2025, Scienceline Publication
World's Veterinary Journal
World Vet J, 15(1): 23-30.
ISSN 2322-4568

DOI: https://dx.doi.org/10.54203/scil.2025.wvj3
PII: S232245682500003-15

Effects of Post-Therapy Changes on the Level of Immunoglobulin M in Dogs with Dermatitis

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ORIGINAL ARTICLE
Received: December 29, 2024
Revised: January 27, 2025
Accepted: February 18, 2025
Published: March 30, 2025

ABSTRACT

Dermatitis is an inflammation of the skin characterized by itching, hair loss, lesions, and redness. Various agents can cause dermatitis, including *Sarcoptes scabiei*, *Demodex canis*, and *Microsporum canis*. Animals experiencing dermatitis undergo internal changes in their bodies, particularly in the immune system. The presence of an infection is usually preceded by the appearance of Immunoglobulin M (IgM). This study aimed to determine the differences in IgM levels in dogs with dermatitis before therapy (pre-therapy) and after therapy (post-therapy), as well as the differences in IgM levels between dogs with mild and severe dermatitis. The study involved 40 local dogs, divided into two groups, including 20 dogs with mild dermatitis and 20 dogs with severe dermatitis. Serum sampling was conducted in two phases: the first phase was pre-therapy, and the second phase was 14 days after therapy (post-therapy). The therapy administered to dogs with mild dermatitis consisted of diphenhydramine HCl and ivermectin, while the therapy for dogs with severe dermatitis included diphenhydramine HCl, ivermectin, amoxicillin, and dexamethasone. Serum samples from the dogs were then tested using the Enzyme-Linked Immunosorbent Assay method. The results of the study revealed that serum IgM levels in dogs with mild and severe dermatitis did not show any significant difference. In dogs with mild dermatitis, serum IgM levels before therapy were not statistically different compared to those after therapy. However, in dogs with severe dermatitis, serum IgM levels before therapy were significantly higher compared to after therapy. The results of this study indicate that therapy can impact serum IgM levels in dogs with severe dermatitis, while it does not significantly affect these levels in cases of mild dermatitis.

Keywords: Dermatitis, Dog, Enzyme-linked immunosorbent assay, Immunoglobulin M, Ivermectin, Therapy

INTRODUCTION

Dogs are among the animals that can live alongside humans. One of the health issues frequently encountered in dogs is skin disorders, such as dermatitis (Marsella and De Benedetto, 2017). The occurrence of dermatitis in dogs is often closely related to poor management practices. Several triggering factors for the emergence of dermatitis include cleanliness and skin care, improper nutrition, parasite control, and an uncomfortable environment. Stress and the mental health of dogs, such as a lack of playtime, exercise, and sufficient social interaction, can reduce their resistance to infections (Valenzuela et al., 2013).

Dermatitis is an inflammation or irritation of the skin characterized by symptoms such as itching, hair loss, sores, and redness (Ali et al., 2024). The causes of dermatitis can vary, including parasitic infections (ticks and mites), bacterial infections, fungal infections, nutritional deficiencies, physiological stress, and genetic factors (Trinh et al., 2024). Additionally, other factors, such as the environment, the cleanliness of dog handlers, and the immunity of each individual, influence the incidence of dermatitis (Kristianty et al., 2017). Dermatitis can cause inflammation or lesions on the skin, with varying degrees of severity. These lesions can be categorized as mild, moderate, or severe, and can be differentiated into primary and secondary lesions (Suwiti et al., 2022). Dogs experiencing mild dermatitis show mild itching, hair loss, and the formation of non-extensive primary lesions (Suwiti et al., 2022). Conversely, dogs with severe dermatitis experience intense itching, scratching, and continuous biting of their bodies, which can lead to skin damage and inflammation. This condition is often accompanied by open wounds due to excessive scratching, as well as primary and secondary lesions that extend throughout the body (Almutawa et al., 2024).

