Polish Journal of Veterinary Sciences Vol. 18, No. 2 (2015), 415–424

DOI 10.1515/pjvs-2015-0053

Original article

The influence of non-specific anti-pruritus treatment with cyclosporine A on transepidermal water loss (TEWL) in natural atopic dermatitis in dogs

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Abstract

Atopic dermatitis is a common allergic skin disease in dogs. Monitoring the progress of treatment and the assessment of the severity of disease symptoms are crucial elements of the treatment procedure. One of the common means of assessing the severity of the clinical signs of the disease is the CADESI 03. Research studies have pointed to a possibility of assessing the severity of skin lesions by means of measuring biophysical skin parameters such as TEWL, skin hydration and erythema intensity. The aim of the study was the assessment of changes in TEWL and CADESI values measured in ten different body regions during non-specific anti-pruritus treatment. The examination was performed on ten dogs with atopic dermatitis (age from 2.5 years to 7 years, mean age 3.8 years). The measurements were performed in the following body regions: the lumbar region, the right axillary fossa, the right inguinal region, the ventral abdominal region, the right lateral thorax region, the internal surface of the auricle, interdigital region of the right forelimb, cheek, bridge of nose and the lateral site of antebrachum. A statistically significant decrease in CADESI values was reported starting from the second week of treatment. In the case of the mean TEWL values, a fall was observed after one week of treatment in the ventral abdominal region and the interdigital region, after two weeks of treatment in the axillary fossa and the inguinal region, and after three weeks in the cheek and the lateral thorax region. There was no statistically significant decrease in TEWL values in the course of treatment in four other regions.

Key words: TEWL, CADESI, atopic dogs

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Introduction

Atopic dermatitis is one of the most common allergic skin diseases in dogs. Genetic factors, which manifest themselves in a strong breed and family predisposition to the disease, have been found to play a major role in its pathogenesis. A full pathogenesis is still unknown but it is certain that the disease can be attributed to immunological aberrations and skin barrier dysfunctions (Marshela et al. 2006, 2010, Pin at al. 2008). Aberrations of both structure and function of the epidermis increase the risk of allergy development and intensify changes in the skin (Pin et al. 2008). The treatment of the disease involves, among others, administering systemic anti-pruritics such as glucocorticosteroids or cyclosporin, specific immunotherapy and topical treatment improving skin condition. The treatment is long-lasting and atopic patients receive medical care throughout their lives. Monitoring the progress of treatment is therefore crucial in therapy. The progress of treatment and the severity of symptoms can be monitored by assessing the intensity of pruritus (for example with the PVAS system) (Olivry et al. 2002) and the intensity of skin changes with the CADESI method (Olivry et al. 2007). These methods, although repetitive, have some limitations and heavily depend on the experience of the physician performing the examination (in the case of CADESI) as well as the pet owner (in the case of PVAS). The limitations of these methods result in using such objective methods as the assessment of transepidermal water loss (TEWL), skin hydration, erythema intensity and skin pH. These methods, and especially the assessment of transepidermal water loss, are commonly used with human patients and have recently also been used more widely with animals. The most commonly applied method has been the assessment of TEWL, which was measured in healthy dogs, cats and horses (Shimada et al. 2008, Szczepanik et al. 2011, 2012) as well as in atopic dogs (Hightower et al. 2010, Cornegliani et al. 2012, Marrsella 2012, Zając et al. 2014). The studies have demonstrated that in atopic dogs the parameter takes higher values than in healthy dogs, and that the values are also higher on clinically affected skin. The studies published in 2012 by Marsella and in 2014 by Zając et al. have additionally reported a positive correlation between this parameter and the severity of the clinical signs of the disease as assessed by the CADESI (Marsella 2012, Zając et al. 2014). Furthermore, studies have demonstrated that TEWL values decrease in remission during specific immunotherapy and non-specific anti-pruritus treatment (using cyclosporine) (Cornegliani et al. 2012). A simultaneous decrease in CADESI and TEWL values during local treatment (using hydrocortisone aceponate and polyunsaturated fatty acids) was reported by Eui-Hwa Nam et al. and Tretter and Mueller (Tretter and Mueller 2011, Nam et al. 2012)

The aim of the present study was the assessment of changes in transepidermal water loss in dogs treated with anti-pruritic drugs (cyclosporine A in a dose of 5 mg/kg BW).

Materials and Methods

12 dogs with atopic dermatitis were selected for the study. The age of the animals ranged from 2.5 to 7 years (mean age 3.8). The experimental group comprised 4 females and 8 males. The dogs were of the following breeds: shih tzu, fox terrier, pug, English bulldog, Labrador retriever (n=3), German shepherd (n=2), west highland white terier (n=3). All animals were privately owned and were patients of the Sub-Department of Clinical Diagnostics and Veterinary Dermatology, Faculty of Veterinary Medicine, University of Life Sciences in Lublin(Poland) and of the private veterinary practice Befar in Czeladź(Poland). All the animals were diagnosed with atopic dermatitis using the Favrot diagnostic criteria (set 2) (Favrot et al. 2010). Other inflammatory-pruritic diseases were ruled out on the basis of hair examination, skin scratch tests and elimination diet lasting at least 6 weeks. Animals with medium severe to severe clinical signs of atopy (CADESI > 66) (Olivry et al. 2008) were included in the study.

All dogs were diagnosed for allergy-inducing factors with intradermal tests (Agrolabo, Agroskin RTU 20, Scarmagio, Italy). Positive results were decided to be those assessed as at least 2+ (0-4 scale). Additionally, IgE levels were evaluated according to the manufacturer's instructions (Policheck Allergie Dog Panel, BioCheck GnBH, Munster, Germany).

