Veterinary Integrative Sciences 2024; 22(3): 713 - 737 DOI; 10.12982/VIS.2024.048

Vet Integr Sci

Veterinary Integrative Sciences

Faculty of Veterinary Medicine
Chiang Mai University

ISSN; 2629-9968 (online)

Website; www.vet.cmu.ac.th/cmvj

Review article

Clinical applications of current biomarkers in canine chronic enteropathies

Pinkarn Chantawong[1,2]

[1]*Department of Companion Animal and Wildlife Clinic, Faculty of Veterinary Medicine, Chiang Mai University, Chiang Mai 50100, Thailand*

[2]*Research Center for Veterinary Biosciences and Veterinary Public Health, Faculty of Veterinary Medicine, Chiang Mai University, Chiang Mai 50100, Thailand*

Abstract

Chronic enteropathies (CEs) are a group of multifactorial gastrointestinal diseases in dogs, which are defined by chronic persistent or recurrent gastrointestinal symptoms, along with histopathological indications of mucosal inflammation. These disorders have gained significant interest in recent years due to their unclear etiopathogenesis, the severity of symptoms and lack of response to conventional treatments. The diagnosis of canine CEs is challenging because of their non-specific clinical symptoms, which require an extensive diagnostic investigations to exclude alternative causes of chronic gastrointestinal signs. Currently, the gold standard for diagnosing CEs relies on histopathologic evaluation and assessing responses to therapeutic trials. However, these methods have limitations in terms of invasiveness, cost and time consumption. Therefore, biological markers that objectively reflect the severity of gastrointestinal disease, assist in diagnosing clinical practice, predicting treatment response, determining prognosis and monitoring disease progression may offer valuable clinical benefits for dogs with CEs. This article provides an overview of the current biomarkers for canine CEs and discusses their potential clinical applications, as well as their advantages and limitations. Furthermore, this review expects to contribute to the identification of future directions for advancing biomarkers in canine CEs research.

Keywords: Biomarkers, Chronic enteropathies, Clinical applications, Dogs

***Corresponding author:** Pinkarn Chantawong, Department of Companion Animal and Wildlife Clinic, Faculty of Veterinary Medicine, Chiang Mai University, Chiang Mai 50100, Thailand. E-mail: pinkarn_@hotmail.com.

Article history; *received manuscript: 24 June 2023, revised manuscript: 24 August 2023, accepted manuscript: 18 September 2023, published online: 18 December 2023*

Academic editor: *Korakot Nganvongpanit*

INTRODUCTION

Chronic enteropathies (CEs) refer to an important group of gastrointestinal diseases in dogs defined by persistent or intermittent gastrointestinal symptoms for over 3 weeks. CEs are diagnosed after excluding of extra-gastrointestinal diseases, parasitic diseases and mechanical gastrointestinal obstruction (Dandrieux and Mansfield, 2019; Sacoor et al., 2020). Clinically, CEs are classified into different categories based on the treatment response: food-responsive enteropathy (FRE) for dogs showing a positive response to an elimination diet, antibiotic-responsive enteropathy (ARE) for dogs displaying a sustained effect from antimicrobial therapy, immunosuppressant-responsive enteropathy (IRE) if immunosuppressive drugs are required, and non-responsive enteropathy (NRE) for dogs that do not exhibit any response to treatment (Becher et al., 2021). In cases of IRE that exhibit unsuccessful responses to dietary and antimicrobial trials, along with confirmed mucosal inflammation observed through histopathological analysis, dogs are diagnosed as idiopathic inflammatory bowel disease (IBD) (Dandrieux, 2016).

The exact etiopathogenesis of CEs have not been clearly elucidated. However, it is considered that the disruption of immunologic tolerance towards dietary and microbial antigens, along with an inherited susceptibility, plays a crucial role in pathological inflammation (AlShawaqfeh et al., 2017; Heilmann and Allenspach, 2017). The failure of immunologic tolerance occurs due to intestinal barrier dysfunction, disruption of gut-associated lymphoid tissue (GALT) and disturbance of intestinal microbiota, leading to inflammation and injury of the mucosal lining (Osada et al., 2016; Eissa et al., 2019). Clinical signs from uncontrolled inflammation can vary depending on individual immunity and the severity of the disease (Dandrieux and Mansfield, 2019). Valuable tools for clinical assessment include the canine IBD activity index (CIBDAI) and the canine chronic enteropathy clinical activity index (CCECAI), which provide information on the clinical disease activity (Cerquetella et al., 2010; Heilmann and Steiner, 2018).

The diagnosis of CEs primarily relies on histopathologic evaluation and the response to therapeutic trials (Makielski et al., 2019). Histopathology remains a reliable method for identifying and evaluating intestinal inflammation. Nevertheless, its findings may not be sufficient for distinguishing among the different categories of CEs (Heilmann and Steiner, 2018). Furthermore, histologic evaluation of tissue biopsies obtained through endoscopy or surgery is invasive, costly, time-consuming and can be influenced by surgeon experience (Heilmann et al., 2014; Sacoor et al., 2020). Therefore, the simple, non-invasive and objective assessment for CEs is promptly required. Over the past decades, there has been great interest in biomarkers for clinical indices that can be useful in identifying disease severity, diagnosing clinical practice, predicting treatment response and determining the prognosis of dogs with CEs (Gerou-Ferriani et al., 2018; Otoni et al., 2018; Sacoor et al., 2020). Thus, the objective of this review is to provide an overview of current biomarkers for canine CEs and discusses their potential clinical applications, as well as their advantages and limitations.

PATHOGENESIS OF CHRONIC ENTEROPATIES

The pathogenesis of CEs involves complex interactions between innate and adaptive immunity, with various factors, including intestinal microbiota, host genetics, dietary constituents, and environmental triggers, contributing to disease development (Figure 1) (AlShawaqfeh et al., 2017; Heilmann and Allenspach, 2017).

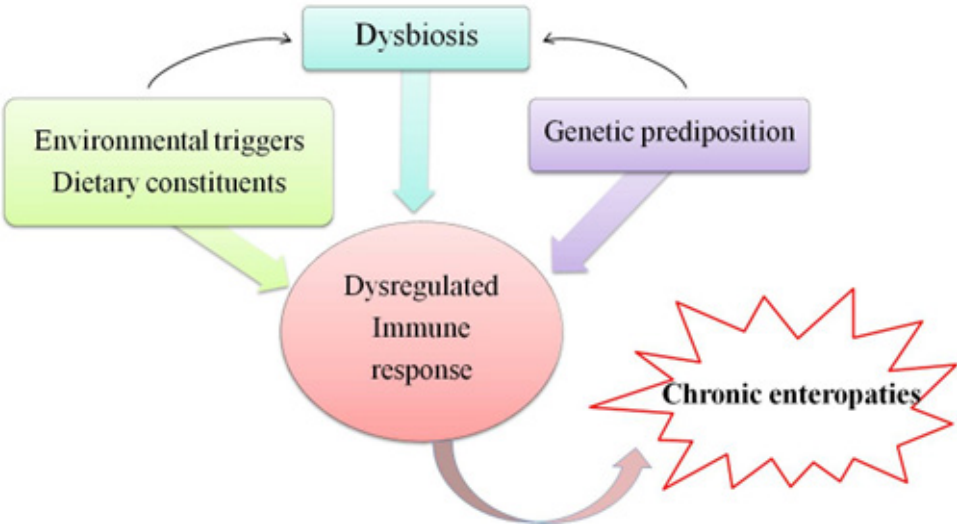

Figure 1 Multiple factors implicated in the pathogenesis of canine chronic enteropathies

The primary defense against pathogens is provided by innate immunity, which consists of the mucosal epithelial barrier, the intestinal microbiota, neutrophils, macrophages, dendritic cells, eosinophils, as well as their derived molecules and secreted products (Siel et al, 2022). In dogs with CEs, the intestinal barrier has increased permeability due to a malfunction in regulating tight junctions, leading to an increased exposure of immune cells to antigens in the intestinal lumen. Bacteria or infectious agents bind to Pattern Recognition Receptors (PRRs), including toll-like receptors (TLRs) and the nucleotide-binding oligomerization domain (NOD)-2, which have a crucial function in recognizing specific molecules expressed by bacteria. In response to antigenic stimulation, cells initiate intracellular signal pathways that lead to the production of Nuclear factor-kappa B (NF-kB). This subsequently triggers the release of pro-inflammatory cytokines and interleukins such as Tumor Necrosis Factor alpha (TNF-α), interleukin-1 (IL-1), interleukin-6 (IL-6), interleukin-8 (IL-8) (Allenspach, 2011; Heilmann and Allenspach, 2017).

The adaptive immune response in the intestine involves CD4+ T cells and B cells responsible for immunoglobulin A (IgA) production within Peyer's patches (PPs), and intestinal epithelial lymphocytes (IELs) collectively contribute significantly to maintaining immune balance (Siel et al, 2022). IgA antibodies play a crucial role in mucosal defense by preventing the penetration of pathogens through the intestinal barrier and avoiding atypical responses to the usual components of the microflora (Allenspach, 2011). In dogs with CEs, a decrease in IgA levels in both intestinal mucosa and feces has been reported when compared with healthy dogs (Maeda et al., 2013; Lee et al., 2015).

Concerning the receipt of antigenic stimuli, activated antigen-

presenting cells (APCs) stimulate an adaptive immune response by presenting antigens to naive CD4+ T helper cells (Th cells) in the mesenteric lymph node. Depending on their cytokine pattern, Th cells can develop and differentiate into Th1, Th2, Th17 cells and regulatory T-cells (Tregs). Th1 cells prompt cell-mediated effector mechanisms, such as cytotoxicity and immunity against intracellular pathogens, through the release of IL-2, IL-12, INF-ɤ and TNF-α (Heilmann and Suchodolski, 2015). Th2 cells release IL-4, IL-5, IL-6, and IL-13, which stimulate B lymphocytes to generate immunoglobulin E (IgE) and recruit eosinophils associated with parasitic infection and allergies (Siel et al, 2022). Th17 cells produce IL-17 and IL-22, proinflammatory cytokines that initiate inflammatory signaling cascades, leading to the recruitment of innate immune cells (Korn et al, 2009). Tregs cells secret anti-inflammatory cytokines such as IL-10 and transforming growth factor-beta (TGF-β) that inhibit an excessive immune response and maintain immunotolerance (Choy et al, 2017). At present, the relationship between Th lymphocyte profiles and CEs in dogs has not been definitively established (Heilmann and Suchodolski, 2015). Nevertheless, an excess of Th1, Th2 and Th17 activity triggered by extensive pathogenic infections can lead to intestinal inflammation (Abraham and Cho, 2009). As for Tregs, these cells have been detected in low numbers among dogs suffering from lymphocytic-plasmacytic enteritis (Maeda et al., 2013; Maeda et al., 2016). A briefly overview of the innate and adaptive immune response in the pathogenesis of canine CEs is illustrated in Figure 2.

