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Evaluation of Serum and Fecal Concentrations of Alpha-1-Antitrypsin by ELISA in Healthy Dogs

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ABSTRACT

Numerous biomarkers are presently utilized to diagnose chronic non-specific enteropathy. Biomarkers are an effective diagnostic option due to their non-invasive and generally uncomplicated measurement. Alpha1 - proteinase inhibitor (cα1-PI), known as alpha-1-antitrypsin (A1-AT), is an early biomarker indicative of protein loss. This study evaluates the serum and fecal concentrations of cα1-PI in 50 healthy dogs at the Small Animal Clinic of the University of Veterinary Medicine and Pharmacy in Košice, categorized by age and size. Levels of cα1-PI were measured to investigate potential variations across these groups. Statistical analysis revealed no significant differences in cα1-PI concentrations among the groups stratified by age. A significant difference was observed in cα1-PI levels between groups of dogs classified by size. These findings suggest that size, rather than age, may influence cα1-PI concentrations in healthy dogs, highlighting the importance of considering body size when interpreting cα1-PI measurements in clinical practice. The mechanisms behind this connection and its consequences for the use of cα1-PI as a diagnostic biomarker require further investigation.

Key words: Alpha-1-antitrypsin, Biomarker, Enteropathy.

INTRODUCTION

Canine chronic inflammatory enteropathies (CIEs) refer to a set of conditions marked by ongoing (lasting more than three weeks) or recurring gastrointestinal issues, either separately or in conjunction with diarrhea, vomiting, nausea, borborygmus, gas, belching, abdominal pain and weight loss (Dossin and Lavoué 2011). A diagnosis is made after excluding other potential causes of gastrointestinal symptoms, including non-digestive disorders, intestinal parasites and digestive cancers or infections (Dandrieux 2016).

Canine chronic inflammatory enteropathies are currently categorized according to how they react to therapy into food-responsive enteropathies, antibiotic-responsive enteropathies, immunosuppressant-responsive enteropathies (IREs) and non-responsive (NREs) or refractory enteropathies (Dupouy-Manescau et al. 2024). Inflammatory bowel diseases (IBD) include IREs and NREs, which are characterized by mucosal inflammation. Another category of CIEs, referred to leakage of proteins is a protein-losing enteropathy (PLE). (Dandrieux and Mansfield 2019; Innocente et al. 2022).

Several biomarkers have been developed that can significantly assist in the diagnostic evaluation and ongoing monitoring of dogs with CIE (Félix et al. 2022). These biomarkers not only help in identifying the presence of the condition but can also be used to assess how well a dog is responding to different treatment options (Parambeth et al. 2019). By providing valuable insights into the effectiveness of various therapeutic approaches, these biomarkers serve as useful clinical tools for managing dogs with CIE (Heilmann and Steiner 2018; Hernandez and Dandrieux 2021).

Canine alpha1-proteinase inhibitor (cα1-PI) is a significant serum proteinase inhibitor that is mostly generated by hepatocytes. Its primary role is to protect the organism by counteracting the proteolytic enzyme impacts on the systemic level (Kuzi et al. 2020; Jandel et al. 2023). It has a molecular weight similar to albumin and is resistant to proteolysis, has been demonstrated to be clinically practical as a marker for the loss of protein in the gastrointestinal tract in dogs (Heilmann et al. 2011; Ozen and Lenardo 2023).

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Protein loss in the gastrointestinal tract can be caused by a wide range of gastrointestinal diseases, including inflammatory bowel disease (Pilla and Suchodolski 2020), intestinal lymphangiectasia (Kobayashi et al. 2007), alimentary lymphoma (Nagata et al. 2020), parasitic infections, viral diseases, or chronic intussusception (Dandrieux et al. 2013; Ozen and Lenardo 2023). Additionally, protein loss can be caused by non-gastrointestinal diseases, such as central nervous system (Günther et al. 2021) or venous hypertension caused by cardiac disease, which can result in protein malabsorption or leakage of proteins via the intestinal wall (Vaden 2008; Nakashima et al. 2015).

Fecal cα1-PI level should be assessed in order to diagnose dogs suspected of having protein-losing enteropathy (PLE). This is due to the fact that PLE is linked to an increased leakage of cα1-PI into the gastrointestinal system, and it has been shown that fecal cα1-PI concentrations are higher in dogs that have PLE. The process of persistent loss of cα1-PI has the ability to drain the cα1-PI, which might potentially disrupt the equilibrium between proteinase and proteinase inhibitors. In healthy dogs, the serum cα1-PI level is regulated within a narrow range, and it has been shown that these concentrations are decreased in a subgroup of canines that have IBD and PLE. Concentrations of serum cα1-PI have the potential to facilitate further characterization of gastrointestinal illnesses, including PLE and IBD (Grützner et al. 2013).

