

## Assessment of the relationship between transepidermal water loss (TEWL) and severity of clinical signs (CADESI-03) in atopic dogs

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**Background** – Atopic dermatitis (AD) is a common allergic skin disease of dogs. Objective documentation of disease severity is important for the assessment of responses to therapeutic interventions. One common means of assessing the severity of clinical signs is the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03. In addition, studies of the biophysical parameters of the skin suggest that assessment of transepidermal water loss (TEWL) may also have value for estimation of disease severity.

**Hypothesis/Objectives** – The aim of the present study was to verify the correlation between TEWL and CADESI-03 measured at 10 different body sites.

**Animals** – Twenty-six dogs with AD (age range 1–7 years, median age 3 years).

**Methods** – The assessment was performed at the following 10 body sites: the lumbar, inguinal, ventral abdominal, interdigital regions, axillary fossa, lateral thorax, lateral aspect of the antebrachium, concave surface of the auricle, cheek and bridge of the nose.

**Results** – Positive correlations were found between TEWL and the total CADESI-03 for the auricle ( $r = 0.59$ ), bridge of nose ( $r = 0.62$ ) and interdigital skin ( $r = 0.47$ ). Positive correlations were also observed between TEWL and local CADESI-03 scores for the axillary fossa ( $r = 0.73$ ), inguinal region ( $r = 0.55$ ) and interdigital skin ( $r = 0.77$ ).

**Conclusions and clinical importance** – The results indicate that it may be possible to use measurement of TEWL to assess the severity of skin lesions, but a positive correlation was found in only five of 10 body regions examined.

### Introduction

Atopic dermatitis (AD) is a common disease of dogs, which affects ~10% of the population. Immunological factors connected predominantly with the development of immunoglobulin E (IgE)-dependent hypersensitivity play a crucial role in the pathogenesis of the disease. Equally important to disease pathogenesis are skin barrier dysfunctions, including ultrastructural changes and abnormalities of intercellular lipid content.<sup>1–6</sup> These aberrations have been associated with both the structure and the function of the stratum corneum, where they may confer an increased risk of allergen sensitization and contribute to the dysregulated immune response that is characteristic of canine AD.<sup>1</sup>

A method used to assess the barrier function of the skin is measurement of transepidermal water loss

(TEWL).<sup>7</sup> A study of an experimental model of canine atopy has shown that TEWL increases in diseased animals (especially young ones) in body regions commonly associated with AD lesions, including the auricle and the antebrachium.<sup>8</sup> An increase in TEWL was also noted in the inguinal region of atopic dogs, for both lesional and nonlesional skin.<sup>5</sup> Higher TEWL values were reported for atopic dogs than for healthy dogs.<sup>5</sup> A prior study has also shown that TEWL values tend to decrease in dogs with AD when remission of lesions is achieved through allergen-specific immunotherapy or use of ciclosporin.<sup>9</sup>

A method commonly used to quantify the clinical effects of AD is the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03.<sup>10</sup> The method is based on the assessment of erythema, lichenification, excoriation and self-induced alopecia, across various body regions. The index has been validated for the assessment of disease severity over time,<sup>10</sup> although interobserver variability does occur.<sup>11</sup> One study has reported correlation between the CADESI-03 and TEWL in atopic dogs, although this was significant for only one of eight body regions examined.<sup>12</sup> Both methods have also been used

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to monitor therapeutic progress in dogs during topical treatment.<sup>13</sup>

The aim of the present study was to verify whether a correlation between TEWL and CADESI-03 exists in atopic dogs, as assessed from 10 body regions. Demonstration of correlation could enable use of TEWL measurement as an objective measure of disease severity, as is the case in human medicine,<sup>14</sup> and provide an additional tool for monitoring the activity of AD during clinical therapy trials.

