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Evaluation of oxidative stress in dogs with demodicosis

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ABSTRACT

Objective: To investigate the effects of oxidative stress in dogs with demodicosis.

Materials and Methods: The material of the study was based on a total of 32 owned dogs, of which 21 were diagnosed with demodicosis and 11 were healthy, with different ages, genders, and breeds. Demodex examination for diagnostic evaluation was performed by examining samples under the microscope that were taken using the trichogram and deep skin scraping methods. In order to evaluate the effects of oxidative stress in dogs with demodicosis in the pre- and post-treatment groups and the control group without demodex diagnosis, the superoxide dismutase (SOD), glutathione peroxidase (GPX), and glutathione (GSH) values, as antioxidants and malondialdehyde (MDA) as an oxidant, were investigated.

Results: In the clinical examinations, manifestations such as alopecia, erythema, generalized pruritus, hyperpigmentation, lichenification, pododermatitis, interdigital pruritus, and lymphadenopathy were observed in the dogs with demodicosis both pre- and post-treatment. In the analyses performed in order to evaluate the oxidative stress, MDA: 20.30 nmol/mL, GSH: 4.9 nmol/mL, GPx: 0.42 U/L, and SOD: 4.1 U/L were measured in the dogs with clinical demodicosis. Post-treatment, the average values in the same dogs were measured as MDA: 6.08 nmol/mL, GSH: 8.11 nmol/mL, GPx: 0.83 U/L, and SOD: 6.67 U/L, while in the control group, they were measured as MDA: 4.94 nmol/mL, GSH: 9.73 nmol/mL, GPx: 0.97 U/L, and SOD: 7.20 U/L. It was determined that the GSH, GPx, and SOD values in the control and post-treatment groups were significantly higher ($P < 0.001$) and the MDA values were lower ($P < 0.001$) than in the clinical demodicosis group.

Conclusion: In dogs with clinical demodicosis, when compared to the control and post-treatment groups, higher levels of MDA, which is an oxidant, and lower levels of GSA, GPx, and SOD, which are antioxidants, showed that demodex caused oxidative stress in the dogs..

Keywords: *Dermatitis, demodex, scabies, antioxidant, oxidative stress, oxidant*

INTRODUCTION

Demodex is a member of the Acari subclass of the Arachnida class of arthropods. These mites are considered a part of the normal skin microbiome of most mammals, including dogs (Gökalp and Kırbaş, 2020). Demodicosis in dogs, when the immune system is suppressed, allows the mites to overbreed and leads to the development of clinical signs. This disease is often caused by Demodex canis. However, there are other species, such as Demodex injai and Demodex cornei (Ural et al., 2019). The cause of the disease spends its whole life commensally in the skin, in the hair follicles placed on the head area, and in the follicles of the

sebaceous and embedded in the Meibomian glands. The agent cannot be separated from its host. All life stages of the agent can be found simultaneously in a follicle. The completion duration of the life cycle varies between 18 and 24 days (Hnilica and Petterson, 2017).

On the host, it completes its effective life cycle within the hair follicles and related glands. Demodex agent serum feeds on cells and debris (Aytuğ, 2012). In some generalized demodicosis patients, pyoderma occurs secondary to the overbreeding of pathogens such as Malassezia and Staphylococcus species, possibly due to the immunosuppressive effect on the skin microenvironment of the dog affected by the disease. In such cases, it is necessary to treat it with antibiotics suitable for the structure of the skin (Pekmezci et al., 2014).

Under natural circumstances, demodicosis symptoms are rarely seen. When occlusion and/or enlargement of the ostia of hair follicles and hyperpigmentation are observed, these clinical findings should be a clue to the disease (Mueller et al., 2020). During a dermatological examination, along with diffuse alopecia, seborrhea, epidermal choleretic also mediocre papulopustular dermatitis, comedones, and hyperpigmented macules can be seen (Hillier and Desch, 2002). In this disease, the proliferation of Demodex canis in the hair follicles can cause hair loss, inflammation of the hair follicle and sebaceous gland, and in severe forms, bleeding crusts and furunculosis. (Hnilica and Petterson, 2017). Pododemodicosis is characterized by interdigital pruritus, pain, erythema, alopecia, hyperpigmentation, lichenification, scaling, crusting, pustules, bullae, and drainage channels. Peripheral lymphadenopathy is common. If secondary bacterial sepsis develops, systemic findings (e.g., fever, depression, anorexia) may occur (Hnilica and Petterson, 2017). Among the clinical symptoms of the disease, there are dyskeratosis, malodor, alopecia, erythema, papules and pustules, hyperpigmentation, comedones, and secondary bacterial infection (Sgarbossa et al., 2017).