BIOMARKERS IN CHRONIC ENTEROPATIES

A biomarker refers to a substance that is objectively measured and assessed as an indicator of both normal and pathogenic processes or as a response to pharmacological interventions (Alghoul et al., 2022). It provides information on biologically produced changes in the body that are related to diseases or health conditions (Sacoor et al., 2020). In CEs, biomarkers play a crucial role in diagnosis, treatment, management and prognosis. Potential biomarkers that could be clinically relevant for CEs should reflect the individual risk of inducing intestinal inflammation, evaluate gastrointestinal function, determine the progression and severity of the inflammatory diseases, predict treatment response or disease outcome, and monitor the severity of gastrointestinal inflammation (Duvoisin et al., 2017).

Over the past decade, several biological markers have been established as valuable measures for CEs in dogs (Gerou-Ferriani et al., 2018; Otoni et al., 2018; Sacoor et al., 2020). They offer the advantages of being minimally invasive, cost-effective and time-efficient compared to endoscopy and biopsy techniques (Sacoor et al., 2020). However, some biomarkers have limitations

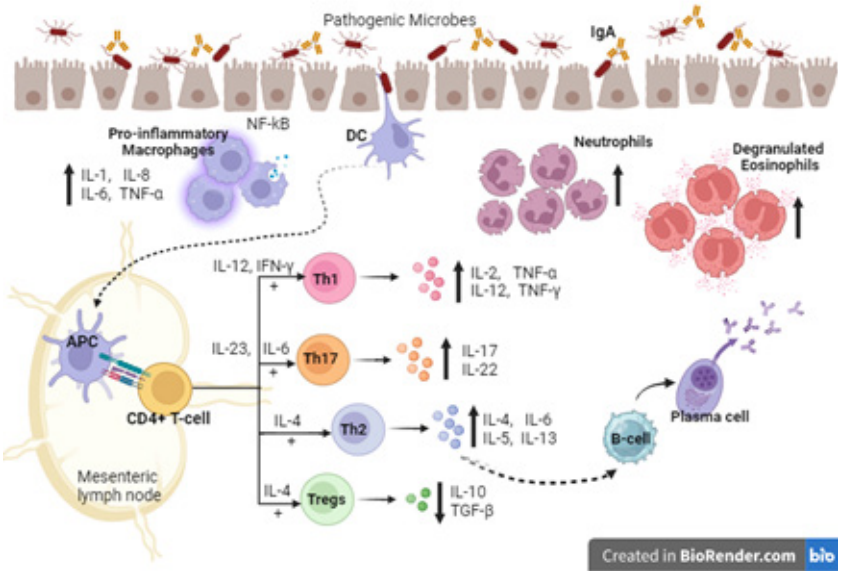

Figure 2 Pathogenesis of canine chronic enteropathies (CEs). In CEs, the breakdown of intestinal barrier integrity leads to increased exposure of pathogenic microbes to immune cells. Innate immunity, including mucosal epithelial cells, dendritic cells, neutrophils, eosinophils, macrophages and secreted products, defends against pathogens and triggers inflammatory process. As a consequence, activated antigen-presenting cells (APCs) stimulate the adaptive immune response by phagocytizing pathogens and migrating to mesenteric lymph nodes to present antigens to naive CD4+ T helper cells, which differentiate into Th1, Th2, Th17 cells and regulatory T-cells (Tregs), leading to the production of specific cytokines. An imbalance between proinflammatory and anti-inflammatory cytokines causes disrupted intestinal immunity. (Original illustration based on: Allenspach, 2011; Eissa et al., 2019).

in terms of sensitivity, specificity and responsiveness in clinical practice (Alghoul et al., 2022). Furthermore, it is improbable for a single biomarker to possess all the characteristics of an ideal marker. Therefore, it is essential to consider the clinical information of a specific biomarker in order to enhance the comprehension of data within a particular clinical context (Sacoor et al., 2020). The biomarkers discussed in this review are classified as functional, biochemical, genomic, microbiomic and metabolomic markers.

FUNCTIONAL BIOMARKERS

The functional biomarkers that have been evaluated in dogs with CEs include cobalamin, folate, methylmalonic acid and alpha 1-proteinase inhibitor, as documented in Table 1.

Table 1 Summary of research findings on selected functional biomarkers in dogs with chronic enteropathies

Biomarker	Sample	Study Groups	Main Findings	Insignificant correlations or Limitations of biomarker	Ref.
Cobalamin	Serum	136 dogs with chronic diarrhea	- Severe hypocobalaminemia in both IBD an EPI groups - Significant correlation with increased disease severity scores and poor prognosis	- Cannot distinguish between dogs with IBD and EPI	Volkmann et al., 2017
		203 dogs with CEs	- No significant differences in hypocobalaminemia levels among dogs with ARE, FRE and IRE	- Cannot distinguish among subtypes of CEs	Allenspach et al., 2016
Folate	Serum	127 dogs with CEs	- Dogs with CEs, 14% exhibited hypofolatemia, while 5% had hyperfolatemia	- Not specific to CEs	Heilmann et al., 2018b
		203 dogs with CIE	- No significant differences in folate levels among dogs with ARE, FRE and IRE	- Cannot distinguish among subtypes of CEs	Allenspach et al., 2016
		29 dogs with chronic GI signs and 38 healthy dogs	- 66% of the clinical dogs had hyperfolatemia - No significant differences in folate levels between dogs with ARE and those not responding to antibiotic	- Cannot distinguish between ARE and other GI disorders	German et al., 2003
Methylmalonic acid	Serum	56 dogs with chronic GI diseases and 43 healthy dogs	- 25% of hypocobalaminemic dogs had increased MMA concentrations	- No correlation between CCECAI and MMA concentrations - Not specific to CEs	Berghoff et al., 2013
α1-PI	Feces	16 dogs with GI diseases and 21 healthy dogs	- High fecal α1-PI concentration in dogs with histological abnormalities	- No correlation between fecal α1-PI and serum albumin concentrations	Murphy et al., 2003
	Feces Serum	120 dogs receiving GI tissue biopsies	- High fecal α1-PI concentration in dogs with crypt abscesses and/or lacteal dilation - Low serum α1-PI and albumin concentrations in dogs with crypt abscesses and/or lacteal dilation - Severe intestinal lesions were associated with both fecal & serum α1-PI concentrations	- Serum α1-PI concentrations may increase in corticosteroid-treated dogs.	Heilmann et al., 2016a

Abbreviations: CEs= Chronic enteropathies; IBD = Inflammatory bowel diarrhea; EPI= Exocrine pancreatic insufficiency; ARE=Antibiotic-responsive enteropathy; FRE=Food-responsive enteropathy; IRE= Immunosuppressant-responsive enteropathy; GI= Gastrointestinal; MMA= Methylmalonic acid; CCECAI = canine chronic enteropathy clinical activity index; α1-PI= Alpha 1-proteinase inhibitor

COBALAMIN AND FOLATE

Cobalamin (vitamin B12) and folate (vitamin B9) are water-soluble vitamins that offer clinical benefits in the diagnosis and treatment of gastrointestinal diseases.

Cobalamin is absorbed in the distal small intestine, where specialized receptors facilitate the uptake of the cobalamin-intrinsic factor complex (Berghoff and Steiner, 2011). The malabsorption of cobalamin can be disturbed by various factors such as chronic severe diseases that impact the mucosa of the ileum (resulting in decreased expression of intrinsic factor receptors in enterocytes), secondary dysbiosis in the small intestinal (leading to increased utilization of cobalamin by intestinal bacteria) and genetic predisposition (Chinese Shar Peis, Giant Schnanuzers, Border Collies) (Toresson et al., 2016; Moser et al., 2018). Hypocobalaminemia occurs in 19-54% of dogs with CEs and is considered as a negative prognostic factor associated with hypoalbuminemia (Berghoff et al., 2013; Volkmann et al., 2017; Heilmann et al., 2018). Nevertheless, a normal serum cobalamin level does not exclude the early CEs condition due to the ongoing malabsorption (Berghoff and Steiner, 2011). A previous study revealed that there were no significant differences in serum cobalamin levels among dogs diagnosed with ARE, FRE, and IRE (Allenspach et al., 2016). Additionally, hypocobalaminemia can also be presented in dogs with exocrine pancreatic insufficiency (EPI), and it is not specific to CEs (Volkmann et al., 2017; Sacoor et al., 2020). Low serum cobalamin concentration indicates a requirement for supplementation.

Folate is mainly absorbed in the proximal part of the small intestine (duodenum and proximal jejunum) through specific folate carriers (Berghoff and Steiner, 2011). In dogs diagnosed with CEs, a recent study demonstrated that 14% exhibited hypofolatemia, while 5% had hyperfolatemia (Heilmann et al., 2018b). Chronic malabsorption of the proximal small intestine, caused by damage to the mucosal barrier, can deplete folate body storage and result in hypofolatemia. Nevertheless, lower levels of serum folate are not specific to CEs and cannot be used alone to distinguish between different types of this condition (German et al., 2003; Allenspach et al., 2007; Allenspach et al., 2016). Hyperfolatemia can result from small intestinal dysbiosis due to enhanced folate production by certain gut microorganisms. However, a folate concentration within the reference range should not be used to exclude small intestinal dysbiosis (Sacoor et al., 2020). In case of cobalamin deficiency, serum folate levels may appear normal or elevated due to cobalamin's role as a cofactor in an enzymatic pathway that utilizes folate. Therefore, the serum folate concentration should be reevaluated after cobalamin supplementation to obtain an accurate understanding of folate metabolism (Berghoff and Steiner, 2011).