Biophysical skin parameters assessment was performed in dogs with atopic dermatitis prior to treatment (T0), and then four times at 1-week intervals (T1 after one week of treatment, T2 after two weeks of treatment, T3 after three weeks of treatment, T4 after four weeks of treatment). In the meantime, the animals were treated with cyclosporine (Equoral Teva Pharmaceuticals Poland, 5 mg/kg BW). The assessments were performed after a 60-minute acclimatisation in a room. The temperature in the room was 23+/2°C, and the humidity was 45 +/- 5% (the conditions of using the tewameter TM 300 according to the producer;s instructions are: temperature 10-30°C, humidity 30-70%). The studies were performed in 2012 and 2013. The assessments were made in ten different body regions: the lumbar region, the right axillary fossa, the right inguinal region, the ventral abdominal

region, the right lateral thorax region, the internal surface of the auricle, interdigital region of the right forelimb, cheek, bridge of nose and the lateral site of antebrachum. In each region TEWL was measured. For each region, 10 successful measurements were performed within 30 seconds and the mean value was then calculated. TEWL assessment was carried out using the Courage Khazaka Multi Probe Adapter 5 with the appropriate TEWL probe: Tewameter TM 300 (results in g/m^2 h). During each visit of the animals CADESI was calculated prior to TEWL measurement. The CADESI assessment was performed with the CADESI 03 system (Olivry et al. 2007). All the transepidermal water loss and CADESI assessments were performed by the same person.

Statistical analysis

The Shapiro-Wilk test for normality was used to verify the normal distribution of the results. Statistical differences were calculated between the measurements T0, T1, T2, T3, T4 for the CADESI. For each patient mean TEWL (M TEWL) was calculated during each examination (T0, T1, T2, T3, T4) as the mean value from measurements in 10 different body regions. Statistical differences were calculated between the measurements T0, T1, T2, T3, T4 for the M TEWL. Additionally, differences in TEWL between the measurements T0, T1, T2, T3, T4 were calculated separately for each of ten body regions. A Student t-test was used to estimate the statistical significance of the differences. Also, correlations were calculated between the CADESI score and M TEWL. Correlations were analysed using the Spearman-rank correlation test. All analyses were performed with Statistica 10 software (Statsoft, Tulsa, OK, USA).

Results

CADESI

A gradual decrease in the CADESI score was observed in the course of the treatment. Before the onset of treatment (T0) the mean CADESI score was 173.9, 143 after one week (T1), 115.3 after two weeks (T2), 102.9 after three weeks (T3), and 75.9 after four weeks (T4). After one week of treatment the decrease in the CADESI score was not statistically significant. A statistically significant decrease was found between the result obtained prior to treatment (T0) and the results after two weeks of treatment – T2 ($p=0.002$), three weeks of treatment – T3 ($p=0.0001$), and four weeks of treatment – T4 ($p=0.00002$), as well as between the T1 and T3 scores ($p=0.019$), T1 and T4 scores ($p=0.0015$) and T2 and T4 scores ($p=0.43$). The decrease in the CADESI value between T0 and T4 was 56.3%. The results concerning CADESI values are presented in Fig. 1.

TEWL

Similarly to CADESI, a gradual decrease in the value of the parameter was observed with respect to transepidermal water loss (TEWL). When analyzing the results calculated as the mean score from ten examined body regions (M TEWL), it was found that the value of M TEWL of 35 g/m^2 h at T0 gradually dropped to 25.72 g/m^2 h at T1, 23.99 g/m^2 h at T2, 20.97 g/m^2 at T3 h, and to 20.55 g/m^2 h at T4. Statistically significant differences were noted between M TEWL before the onset of treatment (T0) and T1 ($p=0.03$), T2 ($p=0.019$), T3 ($p=0.003$), T4 ($p=0.001$). The obtained results are shown in Fig. 2.

Analysing the changes of TEWL values in different body regions, a gradual decrease in value of the parameter was observed in most regions. As far as the interdigital region is concerned, the TEWL value at the beginning of the treatment (T0) was 68.28 g/m^2 h, at T1 – 31.70 g/m^2 h, at T2 – 31.14 g/m^2 h, at T3 – 29.81 g/m^2 h, and at T4 – 28.57 g/m^2 h. Statistically significant differences were reported between T0 and T1 ($p=0.013$), T2 ($p=0{,}00056$), T3 ($p=0{,}0003$), T4 ($p=0{,}0002$) .The obtained results are presented in Fig. 3.

As regards TEWL measured in the cheek, a gradual decrease in the value of the parameter was noted. At T0 it was 34.76 g/m^2 h, at T1 32.59 g/m^2 h, at T2 29.89 g/m^2 h, at T3 21.14 g/m^2 h, and at T4 20.77 g/m^2 h. Statistically significant differences were reported between T1 and T3 ($p=0.018$) and between T1 and T4 ($p=0.019$). The results are provided in Fig. 4.

In the case of the lateral thorax region, there was a decrease in TEWL value up to the third week of treatment (T3), after which a growth was observed (T0 – 35.67 g/m^2 h, T1 – 27.15 g/m^2 h, T2 – 27.79 g/m^2 h, T3 – 19.86 g/m^2 h, T4 – 22.77 g/m^2 h). Statistically significant differences were observed between T0 and T3 ($p=0.044$). The results are shown in Fig. 5.

With respect to TEWL assessed in the ventral abdominal region, it was 32.91 g/m^2 h at T0, 15.81 g/m^2 h at T1, 15.04 g/m^2 h at T2, 15.49 g/m^2 h at T3, and 10,54 g/m^2 h at T4. Statistically significant differences were reported between the values at T0 and T1 ($p=0.031$), T2 ($p=0.029$) and T4 ($p=0.0046$). The results are presented in Fig. 6.

In the case of the inguinal region a gradual decrese in TEWL was reported to and the values were