The treatment of dermatitis in dogs generally involves administering antihistamines to reduce itching or pruritus, using ivermectin for antiparasitic purposes, administering anti-inflammatory medications to alleviate skin inflammation, and prescribing antibiotics to prevent secondary infections (Cahyaniarta et al., 2019; Papich, 2023). The occurrence of dermatitis often occurs in the same dog. Dermatitis can lead to changes in the animal's internal body, particularly in the immune system (Ferreira et al., 2021). Immunoglobulin M (IgM) is one type of antibody produced by the animal's

To cite this paper: Pusparini NPDP, Suwiti NK, Suardana IBK, and Besung INK (2025). Effects of Post-Therapy Changes on the Level of Immunoglobulin M in Dogs with Dermatitis. *World Vet. J.*, 15(1): 23-30. DOI: https://dx.doi.org/10.54203/scil.2025.wvj3

immune system. The IgM plays an important role in providing early protection against new infections before other types of antibodies are produced (Erkocoglu and Kocabas, 2015). It helps combat infections by triggering an inflammatory response. Parasitic infections that cause dermatitis can affect the circulation of IgM and IgG, even though an IgE response has already occurred in the body (Laksmi et al., 2019).

The occurrence of an infection by parasites can stimulate and increase the levels of IgE, IgM, and IgG in the body (Mabbott, 2018). Examining IgM levels in dogs suffering from dermatitis is very important, as this information can provide insight into the dog's immune system resilience. If there is an increase in IgM antibodies in a dog with dermatitis, it indicates that the animal's immune system is functioning well. The body responds to the presence of antigens by producing IgM antibodies as an initial line of defense (Ouchida et al., 2012). The administration of anti-inflammatory drugs in cases of dermatitis can influence IgM levels (Kasim et al., 2022). Therefore, it is important to assess IgM profile in dogs with dermatitis both pre-treatment and post-treatment. This study aimed to determine the difference in immunoglobulin M levels in dogs with mild and severe dermatitis and to compare immunoglobulin M levels in pre-therapy and post-therapy.

MATERIALS AND METHODS

Ethical approval

Ethical clearance for this study was approved by the Animal Ethics Committee of the Faculty of Veterinary Medicine Udayana University, Denpasar, Indonesia, No: B/210/UN14.2.9/PT.01.04/2024.

Study design

A total of 40 dogs with dermatitis were used as research samples. The dogs in this study were obtained from owners who had dogs with dermatitis who came to the Taman Griya Pet Care animal clinic, Jimbaran, Badung, Bali for treatment and grouped based on the severity of their condition. The severity was assessed through clinical examination using a standard dermatological scale, which includes the size of the lesion, the intensity of inflammation, and its impact on the dog's behavior. The dogs were then divided into two groups: a group with mild dermatitis (Group 1) and a group with severe dermatitis (Group 2). Each group consisted of 20 dogs. The classification of mild and severe dermatitis in this study was that dogs experiencing mild dermatitis show mild itching, hair loss, and the formation of non-extensive primary lesions. Conversely, dogs with severe dermatitis experience intense itching, scratching, and continuous biting of their bodies, which can lead to skin damage and inflammation. Serum samples for all groups were collected twice, including before treatment (pre-therapy) and 14 days after treatment (post-therapy). Dogs in Group 1 received antiparasitic treatment with ivermectin (Intermectine, PT. Tekad Mandiri Citra, Bandung, Indonesia) at a dose of 0.2 mg/kg BW with subcutaneous route (Pusparini et al., 2023) and antihistamine treatment with diphenhydramine HCL (Dimedryl, PT. Bernofarm, Surabaya, Indonesia) at a dose of 1 mg/kg BW with subcutaneous route (Pusparini et al., 2023). Dogs in Group 2 received the same antiparasitic treatment: ivermectin (0.2 mg/kg BW) and, diphenhydramine HCL (1 mg/kg BW), along with antibiotic amoxicillin (Betamox LA®, Norbrook, Northern Ireland) at a dose of 0.1 ml/BW with intramuscular route and anti-inflammatory dexamethasone (PT. Meprofarm, Bandung, Indonesia) at a dose of 0.5 mg/kg BW with intramusculus route. All treatments were administered by injection on the first day, and followed by oral dexamethasone therapy (Dexaharsen, PT. Harsen, Indonesia) at a dose of 0.5 mg/kg BW for 5 days for dogs with severe dermatitis (Plumb, 2008). Monitoring of dermatitis recovery is done online by asking about the dog's condition, whether the itching has reduced, or whether the redness has reduced. Then, 14 days after therapy, the dog owner brought his dog back to the clinic so we could check the condition of his skin and take blood for post-therapy testing.