Despite its potential, there is still limited research to evaluate the diagnostic utility of ca1-PI in veterinary clinical practice. Most studies have been small-scale, and standardized reference ranges for cα1-PI concentrations in healthy versus diseased dogs are not well established. Further studies are needed to validate cα1-PI's diagnostic accuracy, its correlation with disease severity and its application in routine veterinary practice (Heilmann et al. 2018).

MATERIALS AND METHODS

The study was approved by the ethics committee for research involving animals in accordance with the legislative requirements applicable at the UVMP in Košice, permit No. EKVP/22-17.

Fecal and serum samples were collected at the Small Animal Clinic of the University of Veterinary Medicine and Pharmacy between August 2022 and May 2024. A total of 50 subjects were included in the study. The canines were subjected to a clinical examination, the objective of which was to ascertain their health status. Only healthy canines that exhibited no indications of illness, had received regular vaccinations and deworming treatments, and were not taking any medications were included in the study. Blood samples were obtained via venipuncture of the cephalic vein. Subsequently, the samples were subjected to centrifugation, after which the serum was promptly stored in a freezer at -20°C. Fecal samples were obtained via natural defecation. Subsequently, the feces were processed in accordance with the prescribed instructions and subsequently frozen at -20°C.

The total quantity of animals included in the research was 50. They were of the following breeds: German Shepherd (n=5), Yorkshire (n=8), Maltese (n=2), Poodle (n=8), Shiatzu (n=2), Staffordshire Bull Terrier (n=3), Golden Retriever (n=2). The remaining breeds were represented by a single individual each, including the boxer, Labrador, Hungarian Vizsla, Great Dane, Irish Setter, English Setter, Czechoslovakian Wolfhound, English Cocker Spaniel, Chow Chow, Australian Shepherd, Dachshund, French Bulldog, Mexican Hairless Pointer, Boston Terrier, Bichon, and Spitz. Additionally, three medium-sized crossbreeds (12-20kg) and one small (under 12kg) crossbreed were incorporated into the study.

The canines were classified into five categories based on their age. The initial cohort comprised canines of up to 2 years of age. The second group comprised canines aged between 2 and 4 years. The third group comprised canines aged between 5 and 7 years. The fourth group comprised dogs aged between 8 and 9 years, while the final fifth group consisted of dogs aged between 10 and 12 years.

Canines were classified into three categories based on their weight or size. The category of large dogs comprised canines with a body weight exceeding 20kg. The group of medium-sized dogs comprised canines with a weight range of 12 to 20kg, while the third group, designated as "small dogs," encompassed canines with a weight of up to 12kg.

A specific canine ELISA kit (Canine alpha1 Antitrypsin ELISA Kit, MyBioSource) with a sensitivity of 1.0ng/mL was employed to quantify the concentration of α1-proteinase inhibitor. The entire measurement process was conducted in accordance with the instructions outlined in the respective manual.

Statistical analysis

The statistical analysis of the results obtained was carried out using ANOVA. This approach was applied to assess the concentration of α1-proteinase inhibitor in healthy dogs. The data were carefully monitored, and the significance of the findings was evaluated using a significance level of $P<0.05$.

RESULTS

A total of 50 dogs were observed and divided into two groups based on the established criteria. In Group 1, serum and fecal canine alpha-1 antitrypsin levels were determined in accordance with the age of the dogs. A total of five subgroups were formed, comprising dogs of varying ages, from the youngest to those aged 12 years. In the first group of the youngest dogs (n=5), the mean serum canine alpha-1 antitrypsin value was 19.78ng.mL^{-1}, with the lowest value being 5.650ng.mL^{-1} and the highest value being 36.320ng.mL^{-1}. The second group, comprising 15 dogs aged between two and four years, exhibited a mean value of 11.14ng.mL^{-1}, with the lowest recorded value being 4.550ng.mL^{-1} and the highest value within this subgroup being 31.090ng.mL^{-1}. The mean value for dogs aged 5 to 7 years (n=11) was 17.64ng.mL^{-1}, with the smallest value measured being 0.520ng.mL^{-1} and the highest value being 51.580ng.mL^{-1}. In the group of dogs aged 8-9 years (n=10), the measured value was 12.79ng.mL^{-1}, with the lowest value being 6.128ng.mL^{-1} and the highest value being 27.820ng.mL^{-1}. In the oldest cohort, comprising dogs aged 10 to 12 years (n=9), the mean value was 17.30ng.mL^{-1}, with the lowest value being 1.349ng.mL^{-1} and the highest value being 52.170ng.mL^{-1}. The calculated confidence interval was set between 11.00ng.mL^{-1} and 18.75ng.mL^{-1}. The mean values for each subgroup are presented in Fig. 1.