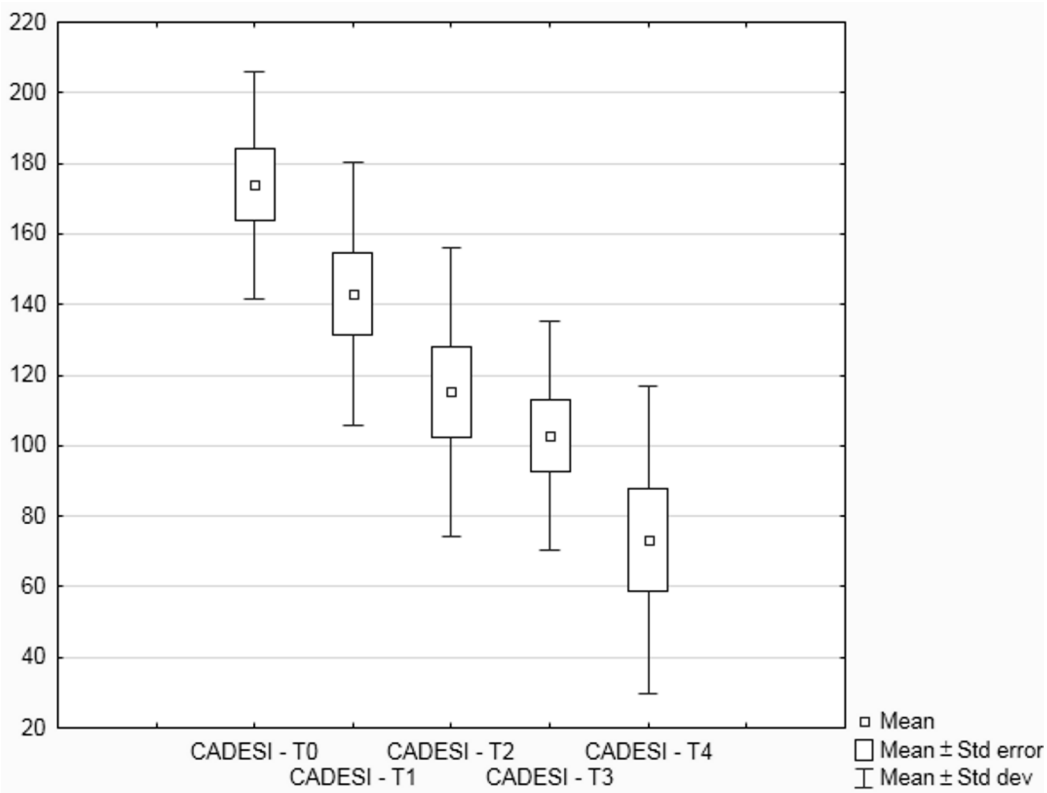

Fig. 1. Changes in CADESI values in the course of treatment.

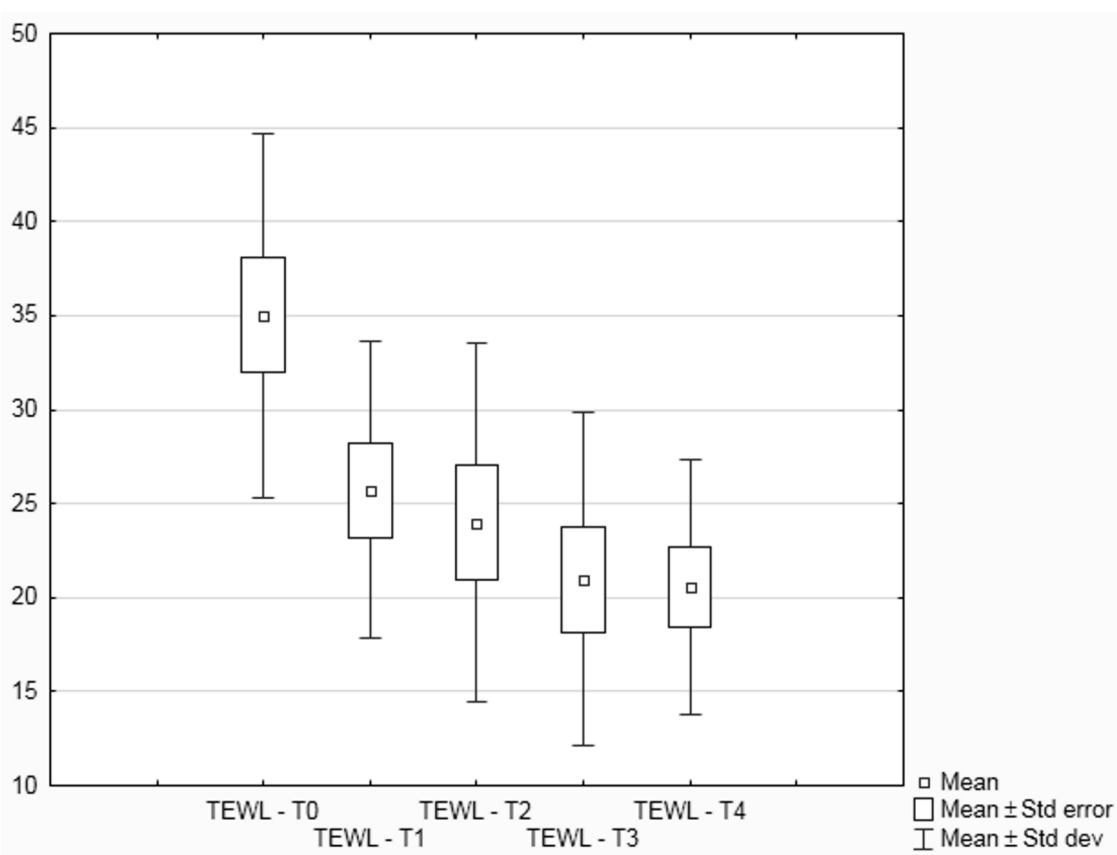

Fig. 2. Changes in mean TEWL values in dogs in the course of treatment.