If it is not treated, hyperpigmentation and lichenification, with increased body odor due to excessive sebum production from the sebaceous glands related to hair follicles, can also arise in these patients (Mueller, 2004).

Oxidative stress can be defined as the phenomenon of cell and tissue damage as a result of the imbalance between oxidant/antioxidant substances in the body (Puppel et al., 2015). Oxidant/antioxidant balance causes piling of oxidant substances in cellular structure and molecules and failure of various physiological events by creating oxidative stress due to increased production of free radicals and deterioration of antioxidants in consequence of them being inactive or insufficient (Tabakoğlu and Durgut, 2013). Therefore, in the evaluation of oxidative stress in the body, the determination of antioxidant consumption can be made by determining the decrease in antioxidant grades or the increase in their metabolites (Puppel et al., 2015).

The leading mechanism of free radical toxicity is the peroxidation of membrane phospholipids pioneered by the creation of lipid peroxides or hydroperoxides, and peroxide radicals are formed to initiate a chain reaction (propagation) in the presence of oxygen (Abd Ellah, 2011). Lipid peroxides (lipid peroxide, cyclic peroxide, and cyclic endoperoxide), created as a result of lipid peroxidation reactions, eventually transform into aldehydes called malondialdehyde (MDA), 4-Hydroxinonenal (HNE), and hexanal, which are secondary or end products (Özcan et al., 2015). MDA is the final product that is formed as a result of the enzymatic or non-enzymatic disintegration of arachidonic acid and larger polyunsaturated fatty acids (PUFA) (Aslankoç et al., 2019).

The defense systems serving in the body to prevent the creation of reactive oxygen species, prevent the damage caused by these substances and provide detoxification are called antioxidant defense systems (Aslankoç et al., 2019). Antioxidants can be examined under two classes, as endogenous and exogenous. Endogenous antioxidants are divided into two categories, as enzymatic and nonenzymatic. Whereas the enzymatic antioxidants are superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and glutathione reductase (GR); glutathione, melatonin, uric acid, albumin, and selenium, and they can be numbered among nonenzymatic antioxidants (Küçük, 2021).

Demodicosis in dogs comprises an important part of dermatological events in veterinary clinics in Turkey and around the World. The disease has a strong relationship with the immune system and other diseases. Oxidative damage formed as a result of oxidative stress is seen as the main cause of diseases characterized by tissue dysfunctions, such as aging, cardiovascular diseases, immune system diseases, degenerative diseases, and cancer. This

study, performed in light of all of this information, aimed to investigate whether oxidative stress is affected in demodicosis events observed in dogs and whether it plays a role in the pathogenesis of the disease or not.

MATERIALS and METHODS

This study was granted the approval of Kırıkkale University Animal Experiments Local Ethics Committee (decision numbered 44, dated 24.11.2021).

The animal material

The animal material of the study was based on a total of 32 dogs, of which 21 were diagnosed with demodicosis and 11 were healthy, with different ages, genders, and breeds, which were brought to Kırıkkale University Veterinary Faculty Training and Research Hospital.

Diagnosing demodicosis

In the presence of clinical symptoms on the skin when widely developed pruritic papulopustular lesions, crusting, and locally alopecia foci were observed, skin scrapings were taken from suspected animals to determine the causative agent and to diagnose them. To take the skin scraping samples from the clinically suspected dogs, the skin on the area with the lesion to be scraped was folded as much as possible, to soften the area, paraffin liquid was dripped on the area and the skin with the lesion was scraped using a scalpel until capillary bleeding occurred. Simultaneously, the hair on the lesioned area and around that area were pulled off together with their roots.

The scraped material sample and the hair pulled off together with their roots were placed on a slide. Mineral oil and 10% KOH solution were dripped on it then the preparate and the slide were covered after it was crushed thoroughly. The prepared preparate was examined under a light microscope at 10x and 40x magnifications. In the microscopic examination, the adult and developmental forms of Demodex spp. were detected on the samples taken from the dogs. In the treatment of demodicosis, until clinical improvement and a negative scraping result were obtained, Sarolaner (Simparica, Zoetis) at a dose of 3 mg/kg was orally given to the dogs, once a month.

