Research Article

Investigation of Skin-Gut Axis Interaction in *Demodex canis*-Infected Dogs via Serum Zonulin Concentrations

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Abstract

Demodicosis is a common dermatological condition in dogs, resulting from the uncontrolled proliferation of *Demodex canis* mites. Disruption of the intestinal barrier integrity can trigger not only infectious and inflammatory diseases but also extraintestinal disorders, including dermatological conditions. In this context, zonulin, the only known physiological regulator of tight junctions within the intestinal epithelium, holds particular significance. The aim of this study was to investigate the effect of *Demodex canis* infection on serum zonulin levels in dogs and to contribute to the understanding of the complex and bidirectional relationship between dermatological diseases and intestinal barrier integrity. The study included a total of 25 adult dogs of various ages and sexes: 15 dogs diagnosed as *Demodex canis*-positive by microscopic examination and 10 healthy control dogs with similar age and sex distribution. Dogs in the affected group were evaluated at two time points —before and after treatment—to assess therapeutic efficacy. Serum zonulin levels in all groups were measured using the ELISA method. The results revealed that pre-treatment serum zonulin levels in dogs with *Demodex canis* infection (mean 12.8 ± 3.735 ng/mL) were significantly higher than both post-treatment values (mean 4.096 ± 2.693 ng/mL) and those of the healthy control group (mean 2.177 ± 1.953 ng/mL). Statistical analysis demonstrated a highly significant mean difference of 8.704 ng/mL between pre- and post-treatment groups ($p < 0.0001$), and a mean difference of 10.623 ng/mL between the pre-treatment and control groups ($p < 0.0001$). Conversely, the difference in serum zonulin levels between the post-treatment and control groups (mean 1.919 ng/mL) was not statistically significant ($p = 0.2706$). These findings indicate that zonulin levels are significantly elevated in dogs with demodicosis, suggesting a disruption of intestinal barrier function during *Demodex canis* infection. The observed increase in zonulin may also reflect an associated systemic inflammatory response. The normalization of serum zonulin levels following treatment implies a restoration of intestinal barrier integrity. Overall, the results highlight the potential involvement of the gut-skin axis in the pathophysiology of *Demodex canis* infections.

Keywords: *Demodex canis*, zonulin, gut-skin axis, gastroenterodermatology

Introduction

Mites of the species *Demodex canis* are commensal organisms naturally residing in the hair follicles of many mammalian species. In dogs, transmission typically occurs from the mother to the puppies during the early stages of life. However, under conditions of immunosuppression, these mites may become pathogenic, leading to clinical manifestations (Mueller et al., 2020). The potential bidirectional interaction between the skin and the gut has increasingly been emphasized in recent studies, suggesting a complex and multilayered communication network. This network primarily involves the gut microbiota, various metabolites, neuroendocrine signaling pathways, dietary components, and the central nervous system. Disruption of the intestinal barrier not only

predisposes the host to pathological conditions such as infection and inflammation, but may also contribute to the development of various extraintestinal diseases, including dermatological disorders (Biscoff, 2011; O'Neill et al., 2016).

When intestinal health is compromised, particularly at the level of tight junctions between epithelial cells, functional loss occurs. This disruption increases intestinal permeability, allowing the translocation of normally restricted substances—such as toxins, microorganisms, and undigested food antigens—across the epithelial barrier and into direct contact with the immune system. Consequently, not only the gastrointestinal tract but also extraintestinal organs like the skin may be affected. This process can trigger inflammatory responses and potentially promote the development of autoimmune conditions (Ullah et al., 2024).

In this context, the protein zonulin plays a crucial role in regulating intestinal epithelial barrier integrity. Zonulin is currently recognized as the only endogenous molecule known to physiologically modulate tight junctions. Certain bacterial components in the intestinal lumen or environmental triggers such as gluten can stimulate zonulin release, initiating this regulatory process. Zonulin interacts with specific receptors located on the apical surface of epithelial cells, activating signaling pathways that weaken intercellular junctions. This biochemical cascade leads to increased epithelial permeability, establishing zonulin as a direct mediator in the pathophysiology of intestinal barrier dysfunction (Wang et al., 2000; Tripathi et al., 2009; Fasano, 2012; Sturgeon & Fasano, 2016).