Serum sample

Samples were collected in December 2024. A total of three mL of blood was taken from the Vena Cephalica and placed into a non-EDTA tube for serum isolation. The serum samples were stored in a cooler box and transported to the laboratory. The examination of IgM levels in dog serum was conducted at the Veterinary Immunology Laboratory, Faculty of Veterinary Medicine, Udayana University, Bali, Indonesia.

Enzyme-linked immunosorbent assay

Examination of serum IgM levels in dogs with mild and severe dermatitis using the Enzyme-Linked Immunosorbent Assay (ELISA) method with the Canine IgM ELISA kit (Wuhan Feiyue Biotechnology Co., Ltd., China, Catalog: FY-EC6352). The ELISA test begins by preparing a 32 µg/mL stock solution. Six Eppendorf tubes are filled with 150 µL of standard diluent. In the first tube, 150 µL of the stock solution is added and mixed to achieve a 16 µg/mL concentration. Subsequently, 150 µL is transferred from one tube to the next, halving the concentration each time (16, 8,

4, 2, 1 µg/mL). The last tube contains only the standard diluent as a control, yielding a concentration of 0 µg/mL. Additionally, 20 mL of wash buffer concentrate is diluted with 580 mL of deionized water to prepare 600 mL of ready-to-use wash buffer. Next, the wells are prepared for samples, standards, and blanks. In the blank well, no sample or Horseradish Peroxidase-Conjugate reagent is added. In the standard well, 50 µL of standard solution is added, while in the sample well, 40 µL of diluent and 10 µL of sample are added, resulting in a final dilution of 5 times. After all wells are prepared, the plate is sealed with a plate sealer. The plate is then incubated for 30 minutes at 37°C. After incubation, the plate was opened, the liquid in the wells was discarded, and each well was washed with wash buffer. The wells are left for 30 seconds and then dried. This washing process is repeated five times. Next, 50 µL of HRP-conjugate reagent is added to each well, except the blank well. The plate is re-covered and incubated for another 30 minutes at 37°C (Laksmi et al., 2019).

After 30 minutes of incubation, the liquid in the wells was discarded again, and the washing process was repeated five times as before. Then, 100 µL of a mixture of substrate reagents A and B was added to each well, followed by a 10-minute incubation at 37°C in the dark. The reaction was stopped with 50 µL of stop solution, and absorbance at 450 nm was measured within 15 minutes using a spectrophotometer. The IgM concentration was determined by comparing the sample's O.D. value with a standard curve plotted on graph paper. The calculation used the equation $Y = a + bx + cx^2$, where X is the IgM concentration, Y is the O.D. value, and a, b, and c are constants.

Statistical analysis

The data obtained were analyzed using SPSS for Windows, version 25 (SPSS Inc., Chicago, IL, USA). The difference in mean serum IgM levels of dogs with dermatitis was analyzed using the Independent T-test. The level of significance measured was 5% ($p < 0.05$).

RESULTS

The IgM levels in 80 serum samples of dogs showed varying results, ranging from 10.435 µg/mL to 13.761 µg/mL. Serum IgM levels are an important indicator in assessing a dog's immune response, especially in dermatological conditions, such as dermatitis (Pan et al., 2021). The IgM levels studied can vary due to several factors, such as exposure time and type of pathogen (Zhang et al., 2022).

The mean IgM level in mild dermatitis was 12.2885 ± 0.6345 µg/mL, while in severe dermatitis it was 12.0531 ± 0.5374 µg/mL. Although the mean IgM level in mild dermatitis was slightly higher than in severe dermatitis, statistical analysis showed no significant difference ($p > 0.05$, Table 1).

This study showed that the average serum IgM levels of dogs with mild dermatitis at pre-therapy were 12.2885 ± 0.6355 µg/mL. Meanwhile, the average IgM levels at post-therapy were slightly higher than pre-therapy; however, this difference was not statistically significant ($p > 0.05$, Table 2).

In this study, the mean serum IgM levels of dogs with severe dermatitis before therapy were 12.0531 ± 0.5374 µg/mL. After therapy, the mean serum IgM levels decreased by 11.6302 ± 0.7131 µg/mL. The decrease in IgM levels post-therapy showed a significant difference ($p < 0.05$, Table 3).