METHYLMALONIC ACID (MMA)

Methylmalonic acid (MMA) is a metabolite that increases when the tissue lacks adenosyl-cobalamin, a cofactor required for the conversion of methylmalonyl-CoA to succinyl-CoA. The absence of cobalamin impairs the metabolism of methylmalonyl-CoA, leading to the accumulation of MMA

(methylmalonic acidemia) (Berghoff et al., 2013). Therefore, the elevated production of MMA is considered as a marker of cellular cobalamin deficiency resulting from cobalamin malabsorption or decreased cobalamin transport (Grutzner et al., 2013a). Previous studies revealed that 25-46% of dogs with CEs and hypocobalaminemia exhibited evidence of tissue cobalamin deficiency, as indicated by an elevation in serum MMA concentration (Berghoff et al., 2012; Berghoff et al., 2013). However, it was not possible to differentiate between the various diseases affecting dogs with CEs. The routine measurement of serum MMP is not commonly conducted in veterinary practice for small animals due to the financial implications and technical complexity of the assay (Heilmann and Steiner, 2018). Additionally, increased serum MMA levels may be observed in dogs with renal insufficiency, and this finding should be confirmed in conjunction with the serum creatinine or symmetric dimethylarginine (SDMA) concentrations (Jergens and Heilmann, 2022).

ALPHA 1-PROTEINASE INHIBITOR

Alpha 1-proteinase inhibitor (α1-PI) is a protein that functions by inhibiting protease enzyme and is primarily synthesized in the liver. This protein is resistant to proteolytic degradation and has similar-sized molecules as albumin; therefore, both proteins are likely to be excreted from the intestinal lumen into feces in cases of gastrointestinal diseases causing protein loss (Melgarejo et al., 1996; Cerquetella et al., 2010). Elevated concentrations of fecal canine α1-PI serve as a clinically useful marker for protein-losing enteropathy (PLE) and are also considered predictive of poor outcomes in dogs with CEs (Berghoff and Steiner, 2011). Furthermore, they have been found to correlate with histopathological lesions observed in dogs with PLE, including dilated lacteal and crypt abscesses (Murphy et al., 2003; Heilmann et al., 2016a). Due to the significant day-to-day variations in fecal α1-PI concentrations, it is recommended to collect fecal samples for three consecutive days to improve the accuracy of the test (Allenspach, 2015). In the case of dogs with CEs that have not responded to elimination diet and antibiotic treatments, a 3-day mean fecal α1-PI concentration over 19.0 µg/g can be used as a reliable confirmatory test for histological lesions associated with PLE (Heilmann et al., 2016a; Heilmann and Steiner, 2018).

The assessment of fecal α1-PI is particularly valuable for detecting gastrointestinal protein loss at the early stage, as it can increase prior to the manifestation of clinical symptoms, hypoalbuminemia or panhypoproteinemia. Moreover, it can help in distinguishing between gastrointestinal protein loss and hypoalbuminemia caused by liver-related conditions (Vaden et al., 2002; Murphy et al., 2003). Although fecal α1-PI exhibits high sensitivity, it is not regarded as a particular marker for CEs, as protein loss through the gastrointestinal tract could be related to various systemic gastrointestinal diseases. Nevertheless, it may be used for monitoring disease progression and assessing the effectiveness of treatment (Collins, 2013).

The chronic gastrointestinal loss of α1-PI caused by PLE leads to decreased serum α1-PI levels, as observed in dogs with IBD. However, it can also increase in corticosteroid-treated dogs and decrease in dogs with protein-losing nephropathies (PLN) (Grutzner et al., 2013b; Grutzner et al., 2014;

Heilmann et al., 2016a). The use of the serum-to-fecal α1-PI ratio seems to enhance the diagnostic precision in dogs with hypoalbuminemia. A previous study indicated that concentrations of serum and fecal α1-PI, along with their ratios, can provide insights into the severity of small intestinal crypt abscesses and/or dilated lacteal in dogs with CEs (Heilmann et al., 2016a).

BIOCHEMICAL BIOMARKERS

In dogs with CEs, previous studies have investigated biochemical biomarkers, including C-reactive protein, perinuclear anti-neutrophilic cytoplasmic antibodies, N-methylhistamine, calprotectin and calgranulin C, as outlined in Table 2.

C-REACTIVE PROTEIN

C-reactive protein (CRP) belongs to a group of proteins known as acute-phase reactants, which are synthesized by the liver in reaction to various types of tissue injury, infection, inflammation or certain cancer (Nakamura et al., 2008). Otoni et al. (2018) demonstrated that dogs with idiopathic IBD exhibited higher CRP concentrations in comparison to both healthy dogs and dogs treated with antibiotics or corticosteroids. However, reports on its correlation with clinical severity and histopathological lesions in dogs with IBD are still controversial (Allenspach et al., 2007; McCann et al., 2007; Jergens et al., 2010; Otoni et al., 2018).

A previous study revealed that the presence of serum CRP level above 9.1 mg/L, along with an increased fecal calprotectin level, can effectively differentiate dogs with IRE from FRE or ARE, achieving a sensitivity rate of 72% and a specificity rate of 100% (Heilmann et al., 2018b). This demonstrates a high positive predictive value for this diagnosis (Heilmann and Steiner, 2018). Nevertheless, the clinical utility of this biomarker for CEs in dogs is limited because of its significant variation among individuals and lack of specificity to gastrointestinal tract (Jergens and Heilmann, 2022). Interestingly, it remains valuable as a surrogate indicator for assessing the advancement of disease and the effectiveness of treatment in dogs with CEs (Collins, 2013). In order to be deemed as a clinically significant alteration, the serum CRP concentration should exhibit a minimum 2.7-fold increase or decrease (Carney et al., 2011).

Table 2 Summary of research findings on selected biochemical biomarkers in dogs with chronic enteropathies

Biomarker	Sample	Study Groups	Main Findings or Significant correlations	Insignificant correlations or Limitations of biomarker	Ref.
C-reactive protein	Serum	127 dogs with CEs	- Elevated serum CRP concentrations were correlated with the severity of morphological lesions - Serum CRP level ≥ 9.1 mg/L distinguished dogs with IRE/NRE from FRE /ARE	- No correlation with histologic lesion scores - Not specific to CEs	Heilmann et al., 2018b
	Serum	16 dogs with IBD and 13 healthy dogs	- Significantly higher serum CRP concentrations in dogs with IBD	- No correlation with CIBDAI or histologic severity	Otoni et al., 2018
pANCA	Serum	21 dogs with PLE and/ or PLN, 7 nephropathy dogs and 12 healthy dogs	- Dogs with PLE and/or PLN had positive results for pANCA - Correlated with hypoalbuminemia	- No correlation with serum globulin, creatinine, BUN or fecal α1-PI	Allenspach et al., 2008
		16 dogs with IBD and 13 healthy dogs	- Serum pANCA was positive in 19% of dogs with IBD	- No correlation with CIBDAI or histologic severity - Not specific to CEs	Otoni et al., 2018
NMH	Feces	16 dogs with chronic GI diseases and 49 healthy dogs	- Significantly higher 3-day maximum fecal NMH concentrations in all dogs with chronic GI diseases - Correlated with histopathological severity	- No correlation with CCECAI or mucosal mast cells numbers	Berghoff et al., 2014
	Urine		- 25% of dogs with chronic GI diseases had increased urinary NMH concentrations - Correlated with histological grading and serum CRP concentrations	- No correlation with CCECAI or mucosal mast cells numbers - Not specific to chronic GI diseases	
	Feces	28 dogs with CEs and 55 healthy dogs	- 14% of dogs with CEs had increased urinary NMH concentrations	- No correlation with CCECAI, histopathological score or mast cells numbers - Not specific to CEs	Anfinsen et al., 2014
	Urine		- 21% of dogs with CEs had increased urinary NMH concentrations	- No correlation with CCECAI, histopathological score or mast cells numbers - Not specific to CEs	

Table 2 Summary of research findings on selected biochemical biomarkers in dogs with chronic enteropathies (Cont.)

Biomarker	Sample	Study Groups	Main Findings or Significant correlations	Insignificant correlations or Limitations of biomarker	Ref.
Calprotectin-	Feces	27 dogs with chronic diarrhea and 69 healthy dogs	- Significantly higher concentrations in dogs with chronic diarrhea - Correlated with the severity of histologic intestinal lesion and CCECAI	-	Grellet et al., 2013
	Feces	127 dogs with CEs	- Dogs with IRE had higher fecal calprotectin concentrations than NRE dogs - Correlated with CCECAI and histologic inflammatory lesions	- No correlation with serum CRP concentrations	Heilmann et al., 2018b
	Feces	16 dogs with idiopathic IBD and 13 healthy dogs	- Significantly higher concentration in dogs with IBD - Correlated with CIBDAI scores before treatment and histological severity	- No correlation with CIBDAI scores after treatment	Otoni et al., 2018
	Serum		- No significant difference in serum calprotectin-levels between IBD and healthy dogs	- No correlation with CIBDAI scores or histological severity - Not specific to IBD	
Calgranulin C	Feces	26 dogs with IBD and 90 healthy dogs	- Significantly higher concentration in dogs with IBD - Correlated with the clinical disease activity, the severity of endoscopic lesions and colonic inflammation	- No correlation with the severity of histopathologic changes	Heilmann et al., 2014
	Feces	64 dogs with CEs	- Dogs with IBD had higher fecal calgranulin C concentrations than dogs with FRE or ARE - Fecal calgranulin C levels ≥ 490 ng/g can distinguish dogs with IRE or NRE from FRE or ARE	-	Heilmann et al., 2016

Abbreviations: CEs= Chronic enteropathies; CRP= C-reactive protein; ARE=Antibiotic-responsive enteropathy; FRE=Food-responsive enteropathy; IRE= Immunosuppressant-responsive enteropathy; NRE= Non-responsive enteropathy; IBD = Inflammatory bowel diarrhea; CIBDAI = canine inflammatory bowel disease activity index; pANCA= Perinuclear anti-neutrophilic cytoplasmic antibodies; PLE= Protein losing enteropathy; PLN= Protein losing nephropathy; α1-PI= Alpha 1-proteinase inhibitor; NMH= N-methylhistamine; GI= Gastrointestinal; CCECAI = canine chronic enteropathy clinical activity index

PERINUCLEAR ANTI-NEUTROPHILIC CYTOPLASMIC ANTIBODIES

Perinuclear anti-neutrophilic cytoplasmic antibodies (pANCA) are a type of autoantibody that targets a specific pattern of antigens within the cytoplasm of neutrophils. These antibodies are associated with inflammation and autoimmune diseases (Wdowiak et al., 2013; Heilmann and Steiner, 2018). Additionally, they exhibit cross-reactivity with pathogen-associated molecular patterns (PAMPs) of gastrointestinal bacteria, which can be identified though indirect immunofluorescence assays by visualization a typical perinuclear staining pattern (Falk et al., 1990).