According to the findings, the measured variable doesn't vary statistically significantly across the five age groups. While the group means vary slightly, the differences are likely due to random variation rather than any meaningful effect of age on the measured variable.

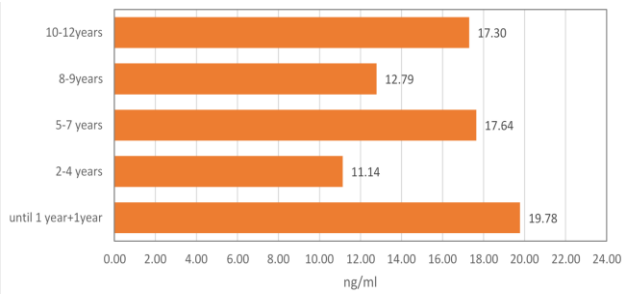

Fig. 1: Average values of serum antitrypsin in healthy dogs in relation to age.

The results of the cα1-PI measure for the second group, classified by size, indicate notable discrepancies in the mean values of the measured variable across the three groups: large breeds, medium breeds, and small breeds. The mean value for large breeds was 8.50ng.mL^{-1}, while that for medium breeds was 13.37ng.mL^{-1}. The highest mean value was observed for small breeds at 18.68ng.mL^{-1}. The lowest value of A1AT was observed in small dogs, at 1.349ng.mL^{-1}, while the highest value in this subgroup was 52.170ng.mL^{-1}. In the medium-sized dog subgroup, the lowest value was 5.650ng.mL^{-1}, while the highest value was 31.090ng.mL^{-1}. In the large dog subgroup, the lowest value was 0.520ng.mL^{-1}, while the highest value measured was 20.980ng.mL^{-1}. The measured values are presented in Fig. 2.

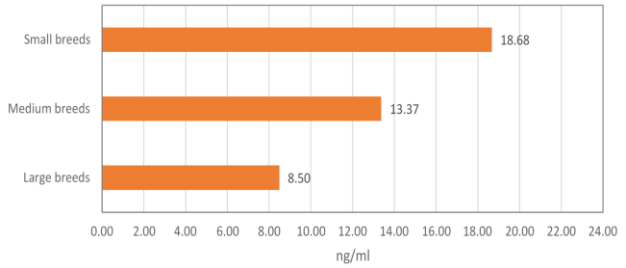

Fig. 2: Average values of serum antitrypsin in healthy dogs in relation to size of dog breed.

The data show increasing variability within groups as breed size decreases, with small breeds exhibiting the highest variance and standard deviation. The p-value of 0.03 is below the standard significance threshold of 0.05, confirming that the observed differences in group means are unlikely to be due to random chance. Findings underline the differences in the distribution of the measured variable across the groups. In conclusion, there is a statistically significant difference in the measured variable across the three breed groups, with small breeds displaying notably higher values on average.

Fecal concentrations of cα1-PI were measured in a cohort of 50 clinically healthy dogs. The dogs were categorized by size and age to assess potential variability in cα1-PI levels across these factors. Remarkably, all fecal samples analyzed revealed an cα1-PI concentration of 0 ng/mL, regardless of the size or age of the individual dogs.

DISCUSSION

In dogs, elevated fecal canine α1PI levels serve as a clinically valuable indicator of gastrointestinal protein loss and histological lesions associated with protein-losing enteropathy, such as lacteal dilatation and crypt abscesses (Vaden et al. 2002). In the study of Murphy et al. (2003) titled "Fecal α1-Proteinase Inhibitor Concentration in Dogs with Chronic Gastrointestinal Disease," the authors investigated the concentration of fecal cα1-PI as a potential biomarker for gastrointestinal (GI) disease in dogs. They found that dogs with persistent gastrointestinal disorders, particularly those with PLE, had significantly higher fecal α1-PI level in contrast to normal dogs. Also, they discovered that elevated fecal α1-PI level was connected to the presence of gastrointestinal disease, indicating that it could be a useful non-invasive biomarker for diagnosing conditions like PLE, which can result in protein leakage via the GI system. The study suggested that higher α1-PI levels might correlate with the severity of the disease and could help in monitoring the progression or resolution of chronic gastrointestinal diseases. While fecal α1-PI was a promising marker, the authors noted that it would be most effective when used alongside other diagnostic tests to evaluate GI conditions comprehensively. Our study was conducted exclusively with healthy patients, a factor that will undoubtedly inform future studies on non-healthy patients.