Table 1. The mean of Immunoglobulin M levels in dogs suffering from mild dermatitis and severe dermatitis

Sample type	Mean serum IgM level (µg/mL)
Mild Dermatitis	12.2885 ± 0.6345[a]
Severe Dermatitis	12.0531 ± 0.5374[a]

[a]: Not significantly different ($p > 0.05$).

Table 2. The mean of Immunoglobulin M levels in dogs with mild dermatitis at pre-therapy and post-therapy

Mild dermatitis	Mean serum IgM level (µg/mL)
Pre-therapy	12.2885 ± 0.6355[a]
Post-therapy	12.3750 ± 0.8254[a]

[a]: Not significantly different ($p > 0.05$).

Table 3. The mean of Immunoglobulin M levels in dogs with severe dermatitis at pre-therapy and post-therapy

Severe dermatitis	Mean serum IgM level (µg/mL)
Pre-therapy	12.0531 ± 0.5374[a]
Post-therapy	11.6302 ± 0.7131[b]

[b]: Real difference ($p < 0.05$).

DISCUSSION

Skin disorders in dogs are a major animal health problem worldwide (Zahri et al., 2024). Dermatitis in dogs is a common condition that can be caused by various factors, such as allergies, bacterial infections, fungi, and parasites (Marsella and De Benedetto, 2017). The IgM is one type of antibody that is first produced by the immune system when exposed to antigens. Serum IgM concentrations in 63 stray dogs with dermatological conditions ranged from 0.59 to 2.08 g/L (Maden et al., 2013). The difference in IgM levels from the results of this study and previous studies is thought to be due to differences in the amount of antigen entering each dog. This condition affects the levels of IgM produced (Laksmi et al., 2019). A study conducted at the Animal Hospital of the Faculty of Veterinary Medicine, Konya, Turkey, showed that IgM levels in 20 healthy dog samples ranged from 0.79 to 2.6 g/L (Maden et al., 2013). Increased IgM levels usually indicate that the immune system is responding to infection or antigen invasion. This is especially relevant in cases of dermatitis, where bacterial or parasitic infections may be the cause of this increase (Maden et al., 2013).

Initially, the immune response is dominated by TH2 cells and involves cytokines, such as IL-4, IL-5, IL-6, IL-13, and IL-31 (Drechsler et al., 2024). IL-4, IL-5, IL-6, IL-13, and IL-31 influence IgM production by regulating B cell activity and adaptive immune pathways. IL-6 plays a major role in supporting IgM production during the early phase of the immune response by inducing B cell activation. In contrast, IL-4 and IL-13 promote isotype switching from IgM to other antibodies, such as IgG or IgE, thereby reducing IgM production in the later phase. IL-31, although associated with chronic inflammation, has an indirect effect on IgM production through the regulation of Th2 cells. TH2 cells are known to play a role in supporting antibody production and the process of immunoglobulin class switching (Nutta et al., 2019). After activation, T lymphocytes will stimulate B lymphocytes by releasing cytokines that trigger the proliferation and differentiation of B lymphocytes. B lymphocytes that recognize antigens through the B cell receptor (BCR) will continue their function with support from T lymphocytes. At this stage, B lymphocytes will differentiate into plasma cells that produce IgM antibodies. Several components of the humoral immune system, such as IgA, IgG, IgE, and IgM, as well as elements of the cellular immune system, including interleukin-2 (IL-2) and IL-10, are also known to contribute to the development of dermatitis (Bou Zerdan et al., 2021).