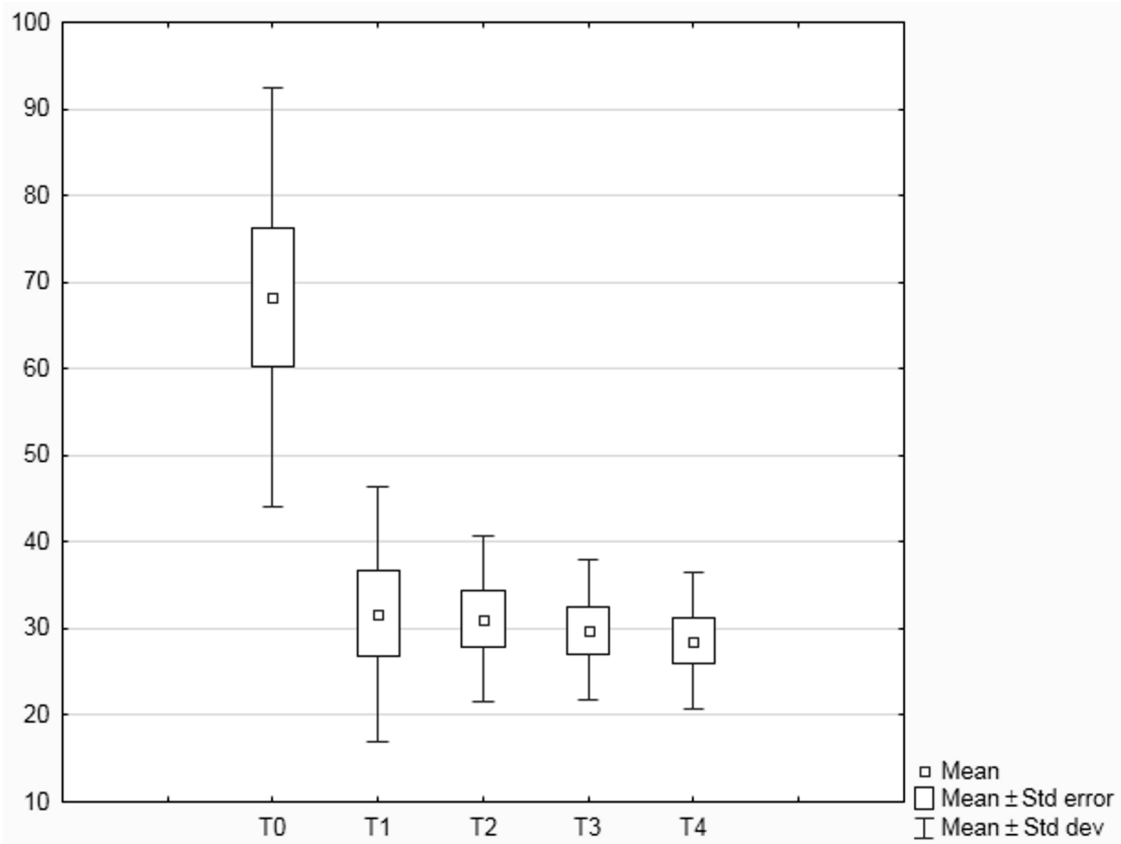

Fig. 3. Changes in TEWL values in the interdigital region in the course of treatment.

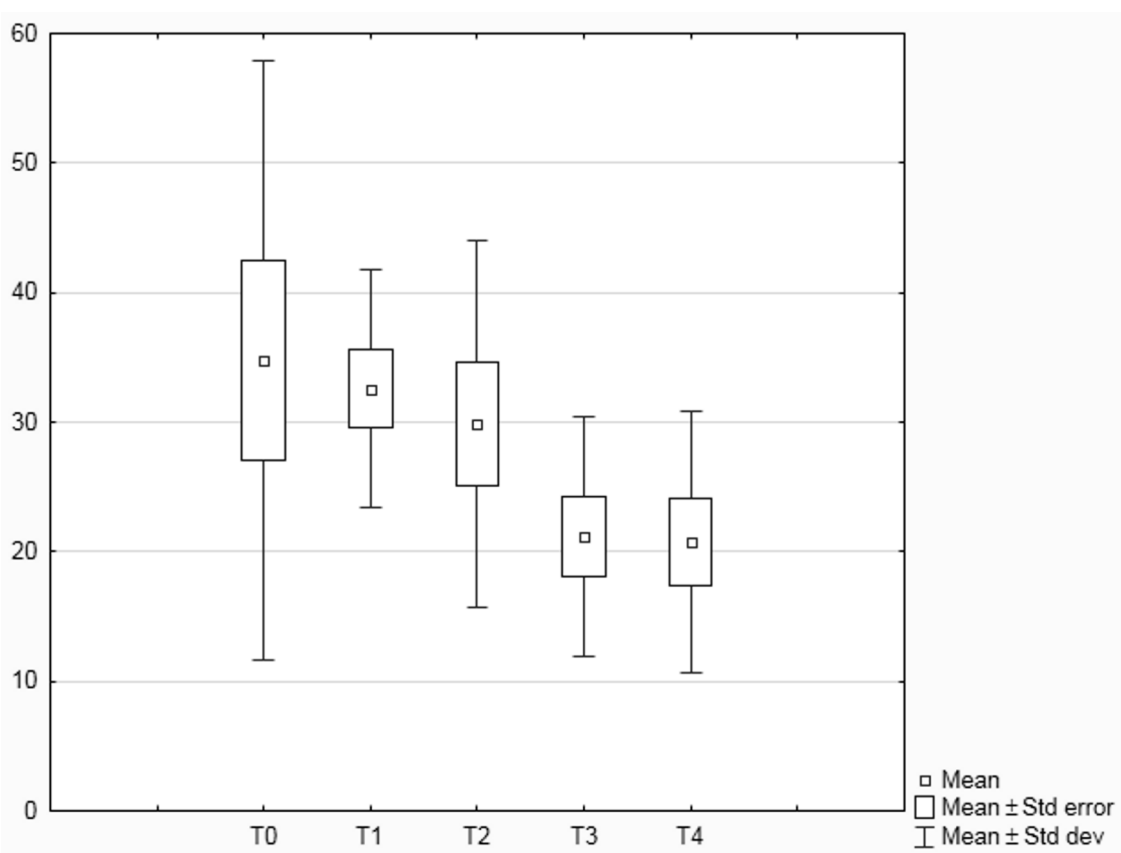

Fig. 4. Changes in TEWL values in the cheek in the course of treatment.

