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GASTROENTEROLOGY & HEPATOLOGY | REVIEW ARTICLE

Drought's potential influence on the increasing prevalence of celiac disease

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Abstract: Celiac disease (CD) is an autoimmune enteropathy triggered by the ingestion of gluten in genetically susceptible individuals. Although the global prevalence of CD is generally estimated at 1%, this number has been found to be increasing. We propose drought contributes to the escalating prevalence of CD by increasing the proline content of gliadin peptides and altering the position of proline residues relative to glutamine residues. These changes increase the likelihood CD will develop when genetically susceptible individuals are exposed to drought-affected gluten. Additionally, selection by farmers of wheat varieties that are more tolerant to drought conditions results in an expansion of high proline gliadin peptides in our food supply. Therefore, we suggest drought directly and indirectly contributes to the increasing prevalence of CD.

Subjects: Environment & Agriculture; Food Science & Technology; Gastroenterology

Keywords: gluten; gliadin; proline; water stress; epidemiology; epigenetics

1. Introduction

Celiac Disease (CD) is an autoimmune disease affecting 1% of the world's population (Catassi, Gatti, & Fasano, 2014; Fasano, Berti, & Gerarduzzi et al., 2003). Recently, the prevalence of CD has been found to be increasing (Catassi et al., 2014). In the absence of a definitive explanation for this increase,

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Maya G. Liester and Mitchell B. Liester have collaborated on research investigating celiac disease for several years. Their research has primarily examined factors that contribute to the development of celiac disease as well as the mental health sequelae of this disorder. The authors previously published an article exploring the relationship between celiac disease and psychiatric disorders [Liester MB, Liester MG (2017) A Review of Psychiatric Disorders Associated with Celiac Disease. Dual Diagn Open Acc Vol.2 No.2: 35].

The authors are also exploring other areas that highlight the interface between medical and psychiatric disorders. Currently, they are preparing two papers: "The role of sigma 1 receptors in mediating the rapid antidepressant effects of ayahuasca" and "Epigenetics and personality changes in heart transplant recipients," which they plan to present at an international conference in 2019.

PUBLIC INTEREST STATEMENT

Celiac disease (CD) is a disorder that occurs when certain people eat gluten, which is a group of proteins found in wheat, barley and rye. CD causes a wide range of symptoms affecting the gastrointestinal (GI) tract and other bodily systems.

About 1% of people throughout the world suffer from CD, and this number is increasing. The reasons behind this growth are unclear. We suggest drought is one factor contributing to the rise in CD. Grains respond to drought by altering gluten. Such changes improve the grains' chances of surviving drought, but also increase the likelihood that the human body will misidentify gluten as a toxin, thereby increasing the chance of developing CD.

numerous hypotheses have been offered. One potential environmental factor that has not been thoroughly explored is drought. Drought alters both the amino acid composition and the positioning of specific amino acids in gliadin peptides (Brzozowski & Stasiewicz, 2017; Johari-Pireivatlou, 2010; Munns, Brady, & Barlow, 1979; Patel & Vora, 1985; Tatar & Gevrek, 2008; Vendruscolo, Schuster, & Pileggi et al., 2007). These changes increase the immunogenicity of drought-affected gliadin peptides, thereby increasing the risk of CD in genetically predisposed individuals (Brzozowski & Stasiewicz, 2017). We examine drought's potential role in the rising prevalence of CD.

2. Materials and methods

We conducted a PubMed literature search (2000–2018) looking for English language articles containing the search terms "celiac disease", "gliadin", "drought", "water stress", and "epidemiology". Retrieved articles were screened and a subset of relevant abstracts was then selected for more detailed evaluation. The biographies of these articles were then searched for additional references. The final studies selected for inclusion in this review consisted of those articles that directly evaluated the prevalence of CD, the pathophysiology of CD, historical trends in drought, or the association between CD and drought.

3. Results

3.1. Pathophysiology of CD

CD is an autoimmune enteropathy triggered by the ingestion of gluten in genetically susceptible individuals (Fasano et al., 2003). The most important genetic risk factor for CD is carrying the genes encoding for HLA-DQ2 and HLA-DQ8 molecules. These genes occur in 30–40% of the population, but only 1% develops active disease (Catassi et al., 2014; Patel & Vora, 1985).

The term *gluten* refers to a variety of water-insoluble storage proteins found in the kernel or seed of cereal grains including wheat, barley and rye. In wheat, gluten proteins are divided into alcohol soluble *gliadins* and insoluble *glutenins*. The gliadin fraction of wheat has been identified as the primary environmental trigger in CD, with immunogenic properties localized within a small region of proline- and glutamine-rich amino acid sequences (Kumar, Kumar, & Pandey et al., 2017).