The measurement of pANCA using assays has been evaluated in dogs, revealing a wide range of sensitivities varying from 23% to 51%, along with a specificity of 83% to 95% in diagnosing dogs with IBD (Allenspach et al., 2004; Luckschander et al., 2006; Mancho et al., 2010). However, researchers were unable to establish a correlation between the positive results of pANCA antibodies and the severity of clinical symptoms or the histopathological scores (Otoni et al., 2018). Previous studies have shown that seropositivity for pANCA is greater in dogs with FRE, ranging from 61% to 62% compared to those with IRE or NRE, ranging from 0% to 37% (Luckschander et al., 2006; Mancho et al., 2010). These findings highlight the clinical utility of pANCA in distinguishing between subtypes of CEs, particularly FRE and IRE. Allenspach et al. (2008) investigated the application of the pANCA assay for early identification of PLE and PLN in Soft-Coated Wheaten Terriers. The result of pANCA seropositivity was observed up to 2 years prior to the manifestation of clinical symptoms, as evidenced by a decrease in serum albumin levels. As a result, this marker seems to be valuable for the early detection of PLE diseases and for diagnosing dogs with FRE. Nevertheless, the positive results of pANCA antibodies are not exclusive to CEs and have also been found in infectious diseases or other autoimmune diseases (Allenspach and Mochel, 2022). Therefore, the pANCA assay has been suggested as a supplementary diagnostic marker to differentiate dogs with CEs from other chronic gastrointestinal diseases (Mancho et al., 2010).

N-METHYLHISTAMINE

N-methylhistamine (NMH) is a consistent metabolite of histamine that has been proposed as an indicator of mast cell activation and degranulation associated with inflammation. It is produced via the enzymatic activity of histamine N-methyltransferase and can be detected in samples of serum, urine and feces (Anfinsen et al., 2014; Berghoff et al., 2014).

In dog with CEs, mast cells contribute to the inflammatory response of the intestinal mucosa by releasing various inflammatory mediators, including histamine (Wdowiak et al., 2013). According to the study conducted by Anfinsen et al. (2014), dogs that positively responded to dietary trials had a greater number of intestinal mast cells than dogs requiring immunosuppressive treatment. This finding suggests that mast cell activation may potentially play a role in the development of FRE. Fecal NMH concentrations have

been demonstrated to be elevated in Norwegian Lundehunds and Soft Coated Wheaten Terriers with CEs (Vaden et al., 2000; Berghoff et al., 2008). Berghoff et al. (2014) also found that elevated levels of NMH in the urine were present in 40% of dogs with CEs and were significantly correlated with the severity of histological lesions. However, there was no association between the NMH levels and the quantity of mast cells in the mucosal of duodenum or the diseases severity (Anfinsen et al., 2014; Berghoff et al., 2014). Additional studies are required to ascertain the sensitivity, specificity and feasibility of using NMH levels as a diagnostic tool for dogs with CEs.

CALPROTECTIN

Calprotectin, the S100A8/A9 protein complex, is recognized as the damage-associated molecular pattern (DAMP) molecules, which tend to gather in inflammatory areas (Heilmann and Steiner, 2018). It is primarily generated through macrophage and neutrophil activation, although it can also be synthesized within epithelial cells. Additionally, it acts as a ligand for Toll-like receptor (TLR-4), contributing to the inflammatory process and it exhibits upregulation in canine CEs (Heilmann et al., 2012; Heilmann et al., 2019).

Calprotectin is detectable in various biological samples, including serum and feces. However, the serum calprotectin lacks specificity for the gastrointestinal tract (Heilmann and Steiner, 2018). In 2018, Otoni et al. demonstrated that there were no significant differences in serum calprotectin levels between dogs with IBD and healthy dogs, or between dogs before and after treatment. Furthermore, they found no association between serum calprotectin levels, CIBDAI scores and histopathologic severity (Heilmann et al., 2012; Otoni et al., 2018). According to fecal calprotectin, it has been identified as a useful marker of inflammation in the canine gastrointestinal tract (Grellet et al., 2013; Heilmann et al., 2018b). Previous studies have shown that elevated concentrations of fecal calprotectin are correlated with the presence of canine CEs and exhibit a positive association with the severity of clinical symptoms and histopathologic findings (Grellet et al., 2013; Heilmann et al., 2018b; Otoni et al., 2018). Moreover, fecal calprotectin concentration seems to have the potential to predict the therapeutic response and distinguish dogs with IRE from NRE with a sensitivity of 80% and a specificity of 75% (Heilmann et al., 2018b; Heilmann and Steiner, 2018). Due to its ability to monitor disease progression and differentiate between periods of disease activity and remission, this fecal biomarker is highly regarded for its value in noninvasively evaluating intestinal inflammation (Otoni et al., 2018b; Sacoor et al., 2020).

CALGRANULIN C

Calgranulin C, also known as S100A12, is a DAMP molecule belonging to the S100 family of calcium-binding proteins and it exhibits a cellular distribution similar to calprotectin (Heilmann et al., 2019). It is primarily produced and released through the activation of neutrophils, macrophages, and monocytes (Wdowiak et al., 2013; Hanifeh et al., 2018). It interacts with various target proteins, including the receptor for advanced glycation end-

products (RAGE), and provides a significant function in inflammatory immune responses (Heilmann et al., 2016b; Heilmann and Steiner, 2018).

Calgranulin C serves as a sensitive and specific marker for localized inflammatory conditions, including gastrointestinal inflammation. Serum calgranulin C has the potential to be superior to calprotectin since its concentrations remain unaffected by corticosteroid treatment (Heilmann and Steiner, 2018; Heilmann et al., 2016b). However, it can be evaluated in serum due to other inflammatory conditions (Heilmann et al., 2011; Craig et al., 2016). Therefore, evaluating the concentration of calgranulin C in feces is more specific than in serum for identifying gastrointestinal inflammatory processes (Sacoor et al., 2020).

Increased fecal calgranulin C concentrations have been identified in dogs with CEs and are associated with a negative outcome. Furthermore, researchers have reported a significant association between calgranulin C levels, the severity of clinical symptoms and the presence of abnormalities observed during endoscopy (Heilmann et al., 2014; Heilmann et al., 2018a). Additionally, fecal calgranulin C levels over 490 ng/g demonstrate the ability to distinguish dogs with IRE or NRE from FRE or ARE with a sensitivity of 64% and a specificity of 77% (Heilmann et al., 2016; Heilmann and Steiner, 2018). These findings emphasize the usefulness of this biological marker in predicting treatment response and disease outcome in dogs with CEs (Sacoor et al., 2020; Jergens and Heilmann, 2022). Therefore, fecal calprotectin C has been considered as a promising biomarker for monitoring gastrointestinal inflammation. However, further studies are needed to investigate the effect of other chronic gastrointestinal diseases, such as neoplasia, on fecal calprotectin C concentrations (Heilmann and Steiner, 2018).

MICROBIOMIC BIOMARKERS

The gastrointestinal microbiota refers to the diverse community of microorganisms, including bacteria, viruses, fungi and archaea. This intricate ecosystem plays a vital part in maintaining gastrointestinal health, primarily in digestion, absorption, energy metabolism and immune system development (Pilla and Suchodolski, 2020). An imbalance of microbes population, define as dysbiosis, is associated with gastrointestinal inflammation and dysfunction (Jergens and Heilmann, 2022). Previous studies have revealed a reduction of species diversity and variations in the abundance of microbial constituents in fecal samples from dogs with CEs. These alterations are defined by a decrease in *Bacteroidetes*, *Fusobacterium* spp., and *Firmicutes*, and an increase in *Proteobacteria* (Suchodolski et al., 2012a; Suchodolski et al., 2012b; Honneffer et al., 2014). Additionally, the fluorescence in situ hybridization (FISH) studies conducted on the colonic mucosal of dogs with CEs demonstrated an increased abundance of mucosal *Escherichia coli* in affected dogs. Conversely, *Helicobacter* spp. and *Akkermansia* spp. were diminished in the colonic crypts and the mucosal surface, indicating that these bacteria play a valuable role as resident species in the colon. They contribute to preventing the colonization by pathogenic bacteria or modulating inflammation in the canine colon (Giaretta et al., 2020). A summary of research findings on selected microbiomic biomarkers in dogs with CEs is presented in Table 3.