## Materials and methods

Twenty-six dogs with AD were selected based upon the criteria established by Favrot *et al.*<sup>15</sup> Pet owners provided written informed consent for each dog to participate. Other pruritic skin diseases were excluded on the basis of microscopic examination of plucked hairs, skin scrapings and cytological preparations. Concurrent adverse food reactions were excluded after 8 weeks of an elimination diet. All dogs received flea treatment; flea hypersensitivity was excluded, in part, on the basis of negative results for flea-allergen intradermal and serological (IgE) testing. Intradermal testing with environmental allergens (Agroskin RTU 20; Agrolabo, Scarmagno, Italy) was performed in all 26 dogs. Positive results were defined as subjective reactions of at least 2+ (0–4 scale) in comparison to saline and histamine controls. Additionally, allergen-specific serum IgE levels were evaluated according to the manufacturer's instructions (Policheck Allergie Dog Panel; BioCheck GmbH, Münster, Germany). Antibody evaluation was performed during the period when clinical signs of the disease were active. All dogs with AD associated with sensitivity to environmental allergens underwent further statistical analysis, and those included in the study fulfilled at least five criteria of Favrot *et al.*<sup>15</sup>

The age range of the animals was 1–7 years (median age 3 years); there were 10 females (three spayed) and 16 males (all intact). The animals were privately owned and were represented by the following breeds: West Highland white terrier ( $n = 6$ ), Labrador retriever ( $n = 5$ ), German sheepdog ( $n = 3$ ), boxer ( $n = 2$ ), fox terrier ( $n = 2$ ), French bulldog ( $n = 2$ ) and one each of shih tzu, Yorkshire terrier, pug, English bulldog, Jack Russell terrier and Nova Scotia duck tolling retriever. Animals in the study had moderate to severe signs of AD (CADESI-03 > 66).<sup>16</sup>

## Assessment of CADESI-03 and TEWL

All TEWL and CADESI-03 measurements were collected when dogs had active clinical disease, and testing was performed prior to undertaking treatment. No anti-inflammatory medications (steroids, antihistamines, ciclosporin or fatty acids) or antibiotics were permitted during the 3 months prior to testing. The CADESI-03 was calculated for all animals directly prior to TEWL assessment. The animals were acclimatized in the test room for 1 h before the measurements were taken, where the room temperature was  $23 \pm 2^\circ\text{C}$  and the relative humidity (RH) was  $45 \pm 5\%$  (operating conditions for Tewameter TM 300 according to the manufacturer's instructions: RH 30–70% and temperature 10–30°C). All assessments were performed over a 24 month period by the same investigator. Clipping was not done prior to TEWL measurement. Dogs were not sedated, and most were restrained in recumbency, although a few were tested while standing. Measurements were taken from the following 10 sites: the lumbar, right inguinal, ventral abdominal, right lateral thoracic, right axillary fossa and right lateral antebrachial regions, an interdigital space of the right forelimb, the concave surface of the right auricle, the cheek and the bridge of nose. A stabilized TEWL value was reached 30 s after probe placement, and 20 successive measurements were taken every 30 s thereafter. The mean value was then calculated. Measurements were produced by the Courage Khazaka Multi Probe Adapter 5 and the Tewameter TM 300 probe (Courage Khazaka, Cologne, Germany).

## Statistical analysis

Spearman correlations were calculated for mean TEWL (at each body site) and the whole-body (total) CADESI score, as well as for TEWL and the corresponding CADESI score at each individual site. Statistical significance was set at  $P < 0.05$ . Analyses were performed with Statistica 10 software (Statsoft, Tulsa, OK, USA).

## Results

Dogs had moderate to severe clinical signs of AD at the time of their assessments (CADESI ranging from 68 to 286, mean 150.23). Positive correlations between TEWL measured in different body regions and the total CADESI-03 score were found for the auricle ( $r = 0.59$ ; Figure 1a), bridge of nose ( $r = 0.62$ ; Figure 1b) and interdigital skin ( $r = 0.47$ ; Figure 1c). Positive correlation between TEWL and CADESI measured at the specific body site were found for the axillary fossa ( $r = 0.73$ ; Figure 1d), the inguinal region ( $r = 0.55$ ) and interdigital skin ( $r = 0.77$ ). Therefore, positive correlation was found in five of 10 body regions depending on the type of comparison undertaken.

