CHAPTER 21

PATHOGENESIS OF GLUTEN-SENSITIVE ENTEROPATHY IN DOG

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INTRODUCTION

Celiac disease (CD) is the name given to gluten-sensitive enteropathy (GSE), which was first discovered in humans (Batt et al. 1984). The disease has been frequently recorded in Irish Setter dogs in England since 1984 (Batt et al. 1984, 1987). Partially villous atrophy, the intestinal mucosa infiltrated with lymphocyte plasma cells, and abnormalities of brush border are all symptoms of this naturally occurring SGE (Batt et al. 1987; Hall & Batt 1990a, b). Gluten triggers an endogenous toxicity mechanism that initiates a cascade of immunological reactions that result in intestinal lining destruction and celiac disease (Stamnaes & Sollid 2015; Juhász et al. 2018).

Increased intraepithelial goblet cells and lymphocytic-plasmacytic infiltration are the first morphological changes detected in the intestinal mucosa of Irish Setters fed gluten at the age of four months. This occurs before villous atrophy and selective changes in brush border enzymes (Hall & Batt 1990b; Hall et al. 1992). These findings have been compared to celiac disease in humans. It has also been validated that susceptible dogs on a gluten-free diet are resistant to gluten challenge, implying that intestinal damage is a result of gluten sensitization, which may be an age-related occurrence (Hall & Batt 1991c; Hall & Batt 1992).

Genetic studies concluded that gluten sensitivity in Irish Setters does not resemble celiac disease in humans (Polvi et al. 1998) and that inheritance is autosomal recessive (Garden et al. 2000).

Due to genetically transferred, Irish Setters acquire wheat-dependent incomplete-villous atrophy with lymphocyte infiltration in intestinal mucosa, and so this model most closely resembles early stages of Celiac disease pathogenesis in newborns that are related with MHC II-dependent (Elli et al. 2015). When on a wheat-containing diet, the Irish Setter model had no elevated levels of antigliadin antibodies, this is showing a purely innate (non-adaptive) response to gliadin (gluten) in these animals, this argument supports the hypothesis that a strong aberrant innate response to gluten may activate or enhance the $CD4^+$ T-cell response to gluten and gliadin (Hall et al. 1992).

GSE is incredibly difficult to diagnose. A non-invasive technique for screening both at-risk patients and the broader public serological assays established in the previous two centuries. The diagnosis is made based on the presence of particular autoantibodies (anti-transglutaminase type 2 IgA) and corresponding features on affected intestinal structures (Ensari 2010; Osman et al. 2012; Elli et al. 2015). The class of drugs had been evaluated or will shortly undergone through clinical trials for GSE. Making modified grains free of immunostimulatory sequences is one option for treating the gluten antigen. This might be done through traditional breeding or, more likely, through genetically modified organisms (Gottlieb et al. 2015).

Keywords: GES, Gliadin, Gluten, Irish Setter, Zonulin.

Epidemiology

Prevalence

The Irish Setter was the first animal model of GSE. Studies conducted in the 1980s discovered that when the Irish setter was fed a wheat-containing diet as a puppy, it developed incomplete villous atrophy and intraepithelial lymphocyte infiltration (Batt et al. 1985). Garden et al. (2000) claimed that GSE is inherited as an autosomal recessive trait.

They add more grains especially those rich in gluten, during processing of feed for economic reasons. Eating gluten in large quantities has resulted in a rise in the prevalence and incidence of gluten allergy (Volta et al. 2013). Sometimes even gluten was detected in samples of food labeled as 'free from grains' and 'free from gluten' diets as a result of productive side contamination (Meineri et al. 2020).