Table 3 Summary of research findings on selected microbiomic biomarkers in dogs with chronic enteropathies

Sample	Methods	Study Groups	Main findings	Ref.
Small intestinal mucosa	454- Pyrosequencing (16S rRNA Gene)	14 dogs with IBD and 6 healthy dogs	- Increase number of *Proteobacteria*, including *Acinetobacter* and *Diaphorobacter* - Decrease number of *Fusobacteria, Prevotellaceae, Bacteroidaceae* and *Clostridiales*	Suchodolski et al., 2012a
Feces	454- Pyrosequencing (16S rRNA Gene) qPCR (16S rRNA Gene)	19 dogs with IBD 13 dogs with AHD 12 dogs with NHD 32 healthy dogs	- IBD group: Decrease number of *Faecalibacterium* spp. - AHD group: Decrease number of *Blautia*, *Turicibacter* and *Ruminococcaceae* Increase number of *Clostridium Perfringens*	Suchodolski et al., 2012b
Colonic mucosa	Fluorescence in situ hybridization	22 dogs with CEs and 11 healthy dogs	- Decrease number of *Helicobacter* spp. and *Akkermansia* spp. - Increase number of *Escherichia coli*/*Shigella* spp.	Giaretta et al., 2020
Feces	Quantitative PCR (qPCR) assay	106 dogs with CEs and 95 healthy dogs	- Decrease number of *Faecalibacterium, Turicibacter, Blautia, Fusobacterium, C. hiranonis* and Total bacteria - Increase number of *E. coli* and *Streptococcus* - Significant correlation between DI and CCEAI	AlShawaqfeh et al., 2017

Abbreviations: CEs= Chronic enteropathies; IBD = Inflammatory bowel diarrhea; ADH = Acute hemorrhagic diarrhea; NHD= Non-hemorrhagic diarrhea; DI= Dysbiosis index; CCECAI = canine chronic enteropathy clinical activity index

The evaluation of the gut microbiome is most effectively conducted through molecular techniques, such as sequencing methods detecting 16S ribosomal RNA genes and metagenomic sequencing. However, these techniques are time-consuming and expensive (Costa and Weese, 2019). To achieve faster results at a lower cost, an alternative approach called the fecal dysbiosis index (DI) has been developed, which utilizes a qPCR assay-based algorithm. The DI evaluates eight bacterial groups that are typically changed in dogs with CEs, which include *Escherichia coli*, *Fecalibacterium* spp., *Turicibacter* spp., *Streptococcus* spp., *Blautia* spp., *Fusobacterium* spp., *Clostridium hiranonis* and the total bacteria (AlShawaqfeh et al., 2017). This index can differentiate between normal and dysbiotic microbiota, assess the effects of treatment, and evaluate the response to therapeutic interventions (Guard et al., 2019; Minamoto et al., 2019). However, additional studies are required to investigate the clinical usefulness of DI as markers for canine CEs.

METABOLOMIC BIOMARKERS

Metabolomic profiling refers to the comprehensive analysis of small molecules, known as metabolites, which are found in biological systems. These metabolites include various compounds such as amino acids, organic acids and lipids (Walker et al., 2022). The gut microbiota exerts a profound impact on the host's metabolome by metabolizing dietary compounds into bioactive metabolites. These metabolites can directly affect to host's metabolism and physiological processes (Minamoto et al., 2015). Changes in microbial function and composition resulting in alterations of the metabolic profile have been reported in canine CEs (Pilla and Suchodolski, 2020; Jergens and Heilmann, 2022). Minamoto et al. (2014) reported low fecal microbiome diversity and significantly increase serum metabolites including gluconolactone, hexuronic acid, 3-hydroxybutanoic acid, and ribose in dog with IBD indicating a potential association with oxidative stress. Furthermore, although the affected dogs showed clinical improvement after treatment, there were no significant changes observed in the microbiota and metabolite profiles. These findings indicate the presence of oxidative stress and functional disruption of the microbiome, even when the dogs with IBD exhibit a clinical response to medical treatment.

A group of metabolites known as short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate, holds significant importance for overall health of the host. These SCFAs are produced from bacterial fermentation of complex carbohydrates and play a vital role in modulating immune responses within the gastrointestinal tract and providing essential energy for colonocytes (Arpaia et al., 2013). The presence of SCFAs-producing bacteria is reduced in dogs with acute and chronic diarrhea (Suchodolski et al., 2012b; Minamoto et al., 2019). Guard et al. (2015) revealed a significant decrease in propionate levels, while butyrate levels were increased in the feces of dogs with acute diarrhea. These results were attributed to a reduction in butyrate absorption or decrease in the utilization of this SCFA by the enterocytes. Similar to the study by Higueras et al. (2022), which reported a reduction in fecal levels of SCFAs particularly propionate, in dogs with FRD, this decrease might contribute to the inflammatory status observed in this disorder. Propionate has been implicated in the pathogenesis of chronic intestinal inflammation.

Amino acid profiling has been studied in dogs with CEs. Investigation of changes in the amino acid profile of dogs with CEs has emphasized tryptophan and serine as promising markers for IBD (Kathrani et al., 2018; Tamura et al., 2019). Tryptophan acts as a precursor for the synthesis of indole compounds by the gastrointestinal microbiota, which supports mucosal homeostasis by enhancing gut permeability and promoting mucin production (Whitfield-Cargile et al., 2016; Kathrani et al., 2018). In dogs with PLE, there is a reduction in serum tryptophan levels, while dogs suffering from idiopathic IBD exhibit a decrease in indole compounds (Kathrani et al., 2018). According to serine, it is involved in various biological processes, including cell growth, immune function and the promotion of mucin production. This helps to maintain the integrity of the intestinal barrier and supports nutrient absorption (Maeda et al., 2014). Tamura et al. (2019) found that dogs with IBD have significantly lower plasma concentrations of four amino acids: serine, tryptophan, proline and methionine, compared to healthy dogs. Interestingly, only the plasma concentration of serine showed a negative correlation with CCECAI scores. Therefore, the plasma concentration of serine may serve as a potential biomarker in dogs with IBD.

Another promising marker for CEs analysis is bile acids, due to their crucial function in regulating host metabolism and their association with the gut microbiota (Giaretta et al., 2018; Guard et al., 2019). Bacteria in the intestinal lumen affect bile acid metabolism by modifying primary bile acids through deconjugation and dehydroxylation processes, resulting in the production of secondary bile acids such as lithocholic acid, deoxycholic acid, and ursodeoxycholic acid (Ridlon et al., 2006). These bile acids are important in maintaining immune regulation and homeostasis within the gastrointestinal tract (Blake et al., 2019). The decrease in secondary bile acids has been reported in dogs with CEs (AlShawaqfeh et al., 2017; Blake et al., 2019). In dogs with dysbiosis, the reduction of Clostridium hiranonis, a bacteria involved in bile acid dehydroxylation, results in increased levels of primary bile acids in the colon. These elevated concentrations are pro-inflammatory and contribute to the secretory diarrhea (Whitfield-Cargile et al., 2016; Giaretta et al., 2018). Toresson et al. (2021) demonstrated the effective treatment of presumptive bile acid diarrhea in dogs with CEs using cholestyramine, a bile acid sequestrant that prevents the reabsorption and accumulation of bile acids in the gastrointestinal tract. As a result, it could be considered as an alternative treatment option for dogs with persistent diarrhea that are unresponsive to conventional therapies. A summary of research findings on selected metabolomic biomarkers in dogs with CEs is demonstrated in Table 4.

In conclusion, metabolomic profiling is an interesting marker investigated in veterinary research. It offers non-invasive strategies to comprehend disease pathophysiology and host-microbe interactions, holding the potential for the development of innovative diagnostic and therapeutic methods. However, additional studies are required to determine the sensitivity, specificity and clinical utility of each metabolomic marker in dogs with CEs.

Table 4 Summary of research findings on selected metabolomic biomarkers in dogs with chronic enteropathies

Metabolite	Samples	Methods	Study Groups	Main findings	Ref.
Short-chain fatty acids (SCFAs)	Feces	GC-MS assay	13 dogs with acute diarrhea and 13 healthy dogs	- Significant decrease in fecal propionic acid concentrations - Significant increase in fecal butyric acid concentrations - Propionic acid concentrations were significantly correlated to a decrease in *Faecalibacterium*	Guard et al., 2015
		Direct-injection Gas chromatography	9 dogs with FRE and 6 healthy dogs	- Significant decrease in fecal propionic acid and isovaleric acid concentrations - Significant correlations between fecal odd-chain, medium or long-chain fatty acids and SCFAs - CIBDAI correlated negatively with C3, iC5 and C15:0	Higueras et al., 2022
Amino acids	Serum	Liquid chromatography amino acid analyzer	30 dogs with PLE and 12 healthy dogs	- Significant decrease in serum tryptophan concentrations - Significant correlations between serum tryptophan and albumin concentrations	Kathrani et al., 2018
		Chromatography Ninhydrin method	10 dogs with IBD and 12 healthy dogs	- Significant decrease in serum serine and tryptophan concentrations - Serine concentrations correlated negatively with CCECAI scores	Tamura et al., 2019
Bile acid	Feces	GC-MS assay	15 dogs with CEs, 36 dogs with EPI and 34 healthy dogs	- Significant decrease in secondary bile acid concentrations in dogs with CEs and EPI	Blake et al., 2019
		GC-MS assay	24 dogs with CEs, and 11 healthy dogs	- Significant increase in primary bile acid concentrations - Positive correlation between primary bile acid concentrations and fecal dysbiosis index	Giaretta et al., 2018

Abbreviations: CEs= Chronic enteropathies; GC-MS= Gas chromatography-mass spectrometry assay; FRE=Food-responsive enteropathy; CIBDAI = canine inflammatory bowel disease activity index; C3 = propionic acid; iC5 = isovaleric acid; C15:0 = Pentadecanoic acid; CCECAI = canine chronic enteropathy clinical activity index; EPI= Exocrine pancreatic insufficiency; PLE= Protein losing enteropathy

GENOMIC BIOMARKERS

Genomic biomarkers refer to specific genetic characteristics that can indicate the presence of a particular disease. These markers include single nucleotide polymorphisms (SNPs) in toll-like receptor-4 (TLR-4), toll-like receptor-5 (TLR-5), nucleotide oligomerization domain-2 (NOD-2) and the neutrophil cytosolic factor (NCF2) gene, as well as alterations in the expression of several other genes (Burgener et al., 2008; Olivero et al., 2011; Kathrani et al., 2014). They are identified though genome-wide association studies (GWAS), which involve analyzing genetic data from individuals to identify associations between specific genetic markers and diseases (Jostins et al., 2012). Additionally, targeted next-generation sequencing (NGS), which focuses on specific regions of interest in the genome, is used to identify potential functional SNPs that could explain the GWAS association signal (Peiravan et al., 2021).