Accordingly, investigating zonulin levels in dermatological conditions such as *Demodex canis* infection represents a promising area of research. Demodicosis is an inflammatory disease that develops in association with immune suppression and is characterized by prominent inflammatory processes. The use of biomarkers such as zonulin for monitoring systemic inflammation may provide insight into the underlying pathogenesis of this parasitic infection. Disruptions in intestinal barrier integrity and the resulting elevation in zonulin levels could reflect not only gastrointestinal involvement but also widespread inflammatory responses affecting the skin. Therefore, the measurement of serum zonulin levels in dogs infected with *Demodex canis* in this thesis is scientifically justified as a means to explore the systemic impacts of dermatological disease and to assess the potential utility of zonulin as a biomarker.

Materials and Methods

In this study, a total of 15 adult dogs (9 females, 6 males) from various age groups and both sexes, diagnosed with *Demodex canis* infestation through microscopic examination following presentation to the veterinary clinic due to dermatological lesions, were evaluated as the patient group. The control group consisted of 10 healthy dogs with similar age and sex distribution, showing no dermatological signs, and presented to the clinic solely for routine vaccinations or general health check-ups. Thus, a total of 25 dogs were included in the study. For the patient group, blood samples were collected at two different time points—prior to treatment and after completion of the treatment—to assess therapeutic efficacy. Between these two time points, an appropriate clinical treatment protocol was applied to each individual, and the obtained data were statistically compared. Furthermore, it was confirmed through detailed clinical history that none of the dogs had received systemic or topical antibiotics for at least one month prior to sampling, nor had they been treated with probiotic products within the last two weeks. These criteria ensured that the study results were obtained independently of external confounding factors, thus enhancing the reliability of the findings.

During clinical examination, dogs exhibiting dermatological signs consistent with demodicosis such as alopecia, erythema, hyperkeratosis, hyperpigmentation, and pruritus were subjected to diagnostic sampling using the deep skin scraping method to confirm the presence of *Demodex canis*. Accordingly, skin scrapings were collected from at least three different anatomical regions where lesions were most prominent, each covering an area of approximately 1 cm². Prior to sampling, a drop of mineral oil was applied to the lesion site, and the skin was gently scraped with a scalpel blade in the direction of hair growth. To facilitate the emergence of mites from hair follicles, the skin was intermittently pinched during the procedure. Scraping was continued until capillary bleeding was observed, indicating sufficient depth. The collected material was transferred onto microscope slides, covered with coverslips, and examined microscopically on the same day to preserve the structural integrity of the mites. The samples were evaluated under light microscopy at 40× and 100× magnification.

From the 15 dogs confirmed to be positive for *Demodex canis* infestation through microscopic evaluation, 4

mL of blood was collected from the *Vena cephalica antebrachii* into plain (non-anticoagulant) tubes for the measurement of serum zonulin concentrations. These samples represented the pre-treatment phase. On the same day, appropriate treatment protocols were initiated. To assess post-treatment changes, a second 4 mL blood sample was collected from the same vein 30 days after the start of treatment using the same method. In addition, blood samples were obtained from healthy dogs using the same technique to serve as the control group. All collected blood samples were centrifuged at 3000 rpm for 15 minutes using an LC-04B centrifuge to separate the serum fraction. The resulting serum was aliquoted into labeled Eppendorf tubes in duplicate for each subject and stored at –80 °C until the day of analysis. Serum zonulin concentrations were measured using an ELISA method, following the manufacturer's instructions.

For statistical evaluation, the Shapiro-Wilk test was employed to assess the normality of data distribution. Since several variables did not follow a normal distribution, logarithmic transformation was applied. However, the data still failed to meet normality assumptions, and therefore, non-parametric statistical methods were adopted. Group comparisons were conducted using the Kruskal-Wallis ANOVA test. All statistical analyses were performed using SPSS software version 26.0 (IBM, USA), and a p-value of <0.05 was considered statistically significant.