Gluten sensitivity is the cause of sensitive enteropathy. Because the dog's immune system reacts when the dog eats gluten-containing items, gluten-sensitive enteropathy is classified as an autoimmune illness. The disease is idiopathic, but genetic factors are thought to have a role in the development of CD (Verlinden et al. 2006). GSI has been seen in a small number of dogs, but not in cats (Gaschen & Merchant 2011). The diseased pups came from a single-family line of Irish Setters and a group of Border Terriers, and the ailment may be shown in puppies as young as three months old. In Irish Setters, digestive issues including inappetence, chronic diarrhea, and weight loss, as well as growth retardation in young animals have been reported in association with gluten consumption. Clinical indications usually appear at six months of age (Daminet 1996). Gluten intake, on the other hand, has been linked to paroxysmal gluten-sensitive dyskinesia (PGSD) in Border terriers (Lowrie 2017). Park et al. (2014) reported a case of PGSD in a nine-

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month-old Yorkshire Terrier. A gluten-free diet is beneficial to these pets. Gluten-free diets are not found to be better for healthy pets than other nutritionally full and balanced diets (Gujral et al. 2012). Canine epileptoid cramping syndrome has also been connected to the consumption of gluten-containing foods in Border Terriers (Black et al. 2014).

Gluten in Grains

Grains are nutrient-dense food for pets. Grains are the seeds of cereal grasses like oats, barley, and corn, which assist the body to meet its critical requirement for glucose, an energy source (Sharma et al. 2013). All grains have 65-75 percent complex carbs and less than 2% sugar. Protein, fiber, vital fatty acids, B vitamins, and minerals are all present in them (Lafiandra et al. 2014).

Wheat's particular baking characteristic is due to gluten proteins. They are made up of two primary categories of linked glutamine and proline-rich proteins (Wieser 2007) which are insoluble in aqueous alcohol glutenins (glutelins) and alcohol-soluble gliadins (prolamines) respectively. Gliadins are monomeric proteins with a variety of secondary configurations. Glutenins are characterized by big, clumpy features (Schalk et al. 2017). Hordeins in barley, avenins in oats, and secalins in rye are all gluten-like proteins that are comparable to wheat gliadins. The two gluten-protein fractions, gliadins, and glutenins were quantified in wheat, barley, rye, and oat flour, each containing a proportional mixture of four cultivars, using analytical reversed-phase high-performance liquid chromatography (RP-HPLC) (Schalk et al. 2017).

Gluten in Dog Food

Glutens are a type of protein found in grains that can cause allergic reactions, but not all glutens are created equal (Biesiekierski 2017). Gliadins are proteins found in wheat, barley, rye, and spelt that can cause celiac disease symptoms (Lacorn et al. 2018).

Gluten-free is generally grain-free, but grain-free is not necessarily gluten-free. Only non-gluten grains, such as corn and/or rice, are allowed in dog food. Gluten hypersensitivity in many dog owners is likely to hunt for gluten-free food or be drawn by this characteristic (Allred & Park 2012). Corn gluten is listed in certain dog food ingredient lists. Gluten immunoassays do not recognize any of the proteins found in corn or rice (Morón et al. 2008). There is no evidence of canine hypersensitivity to corn, rice, barley, rye, or oats, however, wheat allergy has been recorded in dogs (Verlinden et al. 2006).

Several commercially available immune-chromatographic gluten assays are accessible (Allred & Park 2012; Lacorn et al. 2019). Gluten-free test kits are used to check for gluten in meals and beverages. Antibodies that respond with both gliadins and glutenins are used in specific testing (Allred & Park 2012). Uncontaminated rice and corn were found to be gluten-free in the tests, which identify gluten levels as low as 10-20 mg/kg product (Allred & Park 2012; Lacorn et al. 2019).

Pathogenesis

The pathophysiology of canine enteropathies has been discovered to be multifactorial in the last 15 years, involving an abnormally powerful cell-mediated immune response in genetically vulnerable dogs induced by a lack of tolerance to antigens in the diet and a complex commensal microbiota (Day et al. 2008).