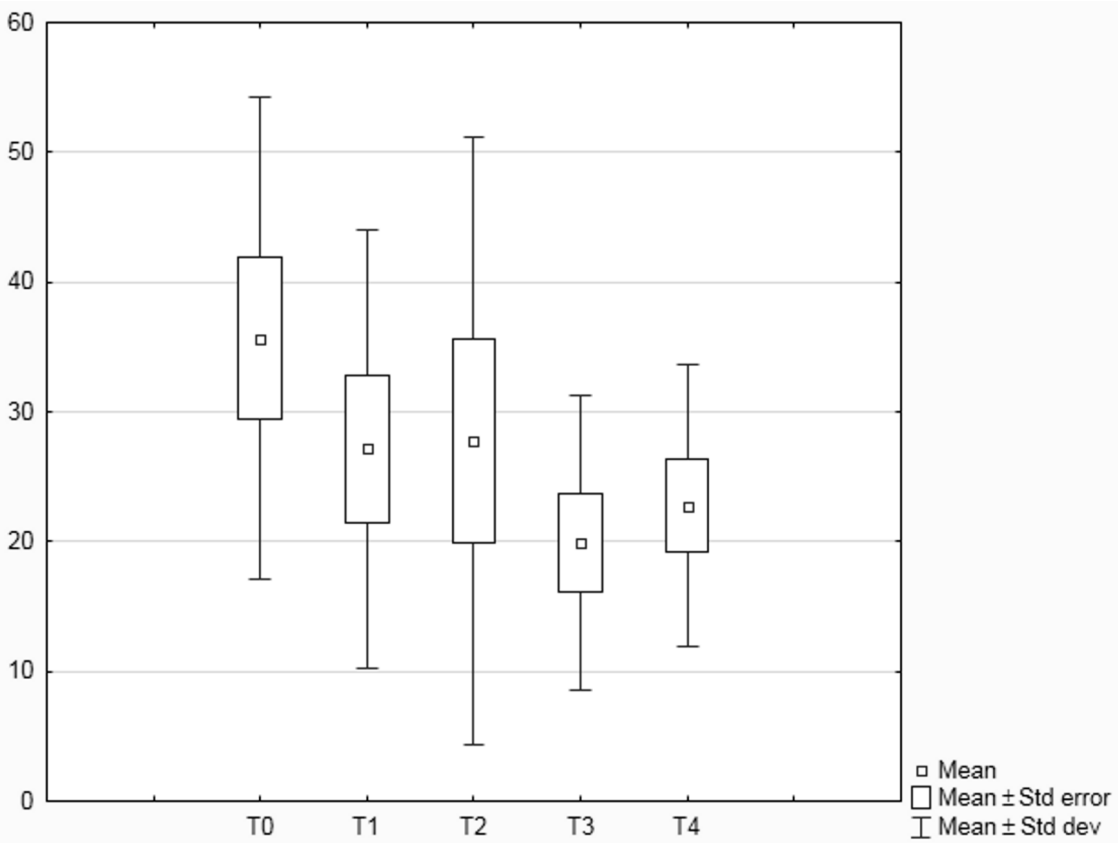

Fig. 5. Changes in TEWL values in the lateral thorax region in the course of treatment.

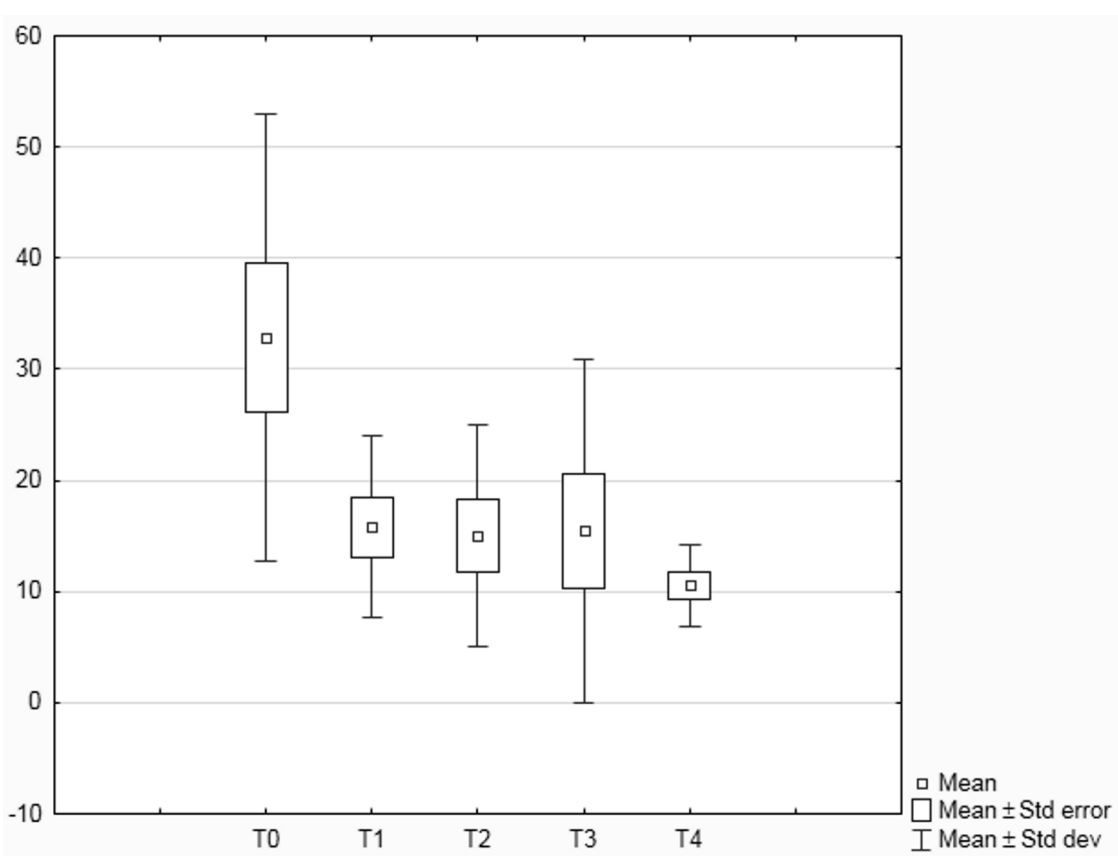

Fig. 6. Changes in TEWL values in the central abdominal region in the course of treatment.