## Discussion

In our study, correlations between total CADESI-03 and TEWL were demonstrated for several locations, including the auricle, the interdigital skin and the bridge of the nose. We observed correlations between TEWL and CADESI-03, both for whole-body CADESI-03 scores and for those localized to specific body sites that are common targets of AD. On the basis of these results, it appears appropriate to use TEWL measurement in the assessment of AD severity.

In human medicine, measurements of biophysical parameters (TEWL and skin hydration) are used to assess the severity of AD and have been shown to correlate with AD scoring systems such as the SCORAD (Severity Scoring of Atopic Dermatitis) and OSAAD (Objective Severity Assessment of Atopic Dermatitis).<sup>14</sup> The assessment of TEWL in animals has also been the subject of studies where it has been examined for different body regions of several animal species.<sup>17–22</sup> It has been assessed in clinically healthy dogs in order to establish normal values and estimate differences according to body region,<sup>17–20</sup> and in atopic dogs to assess its correlation with disease severity.<sup>7–9,13</sup> Two studies have described statistically higher TEWL values in atopic dogs compared with clinically healthy dogs.<sup>7,8</sup> In the assessment of therapeutic interventions, TEWL decreased in dogs undergoing allergen-specific immunotherapy,<sup>9</sup> while a simultaneous decrease of TEWL and CADESI-03 scores during topical treatment using 0.0584% hydrocortisone aceponate has been observed.<sup>12</sup>

In atopic dogs, correlations between TEWL and both total and site-specific CADESI-03 values have been assessed.<sup>12</sup> The one body site that exhibited statistically significant positive correlations between TEWL and both total and site-specific CADESI-03 scores was the auricle. Our study also demonstrated a statistically significant positive correlation for the auricle, but only in relation to the site-specific CADESI-03 score. In addition, we docu-