Immunogenicity of Gluten Associated with the Pathogenesis

Dogs lived for thousands of years by eating raw, fresh, and entire food. Since the last era, commercially processed food was brought to provide accessible food. In developed countries, dogs' lifestyles and environments have changed. As a result of these changes, improved hygiene, and a lack of exposure to diverse microbes, "dogs diseases" have grown by 80 percent in the last few decades. Inadequate dietary nutrients and processed commercial dog food have been linked to an increase in sickness, allergies, enteropathy, inflammation, autoimmune disease, obesity, kidney/liver disease, and digestive problems (Verdu et al. 2015).

Indeed, the recent increase in the number of GSE diagnoses may have been impacted by the introduction of novel grain types for technological rather than nutritional reasons (de Lorgeril & Salen 2014; Lowrie et al. 2015).

GSE in dogs has similarities in morphology and biochemical feature with Celiac disease in humans and pathogenesis appears to be mediated by cell-mediated immunity rather than humoral immunity (Biagi et al. 2019).

Gluten consumption activates autoimmune enteropathy to gluten-sensitive enteropathy in dogs that are hereditary susceptible. Moreover, the increased prevalence is associated with other factors that include the amount and quality of dietary gluten and the introduction of novel grain types for technological modification in feed (de Lorgeril & Salen 2014; Leonard et al. 2020).

Gluten is made up of many non-digestible peptides which are immunogenic and resist being digested regularly (Silano et al. 2009). Gliadin is made up of peptide sequences called epitopes that are resistant to proteolytic processing in the gastrointestinal tract, enabling it to avoid destruction in the intestine. This occurs due to high quantity of amino acids, glutamine, and proline in gliadin which cannot be broken down by many proteases (Wieser 1996). In the period of enteric illness, the immune system become active and this condition may aid in breaking the tolerance to gluten dietary antigen (Silano et al. 2009).

In result of incomplete digestion, combination of peptides are obtained that cause host reactions, increase intestinal absorptivity, also stimulate innate and adaptive immune responses similar to those triggered by the presence of potentially hazardous microbes (Shan et al. 2002).

It's been proposed that a fundamental permeability problem could be the root of gluten-sensitive enteropathy pathophysiology (Menzies et al. 1979). According to this view, an increase in mucosal permeability permits ingested gluten or peptides formed by gluten digestion to pass through the intestinal epithelium, causing mucosal damage by direct toxicity or immune-mediated manners (Behrens et al. 1987).

The presence of two alpha-gliadin receptors has been discovered, and it is possible that they alter gut barrier activity by attaching to chemokine receptor 3 and inducing the synthesis of zonulin, which causes the interepithelial junctional complex to disintegrate. If gluten tolerance is compromised, gluten can potentially get through the intestinal

barrier via the transcellular pathway (Tripathi et al. 2009; Caio et al. 2019).

Importantly, given the availability of dietary cereal, the absence of alkaline phosphatase and aminopeptidase N action in brush border was a unique result of this enteropathy, as disaccharidases were intact. In an investigation of pups reared solely on a cereal-free diet, no structural or biochemical evidence of intestinal damage was detected. An experiment involving two groups of littermates, revealed significant permeability to 51Cr-ethylenediaminetetraacetic acid (EDTA), implying that impairment in permeability may be implicated in the disease development (Hall & Batt 1991a).

The role of the Gut Microbiome in the Pathogenesis of GSE

Considering that the immunity of the intestine may frequently be exposed to a diverse spectrum of antigens derived from food and xenobiotic substances, endogenous microflora, and pathogenic organisms, immunopathology in wounded mucosa develops (Dandrieux et al. 2008).

The enteropathy affects the permeability to nurturing absorption resulting in the changes in the intestinal environment which ultimately causes changes in the structure of a dog's gut microbiome. These factors may influence the maintenance of a healthy microbiome. The gut microbiome is linked directly and indirectly to their general health (O'Mahony et al. 2015).