Results

In this study, pre- and post-treatment serum zonulin levels were measured in dogs diagnosed with *Demodex canis* infection and compared with values from a healthy control group. The analyses revealed statistically significant differences among the groups. All 15 dogs evaluated in the pre-treatment phase of the infected group exhibited hyperkeratosis. Alopecia was observed in all but one of the dogs, indicating that hyperkeratosis and alopecia were the most frequently observed clinical signs. Additionally, 12 dogs presented with crusting and hyperpigmentation, 10 with pruritus, 7 with erythema, and 5 with papular lesions. Although erythema and papules were less commonly detected than the other findings, it was noted that the severity of these lesions increased in parallel with the severity of other clinical symptoms.

Serum zonulin levels were assessed across three distinct groups: pre-treatment (n=15), post-treatment (n=15), and healthy controls (n=10). The results demonstrated that serum zonulin concentrations in dogs infected with Demodex canis prior to treatment (mean 12.8 ± 3.735 ng/mL) were significantly higher than those in both the post-treatment group (mean 4.096 ± 2.693 ng/mL) and the healthy control group (mean 2.177 ± 1.953 ng/mL). Intergroup statistical comparisons were evaluated using mean differences, p-values, and 95% confidence intervals. Statistical analysis showed that the mean difference in zonulin levels between the pre- and post-treatment groups was 8.704 ng/mL, which was highly significant ($p < 0.0001$). Similarly, the mean difference between the pre-treatment group and the healthy controls was 10.623 ng/mL, which was also statistically highly significant ($p < 0.0001$). However, the difference between the post-treatment and healthy control groups (mean difference: 1.919 ng/mL) was not statistically significant ($p = 0.2706$). These results clearly indicate that zonulin levels were significantly elevated in the pre-treatment group compared to both the post-treatment and healthy groups. The decrease in zonulin levels following treatment, approaching those observed in healthy dogs, suggests restoration of intestinal barrier function and a reduction in systemic inflammation. These findings imply that zonulin is not only a marker of intestinal permeability but also a potential indicator of systemic inflammatory processes and distant organ involvement.

Our study supports previously reported observations in the literature that zonulin levels are elevated in chronic inflammatory diseases. Moreover, it suggests that *Demodex canis* infection may represent not merely a localized cutaneous disorder, but rather a complex pathological condition involving intestinal barrier dysfunction and systemic inflammation. In this context, our findings contribute to the limited body of literature in the field of gastroenterodermatology by highlighting that *Demodex canis* infestation is a multifaceted disease process associated with systemic immune and mucosal barrier alterations, rather than being confined solely to dermatologic manifestations.

Discussion

Current scientific data demonstrate that the influence of the gut microbiota is not confined solely to the gastrointestinal system; rather, it plays a direct role in the physiological and immunological functioning of distant organ systems such as the lungs, brain, and skin (Levkovich et al., 2013; Kim et al., 2014). Increased permeability of both the gut and skin barriers—referred to as dysbiosis—facilitates

interactions between various allergens and pathogens with immune cell receptors, thereby triggering inflammatory responses. In this context, the regulatory effects of the gut microbiota on remote organs have led to the emergence of novel pathophysiological concepts such as the gut–lung axis, gut–brain axis, and gut–skin axis (Salem et al., 2018; De Pessemier et al., 2021).

The pathophysiology of *Demodex canis* infection, which is the focus of this study, is directly associated with impairments in the host's immune system. Under normal conditions, Demodex mites coexist symbiotically on the skin; however, in cases of immunosuppression or immune dysregulation, they may proliferate excessively and lead to the development of dermatological lesions (Bernstein et al., 2014; Ferrer et al., 2014; Gökalp & Kırbaş, 2020). Considering that more than 70% of the immune system is linked to the gut, and that the gut microbiota modulates both innate and adaptive immune responses, it becomes evident that intestinal barrier integrity plays a central role in the pathogenesis of systemic diseases (Kim et al., 2014; Chen et al., 2018; Salem et al., 2018).

