) rations provide approximately 1,250 calories composed of 13% protein, 36% fat, and 51% carbohydrates. Service members often mix and match the individual components of MREs based upon dietary preferences. There are currently 24 MRE entrée options with carbohydrate components derived from gluten-based products, which could be readily substituted with gluten-free carbohydrates such as rice, corn, buckwheat, quinoa, millet, sorghum and beans, legumes, and potatoes, while maintaining nutritional requirements. A myriad of healthy alternatives to gluten with extended shelf-lives are commercially available, which could be augmented to develop gluten-free MREs.[31,32] The DoD currently accommodates special dietary constraints with vegetarian MREs and religious MREs that follow kosher and halal regulations, which could be extended to include gluten-free options.[33] A careful cost–benefit analysis of the scale-up to gluten-free MREs is warranted but will not be covered here. The economic feasibility is demonstrated by a commercial vendor,[34] who has begun selling gluten-free MREs

(i.e., beef stew, chicken and rice with vegetables, pinto stew with ham, vegetarian chili, lentil stew, etc.) with labeling[35] that clearly identifies potential food allergens and food intolerance substances (i.e., dairy, eggs, nuts, shellfish, wheat, soy, etc.).

CONCLUSION

Celiac disease (CD) is an autoimmune disorder that results in damage to the small intestine. Ingestion of gluten in a CD patient is usually followed by villous atrophy in the small intestine, often along with other GI symptoms. Around 1% of patients diagnosed with CD can experience complications if the gluten-free diet is not followed, including intestinal lymphoma and hyposplenism.[5] Therefore, a patient showing possible symptoms should discuss the diagnostic process with their healthcare providers to ensure adequate understanding of serological and genetic tests along with the histological examination of intestinal biopsy. Patients should seek consults with registered dietitians to structure their diets appropriately. Considering the prevalence and incidence of CD and gluten intolerances are increasing,[5,36] the military should consider providing gluten-free MREs as an option for all service members. Given the successful retention of service members with CD, subsequent admission of personnel with mild CD that does not affect their military duties will allow the DoD access to a growing population of fully capable service members with critical technical skills who are eager to serve the USA.

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CONFLICT OF INTEREST STATEMENT

None declared.

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