The gut flora interacts with the host on a spectrum ranging from health to disease; in the initial section of the gastrointestinal tract, dietary components have an impact on the microflora's composition and metabolism (Eissa et al. 2019). This proposed that intestinal microbes play role in the pathophysiology of gluten-sensitive enteropathy. The specific microorganisms implicated and the underlying processes in gluten-sensitive enteropathy remain unknown. New evidence from gnotobiotic studies suggests that intestinal microbiota has a complicated monitor in responses of host immunity to gluten (Belkaid & Hand 2014; Verdu et al. 2015).

Mechanisms of Gluten Trafficking from Lumen to Lamina propria and Enhancing Signaling Pathway

The digestive and absorptive processes of the gastrointestinal system have been studied extensively. In phases of gluten's biological effects, scientists found that repeated gluten uptake changes the villi to finger-like structures to become chronically inflamed and damaged. These changes prevent them from acting their normal function of breaking down food and diverting nutrients through the gut wall to the blood circulation (Fasano 2011). The stimulation of the zonulin pathway by food-derived environmental triggers or alteration in gut microbiota, along with genetic susceptibility, miscommunication in both innate and adaptive immunity, and exposure to environmental stimuli, all appear to play a role in the pathogenesis of inflammation and autoimmune disease as seen in Figure 1. It's the only situation in which the presence or absence of a single environmental trigger, gluten, can switch the disease progression on or off. GSE is an extremely useful model for understanding autoimmune conditions (Fasano 2011).

Zonulin is a protein found in both animals and humans that helps to maintain intestinal barrier's integrity. In genetically predisposed cases, deregulation of the zonulin signaling is postulated to increase intestinal leakage and possibly autoimmune syndromes. The basic autoimmune disorder paradigm comprising of unique gene composition, dysbiosis of the microbiota, defective innate-adaptive immunity interactions and exposure to environmental variables, induces tight junction displacement that causes loss of the intestinal barrier junction. The mechanism by which aberrant antigen is transited from the luminal intestine, generates an inflammatory reaction and is assumed to be intestinal hyperpermeability, which is associated with autoimmune disorders. This innovative and creative treatment technique suggests that autoimmunity is not self-perpetuating and that autoimmune impairments can be prevented or treated by altering the interplay between genes and environmental triggers by restoring intestinal barrier function (Fasano 2012).

Prior studies in similar animals, however, had abortive to prove the existence of antigliadin and anti-tTG antibodies, as well as a link between MHC class II and illness (Polvi et al. 1997; Polvi et al. 1998). Antigliadin and anti-tTG immunoglobulin G (IgG) were found in the sera of dogs with enteropathy in one investigation; nonetheless, the link between canine enteropathy and human CD remains largely unknown (Vincenzetti et al. 2006).

Further research found that wheat-sensitive Irish Setters exhibit higher permeability to 51CrEDTA and probe sugars, as well as lower anti-gliadin antibody concentrations, than healthy Irish Setters, unrelatedly of whether they were fed a wheat-free or wheat-containing diet (Hall & Batt 1991b; Garden et al. 1998). GSE in Irish Setters isn't the same as CD in humans, according to genetic studies (Polvi et al. 1998), and that inheritance is autosomal recessive (Garden et al. 2000).

In terms of the pathophysiology of gluten-sensitive enteropathy in humans, competent tight junctions that limit macromolecule transit prevent gliadin from reaching submucosal tissue under normal physiological conditions. Tight junctions are disintegrated in people with the HLA-DQ2 or DQ8 haplotypes, permitting gliadin to pass through and prompting gliadin-induced immunological reactions, ultimately developing CD (Lammers et al. 2008). A set of processes that occur after gluten exposure are hypothesized to promote autoimmune disease. Gliadin and its immunomodulatory and inflammatory fragments bind to chemokine C-X-C receptor 3(CXCR3) in the intestinal lumen, inducing MyD88-dependent zonulin release and subsequent TJ disintegration. When the functional amide group is eliminated by tTG, gliadin peptides pass through the epithelium across opening TJs and connect to HLA molecules on the antigen-presenting cell surface (APC). As a result of this, Zonulin and cytokines that rely on My88 are released. HLA-gliadin peptide complexes presented by APCs activate T-lymphocytes, resulting in humoral (B cell activation leading to plasma cell release of anti-gliadin antibodies (AGA), N-arachidonoylethanolamide (AEA) and anti-tissue transglutaminase (tTG) antibodies) and cell-mediated (natural killer cells that destroy epithelial cells via cytokine release) feedback (Smyth 2017).