Structural or functional disruptions of the intestinal barrier can allow harmful bacteria and microbiota-derived metabolites to enter systemic circulation, thereby impairing skin homeostasis and contributing to the development of various dermatological disorders (O'Neill et al., 2016). Indeed, a study by Levkovich et al. (2013) reported that supplementation with *Lactobacillus reuteri* in mice led to increased dermal thickness, accelerated hair follicle development, enhanced sebocyte activity, and a noticeable improvement in skin brightness. These beneficial changes were attributed primarily to immunologically mediated regulatory mechanisms (O'Neill et al., 2016). In another experimental study conducted by Horii et al. (2014), oral administration of *Lactobacillus brevis* was shown to increase serotonin release, thereby regulating cutaneous blood flow via the parasympathetic nervous system and reducing transepidermal water loss. Similarly, *Lactobacillus helveticus* supplementation was reported to alleviate dermatitis symptoms and strengthen epidermal barrier functions (Baba et al., 2010; Salem et al., 2018).

Recent human studies have demonstrated that the impact of gut microbiota on skin health is primarily mediated through inflammatory pathways (O'Neill et al., 2016). In inflammatory skin diseases such as psoriasis, a reduction in beneficial bacterial populations disrupts immune system balance, leading to increased systemic inflammation and subsequently elevated intestinal permeability, which promotes bacterial translocation (Scher et al., 2015; Visser et al., 2019; De Francesco & Caruso, 2022). In a study by Zheng et al. (2016), an increased abundance of *Akkermansia muciniphila* in infants with atopic dermatitis was significantly associated with impaired gut barrier integrity and the severity of skin lesions. Nutrition serves as a critical regulator within this skin-gut axis; notably, diets containing gluten have been reported to increase intestinal permeability and activate inflammatory processes (Uhde et al., 2016). Conversely, probiotic supplementation supports the production of short-chain fatty acids, providing beneficial effects on both the gut epithelium and the skin barrier (Nagpal et al., 2018). Furthermore, several studies emphasize that dysbiosis related to the gut-skin axis contributes to the pathogenesis and progression of common dermatological conditions such as acne vulgaris and rosacea (Vaughn et al., 2017; Polkowska-Pruszyńska et al., 2019).

The disruption of intestinal barrier integrity leads to the passage of toxins, antigenic structures, incompletely digested food particles, and microbial-derived products from the lumen into the lamina propria. This, in turn, results in the activation of macrophages and dendritic cells, which are the primary cells of the innate immune system. In this context, the protein zonulin stands out as the only known physiological regulator of intercellular tight junctions. Zonulin is a molecule produced on the mucosal surface that can temporarily and reversibly modulate paracellular permeability. Through this property, it directly controls the permeability of the intestinal epithelium, regulating the passage of large molecules (Wang et al., 2000; Tripathi et al., 2009; Fasano, 2012; Sturgeon).

According to our findings, the serum zonulin levels before treatment (mean ± SD: 12.8 ± 3.735 ng/mL) were significantly higher compared to both post-treatment levels (4.096 ± 2.693 ng/mL) and those of healthy dogs (2.177 ± 1.953 ng/mL). Statistical analysis revealed that the mean difference between the pre-treatment and post-treatment groups was 8.704 ng/mL, which was highly significant ($p < 0.0001$). Similarly, the mean difference between the pre-treatment group and the healthy control group was 10.623 ng/mL, also showing a high level of statistical significance ($p < 0.0001$). In contrast, the mean difference in zonulin levels between the post-

treatment group and the healthy control group was 1.919 ng/mL, which was not statistically significant ($p = 0.2706$).

In the field of veterinary medicine, studies measuring zonulin levels in dogs are quite limited. Our findings align particularly with the study by Ural et al. (2021), who reported a significant decrease in serum zonulin levels following probiotic enema treatment in dogs with atopic dermatitis. Both studies suggest that increased intestinal permeability may be associated with dermatological inflammation and support the potential use of zonulin as a measurable biomarker in this process. While Ural et al.'s research highlights the impact of modulating gut microbiota on inflammatory skin diseases, our study contributes a different perspective by directly examining the effect of antiparasitic treatment on zonulin levels. In this respect, our study demonstrates that zonulin levels may reflect treatment response in a parasitic dermatological disease model such as Demodex canis infection, thus offering a novel insight to the existing literature. Similarly, the molecular-level study by Capaccia et al. (2024) investigated the relationship between epithelial barrier and immune response during hypersensitivity reactions in dogs but did not directly measure zonulin levels. Therefore, our study fills this gap by providing direct zonulin measurements and clinically demonstrating the interaction between skin and barrier function. Additionally, the study conducted by Çöllü et al. (2024) on dogs affected by canine distemper reported a positive correlation between serum zonulin levels and disease severity. While that research suggests zonulin as a potential biomarker of disease activity in a viral systemic illness, our study is the first to report zonulin measurements with clinical relevance in a parasitic dermatological disease model.