Creating the workgroups

A total of 21 dogs diagnosed with demodicosis constituted the treatment group and 11 healthy dogs constituted the control group. For the laboratory analyses, two samples of blood were drawn, before and after treatment, from the treatment group, and the blood was drawn from the control group once. Within the scope of the study, the obtained results were examined in 3 groups, as before the Demodicosis treatment (Group 1), after the Demodex treatment of the same dogs (Group 2), and the control group.

Laboratory analyses

To evaluate oxidative stress from all of the animals, 4 mL-blood samples taken from the vena cephalica antebrachi into coagulation-activating straight tubes were centrifuged at 3500 rpm for 10 min and serum samples were extracted. The serum samples were stored at –18 °C until the analysis was performed. Each serum sample removed from the freezer and allowed to thaw until reaching 4 °C before analysis, and then they were allowed to reach room temperature. To evaluate the oxidative stress in the serum samples, the malondialdehyde (MDA) (Yoshioka et al., 1979), glutathione (GSH) (Beutler et al., 1963), glutathione peroxidase (GPx) (Paglia and Valentine, 1967), and superoxide dismutase (SOD) (Sun et al., 1989) activities were measured in accordance with their methods.

Statistical Analyses

The required sample size for the study, for all 3 groups, was calculated as 53 samples, whereas the effect size between the best and worst groups in the received responses was f = 0.50, with a power of 0.95 on error levels Type I $\propto\circledcirc$= 0.05 and Type II β = 0.05. Power Ver 3.00.10 (G*Power, Franz Foul, Universität Kiel, Germany) was used for the sample size and power analysis. The values obtained in the study were transferred to a computer environment and thereby descriptive statistical information (average, standard deviation, etc.) was obtained. The suitability of the measurement and scoring values to the normal distribution were examined graphically and using the Shapiro-Wilk test. It was observed that normal distribution occurred in all of the groups. Although the study seemed to be for three groups, pairwise comparisons were also made according to whether the groups were dependent or independent. The paired samples T-test was used for the statistical evaluation of the data in the pre-treatment group (n=21) and the post-treatment group (n=21). The independent sample T-test was used for the evaluation of the data in the treatment group (pre and post-treatment) and the data in the control group (n=11). As a result of the performed

statistical tests, p<0.05 was accepted as statistically significant.

RESULTS

Clinical findings: In the study, it was determined that the clinical findings of the study groups considerably varied based on the severity and type of disease. While there were no clinical dermatological lesions in the control group dogs, clinical pictures such as alopecia, erythema, generalized pruritus, hyperpigmentation, lichenification, pododermatitis, interdigital pruritus, and lymphadenopathy were observed in the pre- and post-treatment groups (Table 1).

Table 1. Clinical findings of treatment groups.

Clinical findings	Pre-treatment Group (n=21)	Post-treatment Group (n=21)	Control Group (n=11)
Alopecia	80%	19%	-
Erythema	71.4%	4.7%	-
Generalized Pruritus	57.1%	9.5%	-
Hyperpigmentation	38%	9.5%	-
Lichenification	23.8	9.5%	-
Pododermatitis	14.2%	9.5%	-
Interdigital Pruritus	9.5%	4.7%	-
Lymphadenopathy	4.7%	0%	-

Laboratory findings: The clinical findings of the treatment group, control group, and pre- and post-treatment groups, and the average of the groups constituted based on the diagnostic classification result along with their minimum and maximum values and their statistical significance are given in Tables 1 to 5, respectively.

The MDA levels were statistically significantly different (p<0.001) in the 21 dogs in the pre- and post-treatment groups. The arithmetic average and standard deviations of the MDA levels for all of the groups are given in Table 2. The difference between the MDA levels of the pre-treatment group compared to the control group was statistically significant (p<0.001). The difference between the MDA levels of the post-treatment group compared to the control group was not statistically significant (p>0.05).