In the ideal situation, pattern recognition receptors such as toll-like receptors (TLRs) will continuously select antigens from food and the microbiome in the intestinal lumen. This procedure triggers antigen-presenting cells in the lamina propria, causing T regulatory cells to generate anti-inflammatory cytokines interleukin-10 (IL-10) and tissue growth factor (TGF) when only food antigens and typical

commensal microorganisms are noticed. Even though no infections have been discovered in the instance of dog enteropathy, sampling of typical commensals and dietary antigens causes T-lymphocytes to proliferate and produce pro-inflammatory cytokines (Day et al. 2008).

An underlying permeability issue appears to exist in groups of Irish Setter dogs who were given a gluten diet challenge, which may have allowed gluten antigens to enter and result in intraepithelial lymphocyte infiltration. In all sensitive setters in response to gluten, high permeability can increase intraepithelial lymphocyte density which does not always predict instantaneous intestinal harm (Hall & Batt 1992). There has been speculation that there is no concrete evidence that intraepithelial lymphocytes are directly responsible for disease development, and that their role may even be helpful. In untreated gluten-sensitive enteropathy, their increased quantity concerning the number of enterocytes is mostly due to an increase in the density of suppressor T cells (Freedman et al. 1987). Gluten's potential to cause significant intestine damage in Irish setters appears to be linked to early gluten exposure. An early gluten exposure allows the manifestation of intestinal damage, while the absence of early exposure appears to diminish gluten's harmful effect (Hall & Batt 1992).

Diagnosis

Accurate diagnosis of GSE may lead to rapid gluten-free diet treatment, restoring health, and preventing the progression of GSE-related problems (Shakeri et al. 2009). Therefore, several tests are performed to obtain a preliminary diagnosis of GSE (Gheller-Rigoni et al. 2004).