The high proline content of gliadin peptides makes them resistant to gastrointestinal digestion (Hausch, Shan, & Santiago et al., 2002). When undigested gliadin peptides reach the small intestine, they bind to CXCR3 receptors in the intestinal epithelium, triggering the production of zonulin, an intestinal peptide responsible for the regulation of tight junction barrier function. In response to zonulin upregulation, tight junctions loosen, allowing gliadin peptides to enter the submucosa through the paracellular pathway (Lammers, Lu, & Brownley et al., 2008). In the lamina propria, gliadin peptides undergo deamidation by the enzyme tissue transglutaminase 2 (TTG) (Serena, Camhi, & Sturgeon et al., 2015), resulting in glutamine being converted to glutamate (Arentz-Hansen, Korner, & Molberg et al., 2000), which possesses a negative charge (Vader, de Ru, & van der Wal et al., 2002). Not all glutamine residues are modified by TTG, however. The spacing between glutamine and proline significantly influences deamidation. More specifically, the presence of a proline residue two positions from the target glutamine in the C-terminal direction has a strong positive influence on deamidation (Vader et al., 2002).

HLA-DQ2 and HLA-DQ8 molecules prefer negatively charged residues and gliadin contains few negative charges. Deamidated gliadin peptides, on the other hand, contain numerous negative charges and therefore have a strong affinity for HLA-DQ2 and HLA-DQ8 molecules (Sollid & Jabri, 2011; Vader et al., 2002). Additionally, proline-rich gliadin peptides naturally adopt a left-handed polyproline II helical conformation, which is the preferred confirmation of all MHC class II ligands, including HLA-DQ2 and DQ8 (Kim, Quarsten, & Bergseng et al., 2004). Thus, deamidated proline-rich gliadin peptides are preferred by HLA-DQ2 and DQ8 due to their left-handed polyproline II helical structure and their multiple negative charges.

The binding of deamidated gliadin epitopes to HLA-DQ2 and HLA-DQ8 molecules on $CD4^+$ T cells in the lamina propria triggers the production of pro-inflammatory cytokines and a subsequent

inflammatory response (Bjorck et al., 2014). Furthermore, activated $CD4^+$ T cells stimulate B-lymphocytes to differentiate into plasma cells that secrete anti-gliadin antibodies and anti-tissue transglutaminase antibodies, with the latter triggering an autoimmune reaction (Parzanese, Qehajaj, & Patrinicola et al., 2017). These innate and adaptive immune responses produce the characteristic intestinal and extraintestinal symptoms of CD.

3.2. Prevalence of CD

Historically viewed as a rare food intolerance, CD is now known to be a common autoimmune disorder and one of the most common genetic diseases (Fasano et al., 2003). The worldwide prevalence of CD is about 1% (Catassi, Kryszak, & Bhatti et al., 2010; Fasano et al., 2003). The prevalence of CD varies in different populations based upon nationality, age, and gender. The highest prevalence (5.6%) is found among the Saharawi people of the Western Sahara (Catassi, Gatti, & Lionetti, 2015).

The prevalence of CD is increasing in many parts of the world (Catassi et al., 2014). In Finland, the prevalence nearly doubled in the last two decades of the 20^{th} century (Lohi, Mustalahti, & Kaukinen et al., 2007). In the US, the prevalence of CD doubled between 1974 and 1989 (Catassi et al., 2010), increased more than 4-fold in the last 50 years (Rubio-Tapia, Kyle, & Kaplan et al., 2009) and increased 5-fold in the last 30 years (Catassi et al., 2010). In Scotland, the incidence of CD increased 6.4-fold between 1990 and 2009 (White, Merrick, & Bannerman et al., 2013).

A wide variety of factors have been suggested to influence the development of CD and may potentially contribute to the increasing prevalence of this disease. These include: improved diagnostic techniques, increased disease awareness (Catassi et al., 2014), changes in infant feeding patterns (Catassi et al., 2014; Ivarsson, Persson, & Nystrom et al., 2000), altered dietary habits including increased gluten consumption (Catassi et al., 2014; Gobbetti, Rizzello, & Di Cagno, 2007), changes in the manufacturing process of gluten-containing foods (Gobbetti et al., 2007), alterations in intestinal microbiota (Verdu, Galipeau, & Jabri, 2015), enteric infections (Nejad, Ishaq, & Dulaimi et al., 2015; Zanoni, Navone, & Lunardi et al., 2006) and the use of glyphosate in the herbicide Roundup (Samsel & Seneff, 2013). A hypothesis known as the "hygiene hypothesis" also offers an explanation for the increasing prevalence of CD. This hypothesis suggests that infants who are not exposed to antigenic components found in bacteria are more likely to develop immune systems that respond to antigenic components later in life through the development of allergic and autoimmune diseases, such as CD (Lebwohl, Ludvigsson, & Green, 2015).

3.3. Drought

Drought is a condition of below-average precipitation over a prolonged period of time (Dai, 2011). In many regions of the world, drought is becoming increasingly common. The percentage of land affected by drought more than doubled from the 1970s to the early 2000s (Isendahl & Schmidt, 2006). Between 1950 and 2008, most of Africa, Asia, southern Europe, midlatitude Canada, and southern Brazil experienced drought.