In dogs with CEs, researchers have recognized that these conditions appear to be influenced by genetic factors. Certain breeds, such as German Shepherd Dogs (GSDs), Weimaraners, Rottweilers, Border Collies and Boxers, may have a higher likelihood of developing breed-specific enteropathies (Kathrani et al., 2011a). Genetic studies in canine IBD have reveled breed-specific SNPs in TLR-4, TLR-5 and NOD-2 that were identified in GSDs (Kathrani et al., 2010; Kathrani et al., 2011b). Peiravan et al. (2018) identified an additional 16 genes associated with CEs in GSDs. Several of these genes were found to be linked with classical T-helper 2 (Th-2) type cytokine responses, specifically IL-4, IL-5 and IL-13, suggesting the potential involvement of immune-mediated pathways in the progression of CEs. This finding holds significant implications for the exploration of novel therapeutic options in GSDs with CEs, particularly those cases that are difficult to manage using conventional treatments.

Until now, genomic biomarkers have been used as research tools to investigate the risk of individuals developing a disease, but their utility may be limited when dogs already exhibit clinical symptoms. However, as genetic risk factors consistently linked with specific therapeutic responses, these testes will have increased clinical applicability (Heilmann and Steiner, 2018; Allenspach and Mochel, 2021).

SUMMARY

Canine chronic enteropathy biomarkers have been evaluated and potentially offer clinical benefits in the diagnosis, treatment and management of dogs with this condition. In veterinary practice, the widely used biomarkers such as serum cobalamin, folate and fecal α1-PI, together with fecal calprotectin and calgranulin C, provide some advantages in screening diagnosis, distinguishing the different subtypes of CEs and monitoring disease progression. However, these biomarkers are insufficient to accurately predict treatment response and reflect the individual risk of inducing CEs (Heilmann and Steiner, 2018; Otoni et al., 2018). Therefore, the novel and promising markers, including microbiomic, metabolomic and genomic biomarkers, have emerged and

provide valuable information about disease pathophysiology, microbiome-host-interaction, metabolic pathway, as well as the risk of an individual dog developing CEs (Toresson et al., 2021; Allenspach and Mochel, 2022). These potential biomarkers are expected to increase accuracy of diagnosis and improve the individualized therapeutic strategies. While these markers show promise, further research and validation are necessary to fully establish their clinical utility in dogs with CEs.

At the current time, using a single biomarker alone cannot definitively diagnose the disease or accurately predict its progression, treatment response and clinical outcome. Therefore, combining these tools with existing contemporary approaches would be advantageous to enhance accuracy. Furthermore, additional prospective and long-term studies are necessary to assess the effectiveness of conventional biomarker assays in dogs with CEs within the context of routine clinical practice.

ACKNOWLEDGEMENTS

The author would like to express gratitude to the Faculty of Veterinary Medicine, Chiang Mai University for their valuable contribution in providing literature review data throughout this work.

AUTHOR CONTRIBUTIONS

Pinkarn Chantawong: Conceptualization, Writing-Review and Editing.

CONFLICT OF INTEREST

The author declares no conflict of interest.

REFERENCES

Abraham, C., Cho, J.H., 2009. Mechanisms of disease Inflammatory Bowel Disease. N. Engl. J. Med. 361(21), 2066–2078.

Alghoul, Z., Yang, C., Merlin, D., 2022. The current status of molecular biomarkers for inflammatory bowel disease. Biomedicines. 10(7), 1492.

Allenspach, K., Luckschander, N., Styner, M., Seibold, F., Doherr, M., Aeschbach, D., Gaschen, F., 2004. Evaluation of assays for perinuclear antineutrophilic cytoplasmic antibodies and antibodies to Saccharomyces cerevisiae in dogs with inflammatory bowel disease. Am. J. Vet. Res. 65(9), 1279–83.

Allenspach, K., Wieland, B., Grone, A., Gaschen, F., 2007. Chronic enteropathies in dogs: evaluation of risk factors for negative outcome. J. Vet. Intern. Med. 21, 700–708.

Allenspach, K., Lomas, B., Wieland, B., Harris, T., Pressler, B., Mancho, C., Lees, G.E., Vander, S.L., 2008. Evaluation of perinuclear anti-neutrophilic cytoplasmic autoantibodies as an early marker of protein-losing enteropathy and protein-losing nephropathy in Soft Coated Wheaten Terriers. Am. J. Vet. Res. 69, 1301-1304.

Allenspach, K., 2011. Clinical immunology and immunopathology of the canine and feline i ntestine. Vet. Clin. Small. Anim. 41(2), 345–360.

Allenspach, K., 2015. Diagnosis of small intestinal disorders in dogs and cats. Clin. Lab. Med. 35(3), 521–534.

Allenspach, K., Culverwell, C., Chan, D., 2016. Long-term outcome in dogs with chronic enteropathies: 203 cases. Vet. Rec. 178(15), 362– 368.

Allenspach, K., Mochel, J.P., 2022. Current diagnostics for chronic enteropathies in dogs. Vet. Clin. Path. 50, 18-28.
AlShawaqfeh, M., Wajid, B., Minamoto, Y., Markel, M., Lidbury, J., Steiner, J., Serpedin, E., Suchodolski, J.S., 2017. A dysbiosis index to assess microbial changes in fecal samples of dogs with chronic inflammatory enteropathy. FEMS Microbiol. Ecol. 93(11), 1–8.
Anfinsen, K.P., Berghoff, N., Priestnall, S.L., Suchodolski, J.S., Steiner, J.M., Allenspach, K., 2014. Urinary and faecal N-methylhistamine concentrations do not serve as markers for mast cell activation or clinical disease activity in dogs with chronic enteropathies. Acta. Vet. Scand. 56(1), 90.
Arpaia, N., Campbell, C., Fan, X., Dikiy, S., Veeken, J., deRoos, P., Liu, H., Cross, J.R., Pfeffer, K., Coffer, P.J., Rudensky, A.Y., 2013. Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. Nature. 504, 451–5.
Becher, A., Suchodolski, J.S., Steiner, J.M., Heilmann, R.M., 2021. Blood neutrophil-to-lymphocyte ratio (NLR) as a diagnostic marker in dogs with chronic enteropathy. J. Vet. Diagn. Invest. 33(3), 516-527.
Berghoff, N., Suchodolski, J.S., Steiner, J.M., 2008. Fecal N-methylhistamine concentrations in Norwegian Lundehunds with gastrointestinal disease. J. Vet. Intern. Med. 22, 748.
Berghoff, N., Steiner, J.M., 2011. Laboratory tests for the diagnosis and management of chronic canine and feline enteropathies. Vet. Clin. Small. Anim. Pract. 41(2), 311-328.
Berghoff, N., Suchodolski, J.S., Steiner, J.M., 2012. Association between serum cobalamin and methylmalonic acid concentrations in dogs. Vet. J. 191, 306–311.
Berghoff, N., Parnell, N.K., Hill, S.L, Suchodolski, J.S., Steiner, J.M., 2013. Serum cobalamin and methylmalonic acid concentrations in dogs with chronic gastrointestinal disease. Am. J. Vet. Res. 74, 84-89.
Berghoff, N., Hill, S., Parnell, N.K., Mansell, J., Suchodolski, J.S., Steiner, J.M., 2014. Fecal and urinary N-methylhistamine concentrations in dogs with chronic gastrointestinal disease. Vet. J. 201(3), 289–294.
Blake, A.B., Guard, B.C., Honneffer, J.B., Lidbury, J.A., Steiner, J.M., Suchodolski, J.S., 2019. Altered microbiota, fecal lactate, and fecal bile acids in dogs with gastrointestinal disease. PLoS One. 14(10), e0224454.
Burgener, I.A., Konig, A., Allenspach, K., Sauter, S.N., Boisclair, J., Doherr, M.G., Jungi, T.W., 2008. Upregulation of toll-like receptors in chronic enteropathies in dogs. J. Vet. Intern. Med. 22(3), 553-560.
Carney, P.C., Ruaux, C.G., Suchodolski, J.S, Steiner, J.M., 2011. Biological variability of C-reactive protein and specific pancreatic lipase immunoreactivity (Spec cPL) in apparently healthy dogs. J. Vet. Intern. Med. 25, 825–30.
Cerquetella, M., Spaterna, A., Laus, F., Tesei, B., Rossi, G., Antonelli, E., Villanacci, V., Bassotti, G., 2010. Inflammatory bowel disease in the dog: Differences and similarities with humans. World J. Gastroenterol. 16(9), 1050–1056.
Choy, M.C., Visvanathan, K., De Cruz, P., 2017. An Overview of the innate and adaptive immune system in inflammatory bowel disease. Inflamm. Bowel Dis. 23, 2–13.
Collins, M.T., 2013. Canine inflammatory bowel disease: current and prospective biomarkers for diagnosis and management. Vet. Learn. 38(3), 1–7.
Costa, M., Weese, J.S., 2019. Methods and basic concepts for microbiota assessment. Vet. J. 249, 10–15.
Craig, S.M., Fry, J.K., Hoffmann, A.R., Manino, P., Heilmann, R.M., Suchodolski, J.S., Steiner, J.M., Hottinger, H.A., Hunter, S.L., Lidbury, J.A., 2016. Serum C-reactive protein and S100A12 concentrations in dogs with hepatic disease. J. Small. Anim. Pract. 57, 459-464.
Dandrieux, J.R.S., 2016. Inflammatory bowel disease versus chronic enteropathy in dogs: are they one and the same?. J. Small. Anim. Pract. 57(11), 589-599.
Dandrieux, J.R.S., Mansfield, C.S., 2019. Chronic enteropathy in canines: prevalence, impact and management strategies. Vet. Med. Res. Rep. 10, 203-214.
Duvoisin, G., Lopez, R.N., Day, A.S., Lemberg, D.A., Gearry, R.B., Leach, S.T., 2017. Novel biomarkers and the future potential of biomarkers in inflammatory bowel disease. Mediators Inflamm. 2017, 1936315.
Eissa, N., Kittana, H., Gomes-Neto, J.C., Hussein, H., 2019. Mucosal immunity and gut microbiota in dogs with chronic enteropathy. Res. Vet. Sci. 122, 156–164.