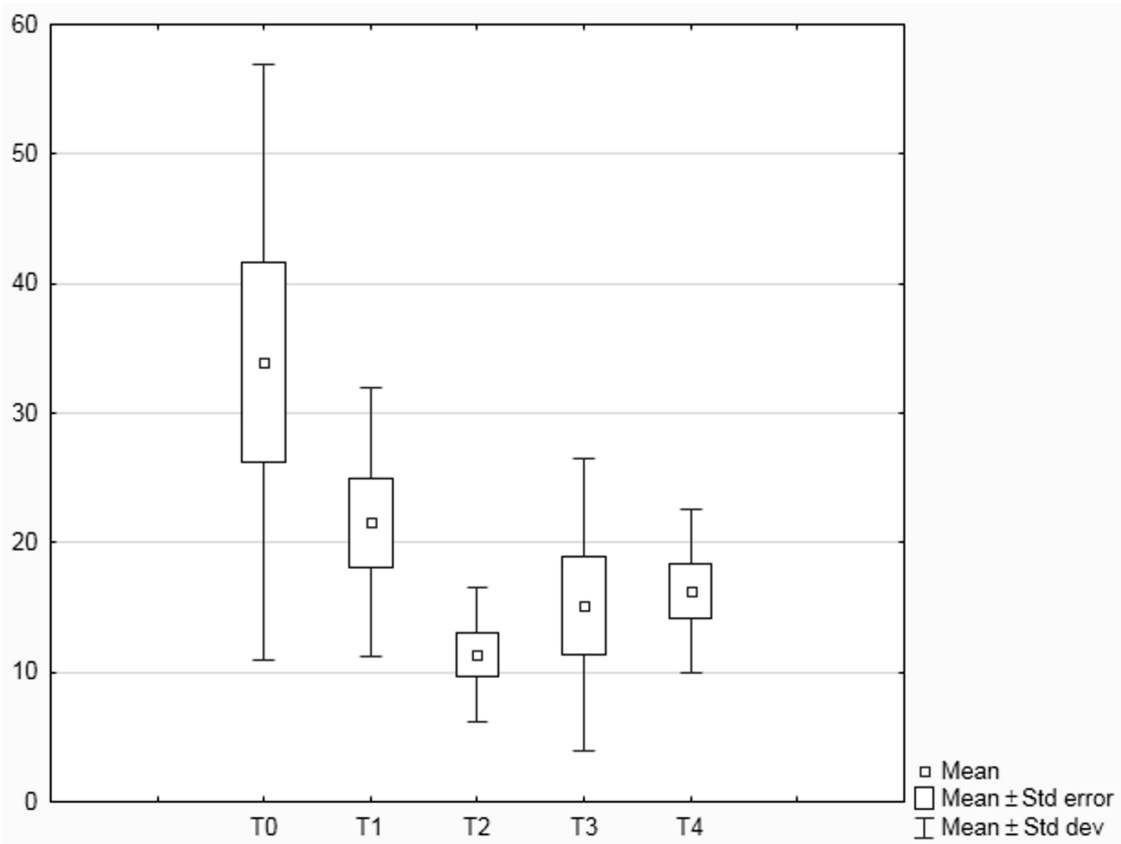

Fig. 7. Changes in TEWL values in the inguinal region in the course of treatment.

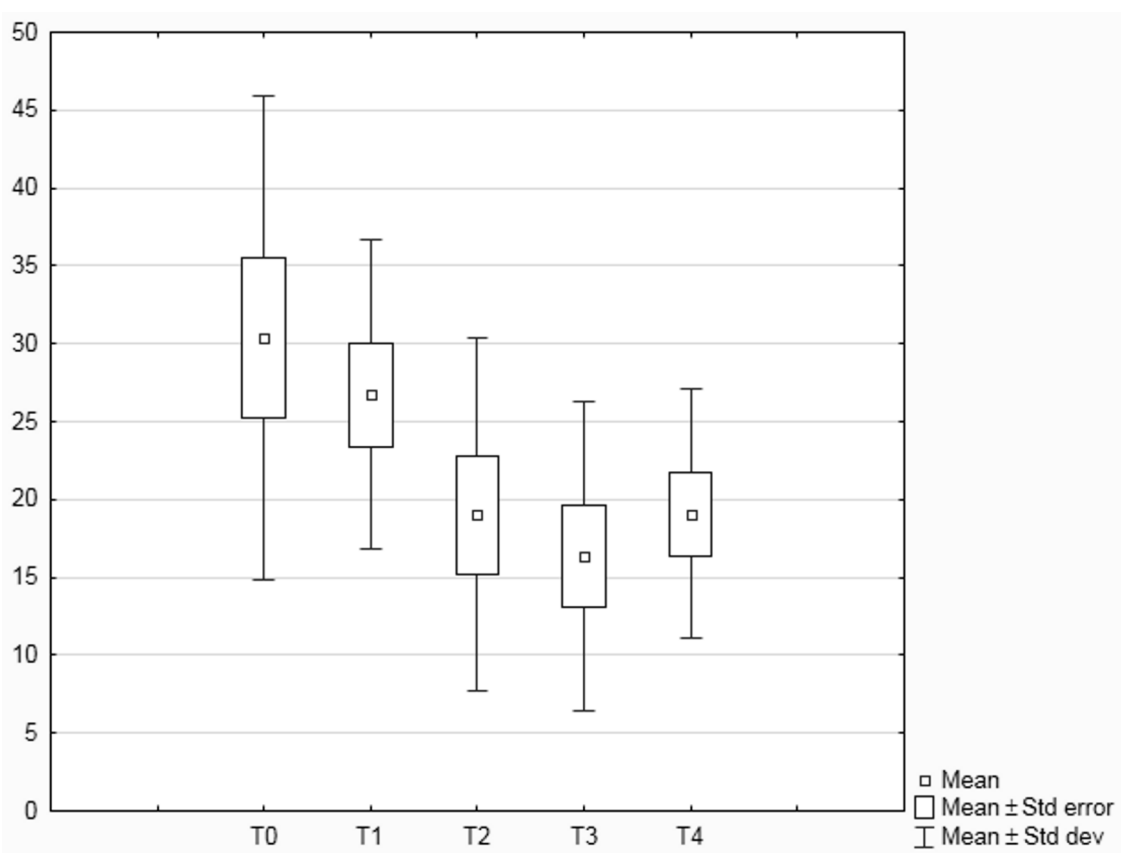

Fig. 8. Changes in TEWL values in the axillary fossa in the course of treatment.