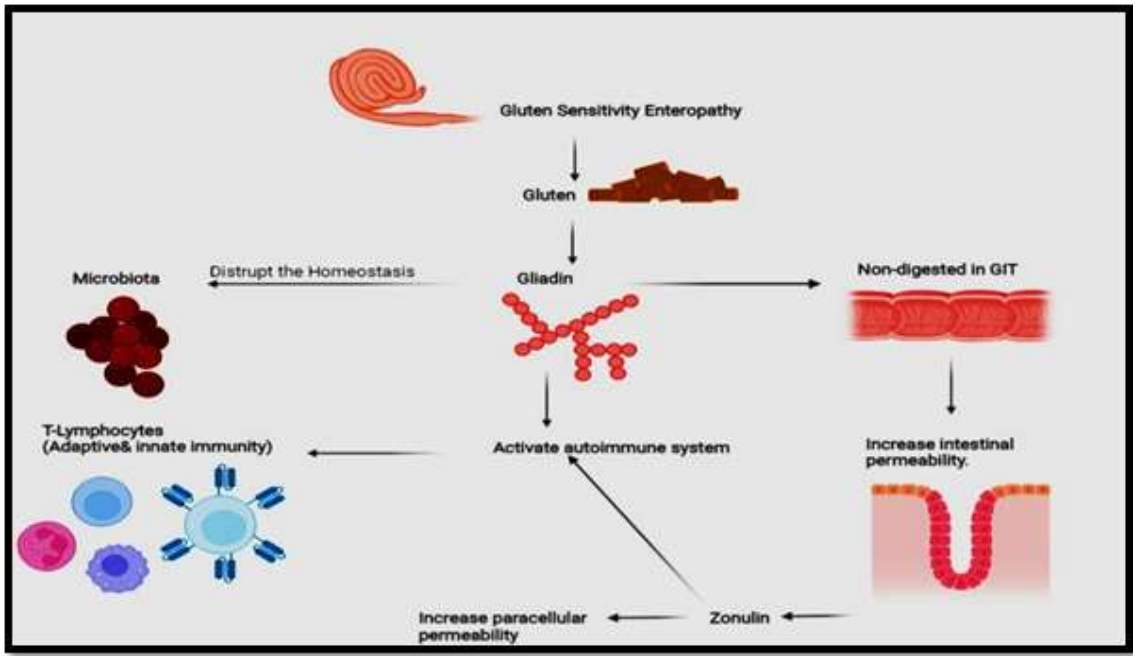

Fig. 1: The pathogenesis of GSE, Gladin important component of Gluten that activates the immune system via disturbing GIT homeostasis and increasing intestinal permeability. Author designed graph by using biorender.com.

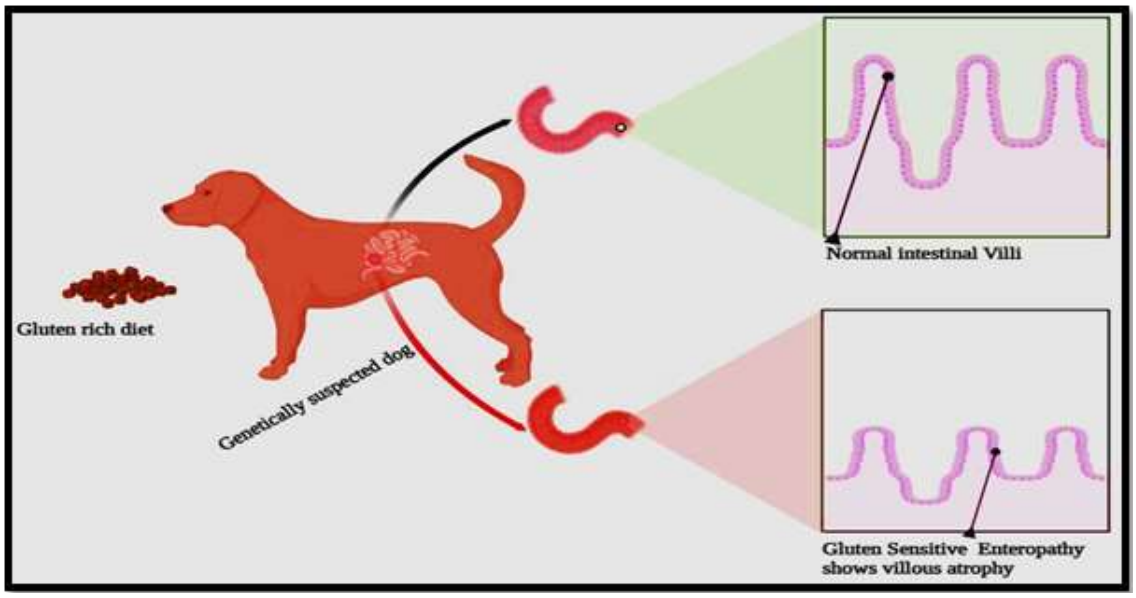

Fig. 2: Graphic presentation reveals the differences between healthy dogs with genetically suspected animals that demonstrate the reduction in the villi length as the mucosal involvement. Author designed graph by using biorender.com.

Clinical Signs

Affected dogs may show the signs of classic chronic enteritis such as intermittent diarrhea, inappetence, weight loss or inability to gain weight, and occasional vomiting (Garden et al. 2000).