Falk, R.J., Hogan, S.L., Wilkman AS, Terrell, R.S., Lauritzen, S., Charles, L.A., Jennette, J.C., 1990. Myeloperoxidase specific anti-neutrophil cytoplasmic autoantibodies (MPO-ANCA). Neth. J. Med. 36, 121-125.

Gerou-Ferriani, M., Allen, R., Noble, P.J.M., German, A.J., Caldin, M., Batchelor, D.J., 2018. Determining optimal therapy of dogs with chronic enteropathy by measurement of serum citrulline. J. Vet. Intern. Med. 32(3), 993–998.

German, A.J., Day, M.J., Ruaux, C.G., Steiner, J.M., Williams, D.A., Hall, E.J., 2003. Comparison of direct and indirect tests for small intestinal bacterial overgrowth and antibiotic responsive diarrhea in dogs. J. Vet. Intern. Med. 17(1), 33–43.

Giaretta, P.R., Rech, R.R., Guard, B.C., Blake, A.B., Blick, A.K., Steiner, J.M., Lidbury, A., Cook, A.K., Hanifeh, M., Spillmann, T., Kilpinen, S., Syrja, P., Suchodolski, J.S., 2018. Comparison of intestinal expression of the apical sodium-dependent bile acid transporter between dogs with and without chronic inflammatory enteropathy. J. Vet. Intern. Med. 32(6), 1918-1926.

Giaretta, P.R., Suchodolski, J.S., Jergens, A.E., Steiner, J.M., Lidbury, J.A., Cook, A.K., Hanifeh, M., Spillmann, T., Kilpinen, S., Syrja, P., Rech, R., 2020. Bacterial biogeography of the colon in dogs with chronic inflammatory enteropathy. Vet. Pathol. 7, 258–65.

Grellet, A., Heilmann, R.M., Lecoindre, P., Feugier, A., Day, M.J., Peeters, D., Freiche, V., Hernandez, J., Grandjean, D., Suchodolski, J.S., Steiner, J.M., 2013. Fecal calprotectin concentrations in adult dogs with chronic diarrhea. Am. J. Vet. Res. 74, 706-711.

Grutzner, N., Heilmann, R.M., Stupka, K.C., Rangachari, V.R., Weber, K., Holzenburg, A., Suchodolski, J.S., Steiner, J.M., 2013a. Serum homocysteine and methylmalonic acid concentrations in Chinese Shar-Pei dogs with cobalamin deficiency. Vet. J. 197, 420-426.

Grutzner, N., Heilmann, R.M., Bridges, C.S. Suchodolski, J.S, Steiner, J.M., 2013b. Serum concentrations of canine alpha1-proteinase inhibitor in cobalamin-deficient Yorkshire Terrier dogs. J. Vet. Diagn. Invest. 25, 376-385.

Grutzner, N., Heilmann, R.M., Hokamp, J.A., Lidbury, J.A., Nabity, M.B., Suchodolski, J.S., Steiner, J.M., 2014. Serum alpha1-proteinase inhibitor concentrations in dogs with gastrointestinal diseases, chronic liver disease, and chronic kidney disease. J. Vet. Inter. Med. 28, 1048.

Guard, B.C., Barr, J.W., Reddivari, L., Klemashevich, C., Jayaraman, A., Steiner, J.M., Vanamala, J., Suchodolski, J.S., 2015. Characterization of microbial dysbiosis and metabolomic changes in dogs with acute diarrhea. PLoS ONE. 10(5), e0127259.

Guard, B.C., Honneffer, J.B., Jergens, A.E., Jonika, M.M., Toresson, L., Lawrence, Y.A., Webb, C.B., Hill, S., Lidbury, J.A., Steiner, J.M., Suchodolski, J.S., 2019. Longitudinal assessment of microbial dysbiosis, fecal unconjugated bile acid concentrations, and disease activity in dogs with steroidresponsive chronic inflammatory enteropathy. J. Vet. Intern. Med. 33, 1295– 305.

Hanifeh, M., Sankari, S., Rajamäki, M.M., Syrja, P., Kilpinen, S., Suchodolski, J.S., Heilmann, R.M., Guadiano, P., Lidbury, J., Steiner, J.M. and Spillmann, T., 2018. S100A12 concentrations and myeloperoxidase activities are increased in the intestinal mucosa of dogs with chronic enteropathies. BMC. Vet. Res. 14(1), 1–13.

Heilmann, R.M., Allenspach, K., Procoli, F., Weber, K., Suchodolski, J.S., Steiner, J.M., 2011. Serum calgranulin concentrations in dogs with inflammatory bowel disease. J. Vet. Intern. Med. 25, 1486.

Heilmann, R.M., Jergens, A., Ackermann, M.R., Barr, J.W., Suchodolski, S., Steiner, J.M., 2012. Serum calprotectin concentrations in dogs with idiopathic inflammatory bowel disease. Am. J. Vet. Res. 73(12), 1900–1907.

Heilmann, R.M., Grellet, A., Allenspach, K., Lecoindre, P., Day, M.J., Priestnal, S.L., Toresson, L., Procoli, F., Grutzner, N., Suchodolski, J.S., Steiner, J.M., 2014. Association between fecal S100A12 concentration and histologic, endoscopic, and clinical disease severity in dogs with idiopathic inflammatory bowel disease. Vet. Immunol. Immunopathol. 158, 156–166.

Heilmann, R.M., Suchodolski, J.S., 2015. Is inflammatory bowel disease in dogs and cats associated with a Th1 or Th2 polarization? Vet. Immunol. Immunopathol. 168, 131–134.

Heilmann, R.M., Parnell, N.K., Grützner, N., Mansell, J., Berghoff, N., Schellenberg, S., Reusch, C., Suchodolski, J.S., Steiner, J.M., 2016a. Serum and fecal canine alpha1-proteinase inhibitor concentrations reflect the severity of intestinal crypt abscesses and/or lacteal dilation in dogs. Vet. J. 207, 131-139.

Heilmann, R.M., Cranford, S.M., Ambrus, A., Grutzner, N., Schellenberg, S., Ruaux, C.G., Suchodolski, J.S., Steiner, J.M., 2016b. Methodological and preanalytical validation of an enzyme-linked immunosorbent assay for the measurement of canine S100A12. Vet. Clin. Pathol. 45, 135-147.

Heilmann, R.M., Allenspach, K., 2017. Pattern-recognition receptors: signaling pathways and dysregulation in canine chronic enteropathies— brief review. J. Vet. Diagn. Invest. 29(6), 781–787.

Heilmann, R.M., Steiner, J.M., 2018a. Clinical utility of currently available biomarkers in inflammatory enteropathies of dogs. J. Vet. Intern. Med. 32(5), 1495–1508.

Heilmann, R.M., Berghoff, N., Mansell, J., Grutzner, N., Parnell, N.K., Gurtner, C., Suchodolski, J.S, Steiner, J.M., 2018b. Association of fecal calprotectin concentrations with disease severity, response to treatment, and other biomarkers in dogs with chronic inflammatory enteropathies. J. Vet. Intern. Med. 32, 679-692.

Heilmann, R.M., Nestler, J., Schwarz, J., Grutzner, N., Ambrus, A., Seeger, J., Suchodolski, J. S., Steiner, J.M., Gurtner, C., 2019. Mucosal expression of S100A12 (calgranulin C) and S100A8/A9 (calprotectin) and correlation with serum and fecal concentrations in dogs with chronic inflammatory enteropathy. Vet. Immunol. Immunopathol. 211, 64–74.

Higueras, C., Rey, A.I., Escudero, R., Diaz-Reganon, D., Rodriguez-Franco, F., Garcia-Sancho, M., Agulla, B., Sainz, A., 2022. Short-chain and total fatty acid profile of faeces or plasma as predictors of food-responsive enteropathy in dogs: a preliminary study. Animals. 12(1), 89.

Honneffer, J.B., Minamoto, Y., Suchodolski, J.S., 2014. Microbiota alterations in acute and chronic gastrointestinal inflammation of cats and dogs. World. J. Gastroenterol. 20, 16489–97.

Jergens, A.E., Crandell, J., Morrison, J.A., Deitz, K., Pressel, M., Ackermann, M., Suchodolski, J.S., Steiner, J.M., Evans, R., 2010. Comparison of oral prednisone and prednisone combined with metronidazole for induction therapy of canine inflammatory bowel disease: A randomized-controlled trial. J. Vet. Intern. Med. 24(2), 269–277.

Jergens, A.E., Heilmann, R.M., 2022. Canine chronic enteropathy—current state-of-the-art and emerging concepts. Front. Vet. Sci. 9, 1-25.

Jostins, L., Ripke, S., Weersma, R.K., Duerr, R.H., McGovern, D.P., Hui, K.Y., Cho, J.H., 2012. Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 491(7422), 119-124.

Kathrani, A., House, A., Catchpole, B., Murphy, A., German, A., Werling, D., Allenspach, K., 2010. Polymorphisms in the TLR4 and TLR5 gene are significantly associated with inflammatory bowel disease in German shepherd dogs. PloS. one. 5(12), e15740.

Kathrani, A., Werling, D., Allenspach, K., 2011a. Canine breeds at high risk of developing inflammatory bowel disease in the south-eastern UK. Vet. Rec. 169(24), 635-635.

Kathrani, A., House, A., Catchpole, B., Murphy, A., Werling, D., Allenspach, K., 2011b. Breed-independent toll-like receptor 5 polymorphisms show association with canine inflammatory bowel disease. Tissue Antigens. 78(2), 94-101b.

Kathrani, A., Lee, H., White, C., Catchpole, B., Murphy, A., German, A., Werling, D., Allenspach, K., 2014. Association between nucleotide oligomerisation domain two (Nod2) gene polymorphisms and canine inflammatory bowel disease. Vet. Immunol. Immunopathol. 161(1-2), 32-41.

Kathrani, A., Allenspach, K., Fascetti, A.J., Larsen, J.A., Hall, E.J., 2018. Alterations in serum amino acid concentrations in dogs with protein-losing enteropathy. J. Vet. Intern. Med. 32(3), 1026-1032.

Korn, T., Bettelli, E., Oukka, M., Kuchroo, V.K., 2009. Il-17 and Th17 Cells. Annu. Rev. Immunol. 27, 485–517.