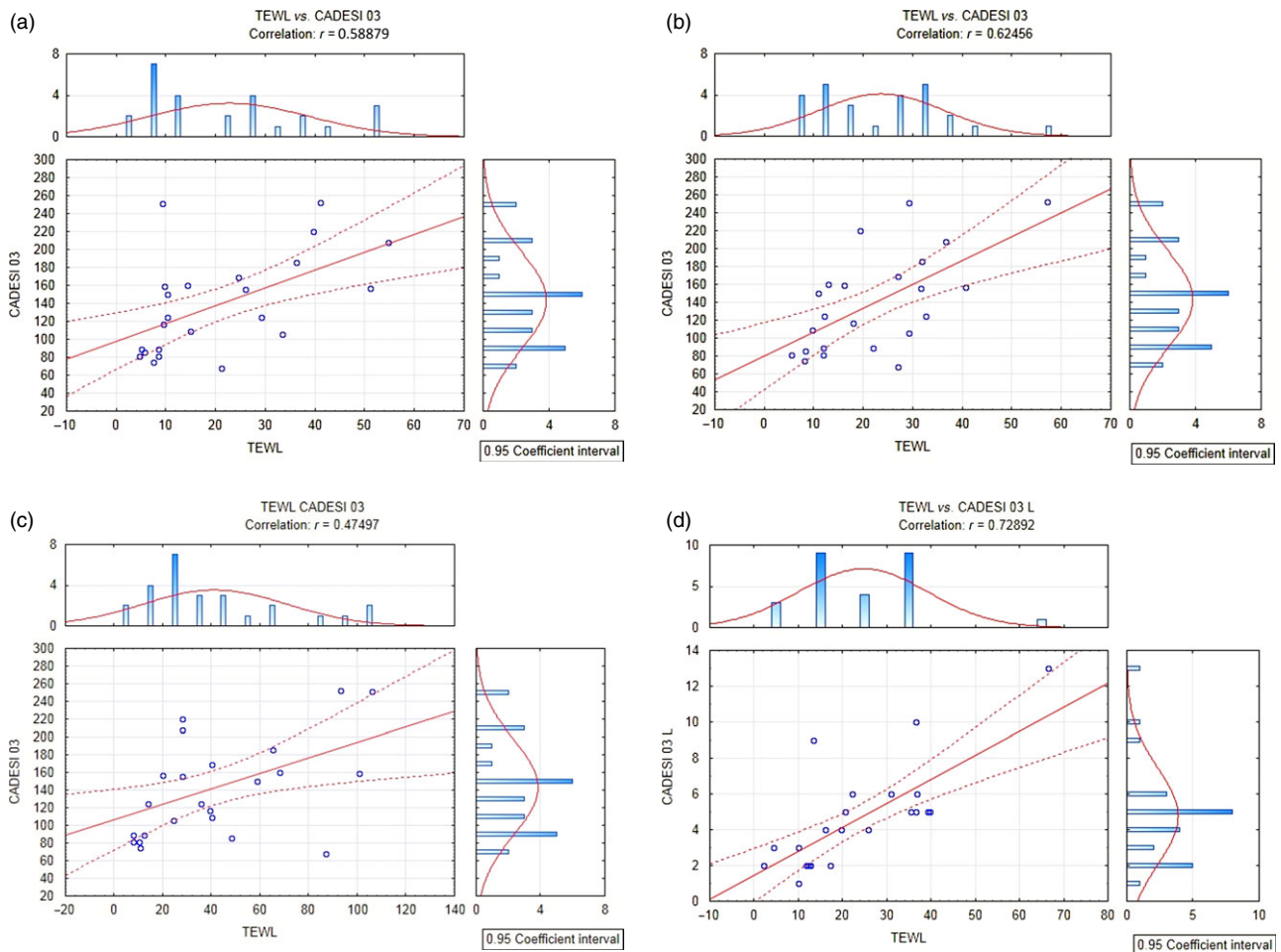


**Figure 1.** Correlation between TEWL of the auricle (a), the bridge of the nose (b) and the interdigital region (c) and CADESI-03. (d) Correlation between TEWL of the axillary fossa and CADESI measured in the same region (CADESI-L). The main diagram shows regression (straight line) and 95% coefficient intervals (dotted lines). Upper and right-hand diagrams are histograms showing the distribution of data.

mented significant correlations for four additional body sites. Differences in results between our study and the previous study<sup>12</sup> may be due to characteristics of the dogs studied. Atopic dogs in the prior study were characterized by lower CADESI-03 scores compared with the dogs in our study. It is possible that the correlations between the parameters under examination could be more likely in dogs with more severe clinical signs. The regions for which the strongest correlations between total CADESI-03 and TEWL were demonstrated included the auricle, the interdigital regions and the bridge of nose. In these regions, especially the bridge of the nose, measurement may be challenging in restless animals, and a single measurement may be insufficient; several attempts at placing the probe are often needed.

Further research involving other dog breeds, additional body regions and other biophysical parameters are necessary to demonstrate whether correlations exist in other body regions and for such biophysical skin parameters as skin hydration and pH. Additional studies are also necessary to correlate changes in TEWL with skin changes during treatment and remission of disease. With such studies it may be possible to validate biophysical parameters for the objective measurement of the severity of canine AD, as is currently used in human medicine.

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## Résumé

**Contexte** – La dermatite atopique (AD) est une dermatose allergique fréquente du chien. La description objective de la sévérité de la maladie est importante pour la détermination des réponses aux traitements. Un moyen fréquent d'évaluation de la sévérité des signes cliniques est le CADESI-03 (Canine Atopic Dermatitis Extent and Severity Index). En outre, des études des paramètres biophysiques de la peau suggèrent que l'évaluation de la perte hydrique transépidermique (TEWL) peut aussi être utile dans l'estimation de la sévérité de l'atteinte.