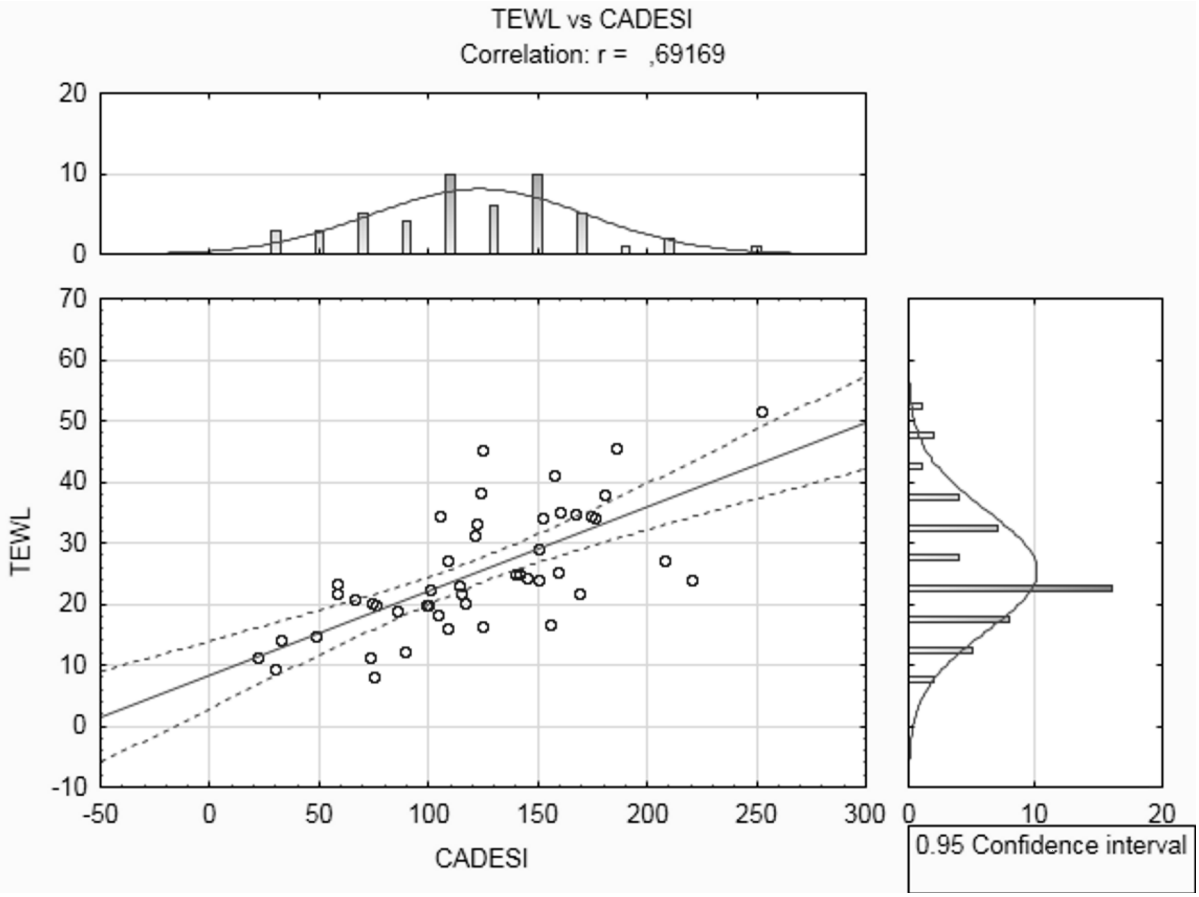

Fig. 9. Correlation between M TEWL and CADESI.

33.93 g/m^2 h at T0, 21.56 g/m^2 h at T1, 11.37 g/m^2 h at T2, 15.17 g/m^2 h at T3, and 16.25 g/m^2 h at T4. Statistically significant differences were reported between the values at T0 and T2 (p=0.01) and T4 (p=0.04) and between T1 and T2 (p=0.018). The results are given in Fig. 7.

As regards the results obtained in the axillary fossa, TEWL values gradually dropped up to the third week of treatment, similarly to other body regions referred to above. However, the value in the last measurement slightly rose. The values were 30.36 g/m^2 h at T0, 26.72 g/m^2 h at T1, 19.02 g/m^2 h at T2, 16.34 g/m^2 h at T3, and 19.08 g/m^2 h at T4. Statistically significant differences were reported between the values at T0 and T3 (p=0.036) and between T1 and T3 (p=0.041) The obtained results are shown in Fig. 8.

As regards the remaining body regions, i.e. the lumbar region, bridge of nose, the internal surface of the auricle, and the lateral site of antebrachium there were no statistically significant differences noted in TEWL values in the course of treatment and these results are therefore not provided in graphs.

Correlations

When calculating the correlations between the CADESI index and M TEWL, there were significant correlations found between the CADESI score and M TEWL (r=0.69 at p=0,05).

Discussion

During cyclosporine A treatment of atopic dogs with a dose of 5 mg/kg BW it was observed that the CADESI values decreased gradually which was an indication of improvement in skin condition. The effectiveness of cyclosporine in atopic dermatitis treatment was previously confirmed by numerous research (Stefan et al. 2003, Taszkun 2010, Kowalik et al 2011) and estimated to be 30-83% after 4-6 weeks of treatment. These findings are similar to ours. In the present study the improvement was gradual and the statistically significant difference was noted after two weeks of treatment. Although there was a decrease in the CADESI value after the first week, but it was not

statistically significant (p=0.06). As regards TEWL measured in all body regions (M TEWL), it was also observed that its values fell gradually in the course of treatment. A statistically significant decrease in the value of the parameter was noted after one week of treatment, however, the subsequent falls were relatively small and were not significantly different from each other. A very similar behaviour of the parameter was observed in the interdigital region. As far as other regions are concerned, a decrease in the parameter was observed too, and a statistically significant fall was noted in the ventral abdominal region as soon as after one week of treatment (there was a slight rise observed after three weeks and then the value of the parameter fell again after four weeks). In the case of the axillary fossa and the inguinal region, a statistically significant decrease of TEWL values were observed only after two weeks, and in the lateral thorax region only after three weeks of treatment. In the cheek a decrease in TEWL value also occured after three weeks of treatment. In four examined body regions, i.e. the lumbar region, bridge of nose, the internal surface of the auricle, and the lateral site of antebrachium, we have not observed a statistically significant decrease in TEWL in the course of treatment. The results obtained indicate that the examination of transepidermal water loss can be used in monitoring the progress of treatment in atopic dermatitis. As regards the assessment of mean TEWL values as well as the values in the interdigital region and in the ventral abdominal region the decrease in TEWL precedes clinical improvement assessed using CADESI. This finding may indicate that the improvement in epidermis integrity appears sooner than it is observable in clinical examination. The parameters assessed in the case of CADESI (lichenification, abrasions and alopeciae) need more time before clinical improvement appears.

The information regarding changes in TEWL in the course of treatment is very scarce. In 2012 Eui-Hwa Nam et al. published a study concerning changes in TEWL and CADESI in the course of treatment using hydrocortisone aceponate. The studies showed a concurrent decrease in TEWL and CADESI after 14 days of treatment. Similarly, Tretter et al. (2011) reported a simultaneous decrease in CADESI and TEWL in the course of treatment using locally administered products containing polyunsaturated fatty acids. Cornegliani et al. (2012) took measurement of this parameter in dogs undergoing specific immunotherapy and symptomatic treatment using cyclosporine and showed that TEWL values are lower during therapy compared to the values in untreated dogs. Nevertheless, these studies did not involve examining the changes in the parameter at different time intervals.