The GSH levels were statistically significantly different (p<0.001) in the 21 dogs in the pre- and post-treatment groups, and the arithmetic average and standard deviations for all of the groups are given in Table 3. The difference between the GSH levels of the pre-treatment group compared to the control group was extremely statistically significant (p<0.001). The difference between the GSH levels of the post-treatment group compared to the control group was not statistically significant (p>0.05).

Table 2. Levels of MDA (nmol/mL) in the treatment and control groups.

MDA (nmol/mL)	n	$\bar{x} \pm S\bar{x}$	p-value
Pre-treatment (PRT)	21	$20.30^{a} \pm 4.18$	PRT-PST = <0.001
Post-treatment (PST)	21	$6.08^{b,c} \pm 1.86$	PRT-C = <0.001
Control (C)	11	$4.94^{b,c} \pm 1.58$	PST-C = >0.05

Table 3. Levels of GSH (nmol/mL) in the treatment and control groups.

GSH (nmol/mL)	n	$\bar{x} \pm S\bar{x}$	p-value
Pre-treatment (PRT)	21	$4.90^{a} \pm 1.25$	PRT-PST = <0.001
Post-treatment (PST)	21	$8.11^{b,c} \pm 1.47$	PRT-C = <0.001
Control (C)	11	$9.73^{b,c} \pm 2.04$	PST-C = >0.05

Table 4. Levels of GPx (U/L) in the treatment and control groups.

GPx (U/L)	n		P-value
Pre-treatment (PRT)	21	$0.42^{a} \pm 0.18$	PRT-PST = <0.001
Post-treatment (PST)	21	$0.83^{b,c} \pm 0.21$	PRT-C = <0.001
Control (C)	11	$0.97^{b,c} \pm 0.15$	PST-C = >0.05

Table 5. Levels of SOD (U/L) in the treatment and control groups.

SOD (U/L)	n	$\bar{x} \pm S\bar{x}$	p-value
Pre-treatment (PRT)	21	$4.10^{a} \pm 1.04$	PRT-PST = <0.001
Post-treatment (PST)	21	$6.67^{b,c} \pm 1.02$	PRT-C = <0.001
Control (C)	11	$7.20^{b,c} \pm 0.99$	PST-C = >0.05

The arithmetic average and standard deviations of the GPx levels for all of the groups are given in Table 4. The GPx levels were statistically significantly different (p<0.001) in the 21 dogs in the pre- and post-treatment groups. The difference between the GPx levels of the pre-treatment group

compared to the control group was extremely statistically significant ($p<0.001$). The difference between the GPx levels of the post-treatment group compared to the control group was not statistically significant ($P > 0.05$).

The SOD levels were statistically significantly different ($p<0.001$) in the 21 dogs in the pre- and post-treatment groups. The arithmetic average and standard deviations of the SOD levels for all of the groups are given in Table 5. The difference between the SOD levels of the pre-treatment group compared to the control group was extremely statistically significant ($p<0.001$). The difference between the SOD levels of the post-treatment group compared to the control group was not statistically significant ($p<0.05$).

DISCUSSION

Demodicosis is a skin disease caused by the ectoparasite Demodex (Demodecidae), which prognoses typically include hair loss, inflammation of the hair follicles, and sebaceous glands. Demodicosis is one of the most common skin diseases in veterinary medicine (Beyazıt et al., 2010).

Even though the diagnosis of dog demodicosis is easy to make, it can be difficult due to the healing duration, defining the underlying causes, the need for healing, the owner's expectations (time and financial commitments), and the requisite for frequent follow-up. Therefore, it is important to analyze the disease mechanism and the treatment process in more detail. Although the general complaint of the patients is alopecia, pruritus may not be observed in cases without secondary skin infection or allergy. If it is not treated, hyperpigmentation and lichenification with increased body odor due to excessive sebum production from the sebaceous glands related to hair follicles can also arise in these dogs.

While constituting the control group within the scope of the study, routine clinical cases which are been brought to the clinic for control and vaccination purposes were preferred. During the performed physical examinations, care was taken that all vital functions complied with the healthy animal profile. The clinical findings detected in the dogs with demodicosis (n=21) with the missing predisposition of gender and breed included in the study, were determined as alopecia, erythema, generalized pruritus, hyperpigmentation, lichenification, pododermatitis, interdigital pruritus, and lymphadenopathy. In addition to that, these clinical findings varied in each animal, which showed similarity to the study of Ural et al. (2019). The correlation between the number of mites detected in the microscope field and the prognosis of the disease was not related to the hypothesis and was not included in the study.