**Hypothèses/Objectifs** – Le but de cette étude était de vérifier la corrélation entre la TEWL et le CADESI-03 mesurés sur 10 zones corporelles différentes.

**Sujets** – Vingt-six chiens atopiques (âgés de 1 à 7 ans, moyenne : 3 ans).

**Méthodes** – La mesure a été réalisée sur les 10 sites corporels suivants : lombes, aine, abdomen ventral, espace interdigité, pli axillaire, thorax latéral, face latérale du membre antérieur, face concave du pavillon auriculaire, joue, chanfrein.

**Résultats** – Les corrélations positives ont été trouvées entre la TEWL et le CADESI total pour le pavillon auriculaire ( $r = 0.59$ ), le chanfrein ( $r = 0.62$ ) et les espaces interdigités ( $r = 0.47$ ). Les corrélations positives ont aussi été observées entre la TEWL et le CADESI local pour le pli axillaire ( $r = 0.73$ ), la région inguinale ( $r = 0.55$ ) et la peau interdigitée ( $r = 0.77$ ).

**Conclusions et importance clinique** – Les résultats suggèrent qu'il est possible d'utiliser la mesure de la TEWL pour évaluer la sévérité des lésions cliniques, mais une corrélation positive n'a été retrouvée que pour cinq des 10 régions corporelles évaluées.

## Resumen

**Introducción** – la dermatitis atópica (AD) es una enfermedad alérgica de la piel común en perros. Documentar de forma objetiva la severidad de la enfermedad es importante para valorar la respuesta a las intervenciones terapéuticas. Una de las formas más frecuentes de evaluar la severidad de los signos clínicos es el índice de severidad y extensión de la dermatitis atópica canina (CADESI-03) además, estudios de los parámetros biofísicos de la piel sugiere que la evaluación de la pérdida de agua transepidermal (TEWL) puede ser también importante para la estimación de la severidad de la enfermedad.

**Hipótesis/Objectivos** – el propósito del presente estudio fue verificar la correlación entre TEWL y CADESI-03 medidas en diez zonas diferentes del cuerpo.

**Animales** – 26 perros con AD (rango de edad de uno a siete años, mediana de edad de tres años).

**Métodos** – la evaluación se realizó en los 10 lugares indicados a continuación: regiones lumbar, inguinal, ventral abdominal e interdigital, la fosa axilar, el tórax lateral, el aspecto lateral del antebrazo, la superficie concava de la aurícula, el carrillo, y el hocico.

**Resultados** – se encontró una correlación positiva entre TEWL y CADESI para la zona de la oreja ( $r = 0.59$ ), hocico ( $r = 0.62$ ) y piel interdigital ( $r = 0.47$ ). También se vieron correlaciones positivas entre TEWL y CADESI local para la fosa axilar ( $r = 0.73$ ), región inguinal ( $r = 0.55$ ) y piel interdigital ( $r = 0.77$ ).

**Conclusiones e importancia clínica** – los resultados indican que es posible utilizar la medida de TEWL

para evaluar la severidad de las lesiones de la piel, pero una correlación positiva sólo se encontró en cinco de las 10 regiones examinadas.

### Zusammenfassung

**Hintergrund** – Die atopische Dermatitis (AD) ist eine häufige allergische Hauterkrankung von Hunden. Eine objektive Dokumentation der Schwere der Erkrankung ist wichtig, um die Beurteilung der therapeutischen Interventionen zu ermöglichen. Ein häufig verwendetes Mittel, um die Schwere der klinischen Symptome zu beurteilen ist der Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03. Zusätzlich liefern Studien der biophysikalischen Parameter der Haut Hinweise, dass der transepidermale Wasserverlust (TEWL) bei der Abschätzung der Schwere der Erkrankung wertvoll sein könnte.