Such studies were also conducted with human patients with atopic dermatitis. It was reported that the improvement in skin condition was accompanied by a decrease in TEWL values in the course of treatment (Aalto-Korte 1995).

Other studies conducted by Pellicoro et al. (2013) concerned the influence of local treatment on skin barrier. Dimethicone, which was used in treatment, did not have an effect on skin condition assessed with CADESI or TEWL. Also, the presence of a correlation between the two parameters was not confirmed.

The correlation between TEWL and CADESI was previously the object of study of Marsella R. (2012) and Zając et al. (2014), who confirmed the existence of such a correlation in atopic dogs.

To summarize, it appears justified to use TEWL measurement in monitoring the progress of treatment.

References

Aalto-Korte K (**1995**) Improvement of skin barrier function during treatment of atopic dermatitis. J Am Acad Dermatol 33: 969-972.

Corrnegliani L, Vercelli A, Sala E, Marrsella R (**2012**) Transepidermal water loss in healthy and atopic dogs, treated and untreated: a comparitive preliminary study. Vet Dermatol 23: 41-e10.

Favrot C, Steffan J, Seewald W, Picco F (**2010**) A prospective study on the clinical features of chronic canine atopic dermatitis and its diagnosis.Vet Dermatol 21: 23-31.

Hightower K, Marsella R, Flynn-Lurie A (**2010**) Effects of age and allergen exposure on transepidermal water loss in a house dust mite-sensitized beagle model of atopic dermatitis. Vet Dermatol 21: 88-95.

Kovalik M, Taszkun I, Pomorski Z, Kozak M, Pomorska D, Szczepanik M Wilkolek P, Palenik L, Shaw DJ, van den Broek AH, Thoday KL (**2011**) Evaluation of a human generic formulation of ciclosporin in the treatment of canine atopic dermatitis with in vitro assessment of the functional capacity of phagocytic cells. Vet Rec 168: 537-542.

Marsella R (**2012**) Are transepidermal water loss and clinical signs correlated in canine atopic dermatitis? A compilation of studies. Vet Dermatol 23: 238-e49.

Marsella R, Olivry T, Nicklin C, Lopez J (**2006**) Pilot investigation of a model for canine atopic dermatitis: environmental house dust mite challenge of high-IgE-producing beagles, mite hypersensitive dogs with atopic dermatitis and normal dogs. Vet Dermatol 17: 24-35.

Marsella R, Samuelson D, Doerr K (**2010**) Transmission electron microscopy studies in an experimental model of canine atopic dermatitis. Vet Dermatol 21: 81-88.

Nam EH, Park SH, Jung J, Han SH, Youn HY, Chae JS, Hwang CY (**2012**) Ewaluation of the effect of a 0.0584% hydrocortisone aceponate spray on clinical signs and skin barrier function in dogs with atopic dermatitis. J Vet Sci 13: 187-191.

Olivry T, Rivierre C, Jackson HA, Murphy KM, Davidson G, Sousa CA (**2002**) Cyclosporine decreases skin lesions and pruritus in dogs with atopic dermatitis: a blinded randomized prednisolone-controlled trial. Vet Dermatol 13: 77-87.

Olivry T, Marsella R, Iwasaki T, Mueller R, Interantional Task Force On Canine Atopic Dermatitis (**2007**) Validation of CADESI-03, a severity scale for clinical trials enrolling dogs with atopic dermatitis. Vet Dermatol 18: 78-86.

Olivry T, Mueller R, Nuttall T, Favrot C, Prélaud P, International Task Force on Canine Atopic Dermatitis (**2008**) Determination of CADESI-03 thresholds for increasing severity levels of canine atopic dermatitis.Vet Dermatol 19: 115-119.

Pellicoro C, Marsella R, Ahrens K (**2013**) Pilot Study to Evaluate the Effect of Topical Dimethicone on Clinical Signs and Skin Barrier Function in Dogs with Naturally Occurring Atopic Dermatitis. Vet Med Int doi: 10.1155/2013/239186.

Pin D, Piekutowska A, Reme CA, Gatto H, Haftek M (**2008**) A qualitative and quantitative evaluation of the effects of a topically applied preparation of epidermal lipids on the stratum corneum barrier structure of atopic dogs. Vet Dermatol 19 (Suppl 1): 1-83.

Shimada K, Yoshihara T, Yamamoto M, Konno K, Momoi Y, Nishifuji K, Iwasaki T (**2008**) Transepidermal water loss (TEWL) reflects skin barrier function of dogs. J Vet Med Sci 70: 841-843.

Steffan J, Alexander D, Brovedani F, Fisch RD (**2003**) Comparison of cyclosporine A with methylprednisolone for treatment of canine atopic dermatitis: a parallel, blinded, randomized controlled trial. Vet Dermatol 14: 11-22.

Szczepanik MP, Wilkołek PM, Adamek ŁR, Pomorski ZJ (**2011**) The examination of biophysical parameters of skin (transepidermal water loss, skin hydration and pH value) in different body regions of normal cats of both sexes. J Feline Med Surg 13: 224-230.

Szczepanik MP, Wilkołek PM, Pluta M, Adamek ŁR, Pomorski ZJ (**2012**)The examination of biophysical parameters of skin (transepidermal water loss, skin hydration and pH value) in different body regions of ponies Pol J Vet Sci 15: 553-559.

Taszkun I (**2010**) The evaluation of canine atopic dermatitis extent and severity idex (CADESI) test in dogs with atopic dermatitis (AD) treated with cyclosporine or prednisone. Pol J Vet Sci 13: 681-688.

Tretter S, Mueller RS (**2011**) The Influence of Topical Unsaturated Fatty Acids and Essential Oils on Normal and Atopic Dogs. J Am Anim Hosp Assoc 47: 236-240.

Zając M, Szczepanik MP, Wilkołek PM, Adamek ŁR, Pomorski ZJ, Sitkowski W, Gołynski MG (**2014**) Assessment of the relationship between transepidermal water loss (TEWL) and severity of clinical signs (CADESI-03) in atopic dogs. Vet Dermatol 25: 503-e83