3.4. Effects of drought on the composition and immunoreactive properties of gliadins

Drought severely limits crop production (Boyer, 1982; Shanker, Maheswari, & Yadav et al., 2014). In fact, wheat yield decreases 25–87% under drought stress (Giunta, Motzo, & Deidda, 1993). Many plants adapt to drought by increasing the production of proline. Wheat increases its proline content during and after drought (Patel & Vora, 1985; Tatar & Gevrek, 2008; Vendruscolo et al., 2007) by as much as several hundred fold (Johari-Pireivatlou, 2010; Munns et al., 1979). This increase in proline helps wheat plants survive and produce grain during times of water stress (Vendruscolo et al., 2007).

Drought affects the composition of gliadins by increasing the share of proline and glutamine residues in gliadins. Water stress also affects the immunoreactive properties of gliadins by

triggering an increase in the amount of proline located two positions from glutamine in the C-terminal direction (Brzozowski & Stasiewicz, 2017), a location preferred by TTG (Vader et al., 2002).

Proline serves a number of functions during drought, including acting as a "compatible solute" which can accumulate to high levels in the cell cytoplasm without interfering with cell structure and/or metabolism (Esfandiari, Shakiba, & Mahboob et al., 2008; Lalelou, Shakiba, & Mohammadi-Nassab et al., 2010; Loutfy, El-Tayeb, & Hassanen et al., 2012). This accumulation of proline, as well as other compatible solutes, facilitates osmotic adjustment, thereby enhancing adaptation to drought (Errabii, Gandonou, & Essalmani et al., 2006; Loutfy et al., 2012). Also, proline stabilizes cellular membranes (Esfandiari et al., 2008) and protects against oxidative stress (Tatar & Gevrek, 2008; Vendruscolo et al., 2007).

However, proline-rich gliadin peptides are highly resistant to proteolysis by gastric, pancreatic, and intestinal brush border membrane enzymes (Hausch et al., 2002). This allows these peptides to build up to high concentrations in the small intestine (Caillat-Zucman, 2008).

HLA molecules responsible for the innate and adaptive immune responses that occur in CD prefer the left-handed polyproline II helical conformation of proline-rich gliadin. TTG also prefers proline-rich gliadin (Kim et al., 2004; Vader et al., 2002), making gliadin peptides that are rich in proline more likely to undergo deamidation. In summary, the quantitative and qualitative changes in proline residues found in the gliadins of water-stressed wheat increase the immunogenicity of these peptides, making them more toxic to individuals who are genetically predisposed to CD (8, 18).

3.5. Potential role of epigenetics in drought's effects on wheat

Research into the effects of drought on water stressed plants has demonstrated an increase in the proline content in multiple parts of the plants. Changes in both the biosynthesis and oxidation rate are responsible for this increase and are affected by changes in gene expression (Raymond & Smirnoff, 2002). Plants are known to undergo epigenetic changes in response to environmental triggers (Sung & Amasino, 2004; Zografos & Sung, 2012). For example, wheat exposed to salt stress produces greater quantities of proline due to epigenetic mechanisms (Kumar, Beena, & Awana et al., 2017). It is suggested that the increased production of proline in water stressed wheat may result from epigenetic changes as well.

3.6. Areas for future research

Further research is needed to improve our understanding of the relationship between drought and CD. In many areas of the world, drought has become more common and persistent severe droughts are predicted for the next 20–50 years (Dai, 2011). Climate change is expected to produce severe drought conditions in the Great Plains and Southwestern United States in future decades at a level that is unmatched in the last millennium (Cook, Ault, & Smerdon, 2015). If this occurs, not only will people in these drought-stricken regions struggle from a lack of water, but the prevalence of CD may increase in populations that consume wheat grown in these dehydrated areas. Epidemiological research is needed to examine whether genetically predisposed individuals who eat wheat from drought-affected areas develop CD at a higher rate than individuals who eat wheat grown in areas with sufficient water. Also, research is needed to examine whether the ingestion of gliadin with lower proline content is associated with a lower prevalence of CD.

Studies are also needed to determine whether a correlation exists between farmers' selection of wheat varieties that are more tolerant to drought and the subsequent development of CD in individuals who ingest these drought tolerant wheat varieties. Although the selection of drought tolerant wheat may benefit the farmers who plant these crops and the consumers who have a more abundant food supply, the increased proline content of these wheat varieties may be more harmful to individuals who are genetically at risk for CD.

4. Conclusions

The prevalence of CD is increasing in many areas of the world and we suggest drought is one of the factors contributing to this increase. Drought conditions are associated with the production of proline rich wheat. Although proline provides adaptive advantages to wheat plants, proline-rich gliadin is toxic to individuals who are genetically predisposed to CD. Both the proline content and the location of proline residues relative to glutamine residues in gliadin peptides are important factors influencing the development of CD in genetically predisposed individuals.

We hypothesize that epigenetically induced changes in the amino acid sequence of gliadin peptides is producing wheat that is more toxic to individuals who are genetically predisposed to CD, thus increasing the likelihood that these individuals will develop CD. Furthermore, we hypothesize that even in the absence of drought conditions, selection by farmers of wheat varieties that are better able to tolerate water stress may be increasing the toxicity of wheat in our food supply.

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Conflicts of Interest
The authors report no conflicts of interest.

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