Clinicopathologic Examinations

GSE can manifest itself in a variety of ways, thus veterinarian should be aware of the different clinical findings it might cause. As a result of improved awareness of the disease's processes, more canines are being diagnosed through utilizing different tests (Lohi et al. 2007). Moreover, the majority of clinical alterations can occur in result of GSE-induced damage to the small intestine, as plasma protein leaks into the intestine's lumen, resulting in hypoproteinemia. Biochemical tests can indicate low levels hypoglobulinemia, hypopal-buminea, hypocholesterolemia, hypocalcemia, hypokalemia, hypomagnesemia and hypochloremia (Donnini et al. 2021). Furthermore, hematological examination determines an iron shortage, neutrophilia, and thrombocytosis, as well as a significant drop in serum folate and cobalamin concentrations due to malabsorption (Allenspach et al. 2007; Craven et al. 2009). Also, many serologic indications can be utilized to assess the dogs with gluten-sensitive enteropathy or subsequent reactions to gluten-free diet therapy. IgA tissue transglutaminase antibody (IgA-tTG) test and IgA endomysial antibody (IgA-EMA) test are two serological tests that are now used in clinical practice. IgA and IgG (AGA) antigliadin antibodies show considerable sensitivity but are less used than IgA-EMA and IgA-tTG antibodies. Antigliadin antibodies are no longer suggested as a screening test as the existence of higher sensitive and specific EMA and tTG antibody tests replaced it. Anti-tTG immunoglobulin G (IgG) and antigliadin antibodies were detected in the serum of dogs with GSE in a prior study (Gheller-Rigoni et al. 2004; Vincenzetti et al. 2006).

Histopathology

Gluten-sensitive enteropathy can be diagnosed by using tissue samples from the distal section of the duodenum or the proximal jejunum, which are susceptible to the highest amounts of dietary gluten. Extensive lymphocyte infiltration from the lamina propria ascended to the surface epithelium has been observed microscopically. Additionally, the villus lengths are reduced with hyperplastic changes in the crypts (Figure 2). Also, the morphology of enterocytes changes from columnar to cuboidal, with numerous vacuoles visible in their cytoplasms (Lowrie et al. 2016; Matsumoto et al. 2018). The malabsorption is most likely caused by the reduction of mucosal and brush-border surface area caused by villous atrophy. Furthermore, greater epithelial turnover, as seen by increased crypt mitotic activity, may impair absorptive enterocytes' ability to properly differentiate and express proteins required for terminal digestion and transepithelial transport. Increased number of plasma cells, eosinophils, and mast cells, exclusively in the upper section of the lamina propria, are the other pathologic characteristics of gluten-sensitive enteropathy. It is important to keep in mind that intraepithelial lymphocytosis and villous atrophy can occur in multiple situations, including viral enteritis. As a result, the diagnosis of gluten-sensitive enteropathy is most specific when histologic and serologic evidence is combined (Freeman et al. 2011; Simpson & Jergens 2011).

Differential Diagnosis

Finally, dogs should be examined for any concurrent clinical problems that could indicate chronic enteritides such as inflammatory bowel disease, lymphangiectasia, metabolic disorders, parasitic infestation (roundworms, hookworms, and Giardia), and dietary allergic reaction (Simpson & Jergens 2011).

Treatment

Changing the Food Component

All GSE therapies begin with a gluten-free diet, suggested to all patients after a correct diagnosis has been established (Sollid & Lundin 2009).

Cereal grains such as wheat, barley, rye, and closely related cereals such as spelt are not included in a gluten-free diet (a wheat breed). Despite uncommon occurrences of oat sensitivity, oat is a related grain that is widely accepted. Oats are intolerant in almost all celiac, and there have been rare occurrences of oat intolerance. Many commercially available oat products are tainted with additional contaminants (Saturni et al. 2010).