The findings of Heilmann et al. (2016) study provide valuable insights into the relationship between serum and fecal concentrations of cα1-PI and various intestinal conditions in dogs. Dogs with intestinal crypt abscesses or lacteal dilatation were found to have considerably decreased serum cα1PI and albumin values, with p-values indicating strong statistical significance. No significant differences were found in mean and maximum fecal cα1PI concentrations over three days in a row, nor in the serum to fecal cα1PI ratios. Moreover, serum albumin concentrations exhibited a moderate correlation with serum cα1PI levels, especially in instances of moderate to severe lacteal dilatation, suggesting that a decrease in cα1PI levels corresponded with a reduction in albumin levels. Additional notable findings comprised markedly reduced serum total calcium and cobalamin levels, as well as increased gastrin concentrations in the affected canines (Heilmann et al. 2016).

Heilmann et al. (2017) found that serum α1-PI concentrations were significantly elevated in canines with systemic inflammatory response syndrome (SIRS) and sepsis compared to healthy dogs. This suggests that α1-PI levels increase in response to systemic inflammation or infection, making it a potential biomarker for these conditions. The researchers observed that higher serum α1-PI concentrations were associated with more severe manifestations of SIRS and sepsis, including organ dysfunction and higher levels of inflammatory markers. This indicates that α1-PI could reflect the intensity of the systemic inflammatory response in critically ill dogs. The study found that α1-PI levels could help in predicting the prognosis of dogs with SIRS and sepsis. Elevated α1-PI levels were associated with a poorer clinical outcome and an increased risk of mortality. This suggests that α1-PI could be a valuable prognostic marker for assessing the

severity of sepsis and the likelihood of survival. The study also compared α1-PI levels to other commonly used biomarkers of inflammation, such as CRP and procalcitonin. Although α1-PI was elevated in sepsis and SIRS, the authors found that it could complement other markers in providing a more comprehensive assessment of the inflammatory status in affected dogs. The authors concluded that measuring α1-PI concentrations could be a useful tool in the clinical management of dogs with SIRS and sepsis. It may help in monitoring the progression of the disease, assessing treatment response, and predicting the prognosis of critically ill dogs.

Healthy dogs were tested by Heilmann et al. (2013) for cα1-PI serum concentrations using a validated 125I-immunoassay (RIA). In study they had 87 healthy canines over 10 months old were sampled, with a median age of 4.3 years. They found no significant variations in serum cα1-PI levels between male and female dogs or across age groups, suggesting that these factors do not impact adult levels. The study found that serum α1-PI concentrations exhibited relatively low intra-individual variation in healthy dogs. This is important because it indicates that α1-PI levels are stable within individual dogs over time, making it a reliable marker for assessing changes in serum levels that may occur due to disease or other health issues. The findings emphasize the importance of α1-PI as a potential biomarker in veterinary clinical practice. It may aid in the diagnosis of conditions like PLE, as changes in α1-PI concentrations could reflect alterations in protease inhibition, often seen in gastrointestinal diseases and systemic inflammation.

An enzyme-linked immunosorbent assay (ELISA) was developed and validated by of Burke et al. (2012) in the study where they measured cα1-PI in cat feces and blood samples. Lower detection levels of 0.02g.L^{-1} for blood sample and 0.04µg.g^{-1} for fecal samples were found using the assay. For serum reference intervals were set at 0.6–1.4g.L^{-1} Up to 1.6µg.g^{-1} for fecal samples.

The findings of Grützner at al. (2014) highlight that monitoring both cobalamin levels and the concentrations of serum albumin and α1-PI could be useful in diagnosing and managing gastrointestinal diseases and protein-losing conditions in dogs. Correcting cobalamin deficiency might improve the overall health and metabolic balance in affected dogs. The study also found that low cobalamin levels were associated with alterations in cα1-PI concentrations. α1-PI is a key protein involved in controlling protease activity in the body, and its levels can reflect inflammatory or gastrointestinal conditions.

Equilino et al. (2015) assessed several serum biochemical markers in dogs with PLE, including albumin, globulin, cα1-PI and other markers related to protein loss. These markers were evaluated to identify potential relationships between their concentrations and disease severity or prognosis. The study noted that other biochemical markers, such as globulin and α1-PI, may have potential roles in assessing the severity of PLE and monitoring the condition, although they were not as strongly associated with survival time as albumin.

Conclusion

In conclusion, our study evaluated serum and fecal antitrypsin concentrations in 50 healthy dogs, highlighting the potential importance of these biomarkers in the future diagnosis of chronic enteropathies, particularly protein-losing enteropathy. Our results revealed a statistically significant difference in the measured variables across three breed groups, with small breeds showing notably higher serum values on average. This finding underscores the need to consider breed-specific factors when interpreting antitrypsin levels. However, to confirm and expand upon these findings, further research involving a larger sample size and a more diverse population of dogs is necessary to enhance the diagnostic value and applicability of antitrypsin as a biomarker for chronic enteropathy.

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