From a broader perspective, the regulatory role of zonulin protein in autoimmune and metabolic diseases has long been recognized. De Kort and colleagues (2011) reported significantly elevated serum zonulin levels in individuals prior to the diagnosis of type 1 diabetes. Similarly, exposure to gliadin, the main component of gluten, in celiac disease stimulates zonulin release, leading to increased intestinal permeability (Capaccia et al., 2024). Smecuol et al. (2005) observed elevated zonulin levels in patients with dermatitis herpetiformis following gluten consumption. Additionally, studies by Moreno-Navarrete et al. (2012) and Zhang et al. (2014) demonstrated a positive correlation between zonulin levels and type 2 diabetes as well as insulin resistance. On the other hand, Hijazi and colleagues (2004) reported that approximately 40% of asthma patients exhibited elevated zonulin levels, suggesting that increased intestinal permeability may trigger inflammation in the respiratory system. Collectively, these findings indicate that zonulin is not only a key regulator of intestinal barrier function but also an important biomarker reflecting various pathophysiological processes including systemic inflammation and metabolic disorders. In this context, a unique contribution of our study to the literature is the observation that alterations in zonulin levels are significantly evident not only in autoimmune or metabolic diseases but also in a parasitic dermatological disease model. The increase in serum zonulin detected in dogs positive for Demodex canis infection suggests that this disease is not merely a localized pathology confined to the skin, but may be associated with broader pathophysiological processes such as compromised intestinal barrier integrity and systemic inflammation. This finding supports the role of zonulin in the pathogenesis of extraintestinal diseases and highlights its potential as a relevant parameter, especially in dermatological-parasitic conditions.

This study represents one of the pioneering investigations evaluating serum zonulin levels in dogs with Demodex canis infection and highlights the potential role of zonulin as a biomarker in dermatological diseases. While most existing literature primarily addresses zonulin levels in the context of atopic dermatitis or viral systemic disease models, the present research provides a novel perspective by assessing zonulin in a parasitic dermatological model, thereby exploring the possible interactions among intestinal barrier integrity, systemic inflammation, and skin disorders. The findings offer valuable insights that may guide future studies investigating the gut-skin axis in veterinary dermatology, suggesting that zonulin could serve as a biomarker for both diagnosis and therapeutic monitoring. Although previous studies have suggested that alterations in the microbiota can influence zonulin levels (Ural et al., 2021), the causality of this relationship in parasitic dermatological diseases remains unclear. This raises the critical question of whether zonulin elevation is a consequence or a trigger of the disease process. One of the major contributions of this study is to lay the groundwork for future research involving larger sample sizes. Comparative analyses of zonulin levels across various dermatological conditions of allergic,

autoimmune, parasitic, and bacterial origin will be essential to elucidate the diagnostic and prognostic potential of this protein more clearly. In conclusion, the measurement of serum zonulin represents a promising and evolving area for the assessment of dermatological conditions such as *Demodex canis* infection. This study establishes a foundational basis for zonulin-centered approaches in veterinary dermatology and underscores the importance of comprehensive future investigations.

Conclusion

In conclusion, this study underscores the necessity of strengthening the interdisciplinary link between gastroenterology and dermatology within the field of veterinary medicine. Future research aimed at elucidating the complex mechanisms underlying the gut-skin axis will facilitate the development of novel, safe, and effective therapeutic strategies targeting gut function and the microbiome in both human and animal health. Treatments focused on regulating intestinal permeability are anticipated to play an adjunctive role in managing inflammatory skin diseases, potentially enhancing the efficacy of existing dermatological therapies. Within this context, our study contributes significantly to the gastroentero-dermatology literature by demonstrating that *Demodex canis* infection a common dermatological condition represents not merely a localized dermatopathy but a complex disease process associated with systemic inflammation and mucosal barrier dysfunction.

Conflict of interest

The authors have no conflicts of interest to report.

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