In mild dermatitis, the immune system works efficiently to manage local antigens, combat pathogens, and protect against infection. IgM, one of the first immunoglobulins produced in response to antigens, plays a role in supporting the initial defense against microorganisms that enter through mildly damaged skin (Xia et al., 2023). In mild dermatitis, inflammation is typically localized and well-regulated, allowing B lymphocytes responsible for IgM production to function normally. In contrast, severe dermatitis involves a more complex and chronic inflammatory response. This response is regulated by cytokines, which play a pivotal role in mediating both pro-inflammatory effects, such as interleukins IL-1, IL-6, IL-8, tumor necrosis factor (TNF), and interferon (IFN)-γ, as well as anti-inflammatory effects such as IL-10 (Tosi et al., 2024). Increased levels of pro-inflammatory cytokines, such as IL-6 and TNF-α can interfere with B cell activity, potentially reducing IgM production (Liu et al., 2021). Severe inflammatory conditions are often accompanied by increased apoptosis or dysfunction of immune cells, including plasma cells responsible for immunoglobulin production (Szymanski et al., 2021). In addition, excessive immune response in severe dermatitis can trigger immunosuppressive mechanisms, such as the release of IL-10 and the activation of regulatory T cells (Tregs), which aim to reduce inflammation and indirectly suppress the production of antibodies, such as IgM (Agrawal et al., 2011). In mild dermatitis pre-therapy, although the immune response was stimulated by local inflammation, the initial IgM levels may not be too high. This is because, in the early phase of inflammation, the immune system may not be fully active in producing antibodies to combat potential infection or irritation, as mild dermatitis is generally associated with lower levels of inflammation severity (Helen et al., 2021). In mild dermatitis, the immune system is only exposed to a small number of antigens, so the immune response tends to be weaker. As a result, B-cell activation and IgM production are limited. Therapeutic management for dogs with mild dermatitis usually involves the use of antiparasitic drugs, such as ivermectin and antihistamines. Ivermectin is often used to treat a variety of parasitic infestations in dogs, including mites that cause conditions such as demodectic mange and scabies. However, its use should be approached with caution due to the potential for serious side effects, especially in certain breeds (Hermawan et al., 2024). Antihistamines are often prescribed to reduce the itching (pruritus) caused by allergic reactions in canine dermatitis. However, their use should be tailored to the needs of each case, and other treatment options may be considered depending on the individual dog's response (Outerbridge and Jordan, 2021). After therapy, these drugs reduce immune and inflammatory activity, which reduces the production of immune cells involved in the initial inflammatory response. Once the inflammation is under control, the body begins to produce more IgM as an additional protective measure, helping the body ward off possible infections or allergies that arise after the skin repairs (Wilson et al., 2019).

Before therapy, dogs with severe dermatitis usually have widespread inflammation throughout their body. This causes an increase in IgM production, as the immune system attempts to respond to tissue damage or the presence of

large amounts of antigen. In cases of severe dermatitis, secondary infections or exposure to large amounts of antigen occur, stimulating B cell activation. This condition causes high levels of IgM production as an initial response to the antigen. Elevated IgM levels pre-therapy reflect an active inflammatory reaction, where the dog's body fights to combat the factors causing severe dermatitis, such as bacteria, stronger allergens, or severe irritation. Treatment for this condition often involves a combination of several drugs, including ivermectin, diphenhydramine HCl, dexamethasone, and amoxicillin (Farhan et al., 2024). In severe dermatitis, corticosteroids work by interacting with glucocorticoid receptors in cells, which in turn affect the expression of genes involved in inflammation and immune system function (Strehl et al., 2019). These mechanisms include inhibition of the production of proinflammatory cytokines, such as IL-6 and TNF-α, as well as regulation of molecular signals important for lymphocyte differentiation and activity (Chen et al., 2023).