Wheat starch as a bread base increases the gluten in the overall load, while wheat starch as a flour adds gluten to the entire bag (Huang et al. 2021).

Certain states, but not all, allow wheat starch to be used as a bread ingredient, which adds gluten to the total load. Another gluten-free food is beer, which is produced from malted barley protein (Lynch et al. 2016).

Alternative and Novel Treatments

Two of the treatments intend to block gluten from interacting with the mucosal immune system that include oral enzyme supplementation to accelerate up the breakdown of gluten into non-immunostimulatory pieces and the addition of a polymer to sequester the gluten proteins (Caputo et al. 2010; Van Buiten & Elias 2021).

Two medicines were tested to deal with the issue of oral glutenase supplementation. ALV003 is made up of microorganisms that produce a glutamine-specific cysteine protease (EP-B2) and a proline-specific prolylendoprotease. Both enzymes function together in the gastrointestinal tract and have a gastric effect (Geßendorfer et al. 2011; Wei et al. 2020).

Another enzyme that breaks down gluten and has gastric activity is Aspergillus niger's prolyl endoprotease (Salden et al. 2015).

For GSE, this class of medicines was examined or was going to be evaluated in clinical studies. Making modified grains devoid of immunostimulatory sequences is one strategy that also addresses the gluten antigen itself. This might be accomplished through traditional breeding or, more likely, through genetically modified organisms (Gottlieb et al. 2015). This technique is difficult to implement due to the vast number of unique peptide epitopes found in many different classes of gluten proteins and gliadins, as well as glutenin,

which were encoded at separate loci in the wheat genome (Sharma et al. 2020).

Another strategy tries to overcome a GSE-related epithelial barrier defect. More immunostimulatory gluten peptides and other compounds that may play a role in intestinal homeostasis have been reported due to increased barrier permeability (Cardoso-Silva et al. 2019).

AT-1001, a zonulin inhibitor, was in phase II research to reduce gluten-induced barrier dysfunction (Bakshi et al. 2012). Drug development is being conducted to develop medicines that disrupt these systems. Peptide-like substances bind to HLA-DQ2 and DQ8, preventing T-cells from identifying gluten peptides, and TG2 inhibitors available in a variety of types. The identification of gluten epitopes implicated in the $CD4^+$ T-cell response to gluten has opened the path for gluten-reactive T-cell peptide vaccines. The discovery of dominant epitopes that react to all GSE instances was a critical step in putting this idea into practice (Yoosuf & Makharia 2019).

Furthermore, a phase II clinical trial in GSE has been conducted to explore whether an intestinal hookworm infection modifies the mode of local immune response and suppresses gluten sensitivity in patients with CD (Daveson et al. 2017; Pearson et al. 2019).

Interfering with cytokines has been used effectively to treat various autoimmune diseases, and a slew of new treatment approaches are being developed in this sector (Moudgil & Choubey 2011). However, due to the unacceptability of complications in GSE therapy, most treatments are unlikely to be used as the main indication for GSE. Anti-IL15 therapy, proposed as a treatment for refractory GSE, may represent an exception to this rule. Uncomplicated GSE may become an indicator if refractory GSE is successful (Rashtak & Murray 2012).

Conclusion

- Gladin is the most cause of host reactions, increases intestinal absorptivity and also stimulates innate and adaptive immune responses.
- Gluten sensitivity in Irish Setters dogs isn't the same as celiac disease in humans, according to genetic studies.
- Antigliadin and anti-tTG immunoglobulin G (IgG) were discovered in the sera of dogs with enteropathy; although, the relationship between canine enteropathy and human CD seems to be mostly unexplained.
- Drug development is now conducted to develop medicines that disrupt immune system systems, which block T-cells from detecting gluten peptides.

Recommendation

Reducing the need for gluten in dog food may be a good choice in the amelioration of GSE development. More studies are needed to fully explain the zonulin pathway that plays important role in the trafficking of cells and activation of the immune system.

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