Lee, A., Kathrani, A., Priestnall, S.L., Smith, K., Werling, D., Allenspach, K., 2015. Lack of correlation between mucosal immunoglobulin A-positive plasma cell numbers and TLR5 genotypes in German shepherd dogs with idiopathic chronic enteropathy. J. Comp. Pathol. 152(2-3), 201-205.

Luckschander, N., Allenspach, K., Hall, J., Seibold, F., Grone, A., Doherr, M.G., Gaschen, F., 2006. Perinuclear antineutrophilic cytoplasmic antibody and response to treatment in diarrheic dogs with food responsive disease or inflammatory bowel disease. J. Vet. Intern. Med. 20(2), 221–7.

Maeda, S., Ohno, K., Uchida, K., Nakashima, K., Fukushima, K., Tsukamoto, A., Nakajima, M., Fujimo, Y., Tsujimoto, H., 2013. Decreased immunoglobulin A concentrations in feces, duodenum, and peripheral blood mononuclear cells of dogs with inflammatory bowel disease. J. Vet. Int. Med. 27(1), 47-55.

Maeda, S., Ohno, K., Uchida, K., Igarashi, H., Goto-Koshino, Y., Fujino, Y., Tsujimoto, H., 2014. Intestinal protease-activated receptor-2 and fecal serine protease activity are increased in canine inflammatory bowel disease and may contribute to intestinal cytokine expression. J. Vet. Med. Sci. 76(8), 1119-1127.

Maeda, S., Ohno, K., Fujiwara-Igarashi, A., Uchida, K., Tsujimoto, H., 2016. Changes in Foxp3-Positive Regulatory T Cell Number in the Intestine of Dogs with Idiopathic Inflammatory Bowel Disease and Intestinal Lymphoma. Vet. Pathol. 53, 102–112.

Makielski, K., Cullen, J., O'Connor, A., Jergens, A.E., 2019. Narrative review of therapies for chronic enteropathies in dogs and cats. J. Vet. Intern. Med. 33, 11–22.

Mancho, C., Sainz, A., Garcia-Sancho, M., Villaescusa, A., Tesouro, M.A., Rodriguez-Franco, F., 2010. Detection of perinuclear antineutrophil cytoplasmic antibodies and antinuclear antibodies in the diagnosis of canine inflammatory bowel disease. J. Vet. Diagn. Invest. 22(4), 553–8.

McCann, T.M., Ridyard, A.E., Else, R.W., Simpson, J.W., 2007. Evaluation of disease activity markers in dogs with idiopathic inflammatory bowel disease. J. Small. Anim. Pract. 48, 620-625.

Melgarejo, T., Williams, D.A., Griffith, G., 1996. Isolation and characterization of α1-protease inhibitor from canine plasma. Am. J. Vet. Res. 57, 258-263.

Minamoto, Y., Otoni, C.C., Steelman, S.M., Buyukleblebici, O., Steiner, J.M., Jergens, A. E., Suchodolski, J.S., 2015. Alteration of the fecal microbiota and serum metabolite profiles in dogs with idiopathic inflammatory bowel disease. Gut. microbes. 6(1), 33-47.

Minamoto, Y., Minamoto, T., Isaiah, A., Sattasathuchana, P., Buono, A., Rangachari, V.R., McNeely, I.H., Lidbury, J., Steiner, J.M., Suchodolski, J.S., 2019. Fecal short-chain fatty acid concentrations and dysbiosis in dogs with chronic enteropathy. J. Vet. Intern. Med. 33, 1608–18.

Murphy, K.F., German, A.J., Ruaux, C.G., Steiner, J.M., William, D.A., Hall, E.J., 2003. Fecal alpha1-proteinase inhibitor concentration in dogs with chronic gastrointestinal disease. Vet. Clin. Pathol. 32, 67-72.

Moser, K., Mitze, S., Teske, E., von Bomhard, W., Stockhaus, C., 2018. Correlation of clinical, diagnostic and histopathological parameters in dogs with chronic lymphocytic-plasmacytic enteropathy. Tierarztl. Prax. Ausg. K. Kleintiere. Heimtiere. 46(1), 15–20.

Nakamura, M., Takahashi, M., Ohno, K., Koshino, A., Nakashima, K., Setoguchi, A., Fujino, Y., Tsujimoto, H., 2008. C-reactive protein concentration in dogs with various diseases. J. Vet. Med. Sci. 70, 127-131.

Olivero, D., Turba, M.E., Gentilini, F., 2011. Reduced diversity of immunoglobulin and T-cell receptor gene rearrangements in chronic inflammatory gastrointestinal diseases in dogs. Vet. Immunol. Immunopathol. 144(3-4), 337-345.

Osada, H., Ogawa, M., Hasegawa, A., Nagai, M., Shirai, J., Sasaki, K., Shimoda, M., Itoh, H., Kondo, H., Ohmori, K., 2016. Expression of epithelial cell-derived cytokine genes in the duodenal and colonic mucosae of dogs with chronic enteropathy. J. Vet. Sci. 79(2), 393–397.

Otoni, C.C., Heilmann, R.M., García-Sancho, M., Sainz, A., Ackermann, M.R., Suchodolski, J.S., Steiner, J.M., Jergens, A.E., 2018. Serologic and fecal markers to predict response to induction therapy in dogs with idiopathic inflammatory bowel disease. J. Vet. Intern. Med. 32(3), 999–1008.

Peiravan, A., Bertolini, F., Rothschild, M.F., Simpson, K.W., Jergens, A.E., Allenspach, K., Werling, D., 2018. Genome-wide association studies of inflammatory bowel disease in German shepherd dogs. PloS. one. 13(7), e0200685.
Peiravan, A., Salavati, M., Psifidi, A., Sharman, M., Kent, A., Watson, P., Allenspach, K., Werling, D., 2021. Targeted next-generation sequencing of Candidate Regions Identified by GWAS Revealed SNPs Associated with IBD in GSDs. bioRxiv. 2021, 4.
Pilla, R., Suchodolski, J.S., 2020. The role of the canine guts microbiome and metabolome in health and gastrointestinal disease. Front. Vet. Sci. 6, 498.
Ridlon, J.M., Kang, D.J., Hylemon, P.B., 2006. Bile salt biotransformations by human intestinal bacteria. J. Lipid. Res. 47(2), 241–59.
Sacoor, C., Barros, L.M., Montezinho, L., 2020. What are the potential biomarkers that should be considered in diagnosing and managing canine chronic inflammatory enteropathies?. Open. Vet. J. 10(4), 412-430.
Siel, D., Beltrán, C.J., Martínez, E., Pino, M., Vargas, N., Salinas, A., Ramírez-Toloza, G., 2022. Elucidating the role of innate and adaptive immune responses in the pathogenesis of canine chronic inflammatory enteropathy—a search for potential biomarkers. Animals. 12(13), 1645.
Suchodolski, J.S., Dowd, S.E., Wilke, V., Steiner, J.M., Jergens, A.E., 2012a. 16S rRNA gene pyrosequencing reveals bacterial dysbiosis in the duodenum of dogs with idiopathic inflammatory bowel disease. PLoS. One.7(6), e39333.
Suchodolski, J.S., Markel, M.E., Garcia-Mazcorro, J.F., Unterer, S., Heilmann, R.M., Dowd, S.E., Kachroo, P., Ivanov, I., Minamoto, Y., Dillman, E.M., Steiner, J.M., Cook, A.K., Toresson, L., 2012b. The fecal microbiome in dogs with acute diarrhea and idiopathic inflammatory bowel disease. PLoS ONE. 7(12), e51907.
Tamura, Y., Ohta, H., Kagawa, Y., Osuga, T., Morishita, K., Sasaki, N., Takiguchi, M., 2019. Plasma amino acid profiles in dogs with inflammatory bowel disease. J. Vet. Intern. Med. 33(4), 1602-1607.
Toresson, L., Steiner, J.M., Suchodolski, J.S., Spillmann, T., 2016. Oral Cobalamin Supplementation in Dogs with Chronic Enteropathies and Hypocobalaminemia. J. Vet. Intern. Med. 30(1), 101–107.
Toresson, L., Steiner, J.M., Suchodolski, J.S., 2021. Cholestyramine treatment in two dogs with presumptive bile acid diarrhoea: a case report. Canine Med. Genet. 8, 1-7.
Vaden, S.L., Hammerberg, B., Orton, S.M., 2000. Mast cell degranulation responses in Soft-Coated Wheaten Terriers with protein-losing enteropathy and/or nephropathy. J. Vet. Intern. Med. 14, 348.
Vaden, S.L., Vidaurri, A., Levine, J.F., Harris, T., Steiner, J.M., Williams, D.A., 2002. Fecal α1-proteinase inhibitor activity in soft coated wheaten terriers. J. Vet. Intern. Med. 16(3), 382.
Volkmann, M., Steiner, J.M., Fosgate, G.T., Zentek, J., Hartmann, S., Kohn, B., 2017. Chronic diarrhea in dogs– retrospective study in 136 cases. J. Vet. Intern. Med. 31, 1043-1055.
Walker, H.K., Boag, A.M., Ottka, C., Lohi, H., Handel, I., Gow, A.G., Mellanby, R.J., 2022. Serum metabolomic profiles in dogs with chronic enteropathy. J. Vet. Intern. Med. 36(5), 1752-1759.
Wdowiak, M., Rychlik, A., Kolodziejska-Sawerska, A., 2013. Biomarkers in canine inflammatory bowel disease diagnostics. Pol. J. Vet. Sci. 16(3), 601–609.
Whitfield-Cargile, C.M., Cohen, N.D., Chapkin, R.S., Weeks, B.R., Davidson, L.A., Goldsby, J.S., Hunt, C.L., Steinmeyer, S.H., Menon, R., Suchodolski, J.S., Jayaraman, A., Alaniz, R.C., 2016. The microbiota-derived metabolite indole decreases mucosal inflammation and injury in a murine model of NSAID enteropathy. Gut. Microbes. 7(3), 246–261.

How to cite this article;
Pinkarn Chantawong. Clinical applications of current biomarkers in canine chronic enteropathies. Veterinary Integrative Sciences. 2024; 22(3): 713 - 737