The decrease in IgM levels after therapy for severe dermatitis is due to the mechanism of action of the drugs used. Ivermectin, as an antiparasitic, works by eradicating parasites that trigger the immune response (Fahmy et al., 2021). With the elimination of parasites, antigenic stimulation is reduced so that B cell activation and IgM production also decrease. Corticosteroids have potent immunosuppressive properties. This drug suppresses the activity of the immune system, including the process of B cell differentiation into plasma cells that are responsible for producing IgM. The combined effect of these two drugs reduces inflammation and suppresses excessive immune responses so that IgM levels in circulation are significantly reduced after therapy (Indayani et al., 2024). Diphenhydramine HCl is a first-generation antihistamine that functions as an inverse agonist, binding to the H1 receptor to inhibit inflammation caused by histamine (Linton et al., 2023). By blocking histamine, diphenhydramine helps reduce the activation of excessive immune responses. Ivermectin is an antiparasitic that works by interfering with the parasite's nerve function. It works by releasing Gamma Amino Butyric Acid (GABA), which prevents neurotransmitters, causing paralysis in parasites (Pandit and Tarkeshwar, 2023). In addition, ivermectin can have an immunomodulatory effect, potentially affecting IgM levels by reducing immune reactivity (Lotfalizadeh et al., 2022). Diphenhydramine HCl and amoxicillin can also affect the decrease in IgM levels in severe dermatitis through different mechanisms. Diphenhydramine HCl, as an antihistamine, helps reduce symptoms of inflammation, such as itching and swelling, by blocking histamine receptors (Doniec et al., 2024). Although it indirectly affects IgM levels, the decrease in inflammation due to the antihistamine effect can reduce antigenic stimulation that plays a role in B cell activation and IgM production. Amoxicillin, as an antibiotic, works by eliminating bacterial infections that may worsen dermatitis. By reducing the infectious load, the antigenic source is reduced, thereby reducing excessive immune responses, including IgM production (Maslakah and Kusumarini, 2023). By treating the infection, amoxicillin can help reduce high IgM levels due to the immune response to infection. A significant decrease in serum immunoglobulin G titers has been observed following amoxicillin administration (Dufour et al., 2005). The decrease in serum IgM levels after therapy for severe dermatitis also indicates that the therapy is effective in reducing the inflammatory process. Immunoglobulin M is usually produced as an initial response to infection or inflammation, so this reduction or decrease in IgM levels may indicate that the inflammatory process underlying dermatitis has been controlled (Saghazadeh and Rezaei, 2020). Some therapies for dermatitis, such as the use of corticosteroids, are known to affect the composition of immunoglobulins (Mustafa, 2023). Administration of corticosteroids can cause a decrease in IgM levels in the body because corticosteroids have an immunosuppressive effect, which can inhibit the immune response and antibody production, including IgM (Hussain and Khan, 2022). This finding indicates that treating dermatitis with various drugs can affect the formation of IgM.

The limitation of this study was the absence of a control group because the use of a control group requires more resources, including time, cost, and access to healthy dogs without dermatitis. It is difficult to ask permission from healthy dog owners to have their dogs' blood taken for research. The second was the passive sample collection method, namely waiting for the owner of a dermatitis dog to come to the clinic; this caused the samples used in this study to be small. This study only focuses on IgM levels alone, not using other immune parameters because researchers want to focus on the results of IgM levels in dermatitis as an initial picture, and it is hoped that in the future, there will be further research on dermatitis by measuring other immune parameters, such as interleukins and cytokines. The decrease in IgM is regarded as an indicator of effective therapy for controlling inflammation. However, the specific mechanisms linking changes in IgM levels to clinical improvement in dermatitis have not been thoroughly evaluated. Additional studies are needed to clarify and strengthen the causal relationship between IgM reduction and clinical recovery.

CONCLUSION

IgM levels in dogs with mild dermatitis were not significantly higher than those with severe dermatitis. In dogs with mild dermatitis, serum IgM levels pre-therapy were not statistically different compared to post-therapy. However, in dogs with severe dermatitis, serum IgM levels in pre-therapy were significantly higher compared to post-therapy. Further

research is needed, including the use of dermatitis drugs that do not suppress the immune response, and also to check the management practices to prevent dermatitis cases.

DECLARATIONS

Acknowledgments

The authors thank the Udayana University Research and Community Services for funding assistance through the Udayana Flagship Research Grant with Contract Number: B/1.542/UN14.4A/PT.01.03/2023, Laboratory of Immunology, Faculty of Veterinary Medicine, and Faculty of Veterinary Medicine Udayana.

Authors' contributions

Ni Ketut Suwiti designed and analyzed the study. Ni Putu Dyah Prashanti Pusparini collected samples, wrote the manuscript, and analyzed the data. Ida Bagus Kade Suardana and I Nengah Kerta Besung supported the implementation of the study. All authors have read and approved the data and the final draft of the manuscript.

Competing interests

The authors have not declared any conflict of interest.

Funding

This study was partially funded by the Institute for Research and Community Service, Udayana University, Bali, Indonesia.

Ethical considerations

The authors confirm that all authors have reviewed and submitted the manuscript to this journal for the first time. Additionally, all authors checked the originality of data and sentences via plagiarism checkers.

Availability of data and materials

The original data presented in the study are included in the article. For inquiries, please contact the corresponding author.

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