Abdulaziz et al. (2019) explained the mechanism of the hypersensitivity reaction as hyperkeratinization of the tissue in the affected area, and along with the free radical production oxidative stress was increased. They observed an increase in erythema, alopecia, severe inflammation of the skin, and allergic reactions when the free radicals took effect. Biological indicators of oxidative stress, even the measurement of antioxidant substances in serum or tissues, may lead to new findings from studies showing the relationship between free radicals and diseases as a cause or an effect of pathological conditions (Russo and Bracarense, 2016). Dündar and Aslan (2000) stated that routinizing the measuring the antioxidant values, which are biomarkers, making them more specific markers, and creating the relevant reference values were an important step in resistance to pathogens, geriatric process, condition, physiological activity, exercise life, efficiency, diagnosis, prognosis, therapy, determining and directing the protective treatment.

Sahin et al. (2004), in their submitted study, determined that oxidative stress and lipid peroxidation activities were increased in patients with dermatological problems, and plasma MDA, which is an indicator of oxidative stress, was higher in the pre-treatment group than in the post-treatment group. They also determined that contrary to the plasma MDA level, the level of GSH-Px, which is an antioxidant enzyme, was increased in the post-treatment group when compared to the pre-treatment group. When free radicals are increased in the organism, antioxidants take place and reduce their maleficence. This also indicates that the applied treatment is effective by lowering the plasma MDA level, which is the cause of cell damage and death. Abdulaziz et al. (2019) showed in their study that, regarding oxidative damage, the total antioxidant capacity (TAC) ($p<0.01$) was more significant than SOD ($p<0.05$) and MDA ($p<0.01$). In the same study, a negative correlation was observed between the MDA and SOD levels. In the current study, it was inferred that the higher levels of MDA in the control group held in the pre-treatment group, and this parameter contributed to the severity of the lesions by causing negative

consequences, such as changes in ion permeability and enzyme activity in demodex-related skin lesions. It was also inferred that the levels of MDA in the control group held in the pre-treatment group were a greater contribution to the severity of the lesions by causing negative consequences, such as changes in both ion permeability on demodex-related skin lesions and enzyme activity. Thus, it was thought that the significantly lower amount of these enzymes in the dogs with generalized demodicosis compared to the control group may have occurred due to a deficiency in the antioxidant mechanism in the dogs with severe skin lesions. In addition, it was determined that, contrary to the results of the study of Şahin et al. (2004), this enzyme level, which was determined to be lower in the pre-treatment group, increased after treatment.

In dogs in which the Demodex agent was detected and treatment was started, a decrease in the MDA levels, and increase in the SOD, GSH, and GPx levels were observed in the blood samples examined after signs of recovery were observed. Statistically significant differences were found between the p-values of the dogs with demodicosis and the healthy dogs ($p<0.001$). Dimri et al. (2008) reported that endogenous antioxidant levels were decreased in dogs with localized and generalized demodicosis, and the disease was related to the occurrence of oxidative stress. Salem et al. (2020) asserted that in dogs, there is a relationship between generalized demodicosis and oxidant-antioxidant imbalance. Proof of this relationship demonstrates itself as an increase in the MDA and TAC levels and a decrease in the GPx and CAT levels as a result of reactive oxygen species released because of Demodex infection. Moreover, herein, it was determined that the Demodex agent reduced the antioxidant capacity of the dogs, regardless of generalized or localized demodicosis.

CONCLUSION

In demodicosis in dogs, it was observed that oxidative stress was affected, and by extension, serious changes in the oxidant/antioxidant parameters occurred. It was observed that the oxidant/antioxidant parameters regressed to their normal values in the dogs that were cured with the applied treatment. It inferred that all of the obtained data herein can be used as a guide in future studies.

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Author Contribution Statement: The creation of the study design and the control of the process are carried out by BBY, while the collection of samples and the follow-up of the analysis processes are performed by GNS. Literature research, writing the article and critical reviews are done by BBY and GNS. Both of the authors have read and approved the final version of the article. BBY: Buğrahan Bekir Yağcı; GNS: Gözde Nur Sivel. All authors have read and agreed to the published version of the manuscript.

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