**Hypothese/Ziele** – Das Ziel dieser Studie war es, die Korrelation zwischen TEWL und CADESI-03 an 10 verschiedenen Körperstellen zu verifizieren.

**Tiere** – Sechszwanzig Hunde mit AD (Alter von 1-7 Jahre, Alter Median 3 Jahre).

**Methoden** – Die Untersuchung wurde an den folgenden 10 Körperstellen durchgeführt: Lendenbereich, Inguinalgegend, ventrales Abdomen, Interdigitale Regionen, Achseln, lateraler Thorax, lateraler Aspekt der Unterarme, konkave Seite der Auriculæ, Wangen und Nasenrücken.

**Ergebnisse** – Eine positive Korrelation wurde zwischen TEWL und dem Gesamt CADESI für die Auriculæ ( $r = 0.59$ ), den Nasenrücken ( $r = 0.62$ ) und die interdigitale Haut ( $r = 0.47$ ) gefunden. Eine positive Korrelation wurde ebenfalls zwischen dem TEWL und den lokalen CADESI Werten für die Achseln ( $r = 0.73$ ), die Inguinalregion ( $r = 0.55$ ) und die interdigitale Haut ( $r = 0.77$ ) festgestellt.

**Schlussfolgerungen und klinische Bedeutung** – Die Ergebnisse weisen darauf hin, dass es möglich sein könnte, den TEWL zu messen, um die Schwere der Hautveränderungen zu beurteilen, aber eine positive Korrelation wurde nur bei fünf von 10 untersuchten Körperstellen gefunden.

### 要約

**背景** – アトピー性皮膚炎(AD)は一般的なイヌのアレルギー性皮膚疾患である。疾患重症度の客観的な文書化は治療の反応を評価する為に重要である。the Canine Atopic Dermatitis Extent and Severity Index (CADESI)-03は臨床症状の重症度の一般的な評価方法の1つである。加えて、皮膚の生物物理学的なパラメーターの研究により経表皮水分蒸散量(TEWL)の評価もまた疾患重症度の評価に価値があることが示唆されている。

**仮説/目的** – この研究の目的は、10ヶ所の異なる身体部位におけるTEWLとCADESI-03の間の相関を検証することである。

**供与動物** – ADに罹患した(年齢幅1-7歳、平均3 歳)26頭のイヌ

**方法** – 以下の10ヶ所の身体部位で評価を行った：腰部、鼠径部、腹部腹側、趾間、腋窩、胸部体側、前腕の側面、耳介の凹面、頬部および鼻梁部

**結果** – 耳介( $r = 0.59$ )、鼻梁部 ( $r = 0.62$ )、および趾間皮膚( $r = 0.47$ )において、TEWLと総CADESIの間に正の相関関係が認められた。腋窩 ( $r = 0.73$ )、鼠径部( $r = 0.55$ )、および趾間の皮膚( $r = 0.77$ ) において、TEWLと局所CADESIスコアの間で正の総相関関係が認められた。

**結論および臨床的な重要性** – この結果はTEWLの測定が皮膚病変の重症度を評価するために使用できる可能性を示したが、正の相関関係は測定した10ヶ所の身体部位の5箇所では認められなかった。

### 摘要

**背景** – 异位性皮炎(AD)是犬常见过敏性皮肤病。客观记录疾病的严重性对于治疗反应的评估很重要。评估临床症状严重程度的常用方法是犬异位性皮炎部位与严重程度指数(CADESI)-03。另外,运用生物物理学可评估表皮水分流失量(TEWL),这也许对评估疾病严重程度有所帮助。

**假设/目的** – 此次研究目的是确定10个不同身体部位TEWL与CADESI-03之间的关联性。

**动物** – 26只异位性皮炎患犬(平均年龄为1-7岁,中值为3岁)。

**方法** – 从以下10个部位取样评估:腰部、腹股沟、腹部、趾部、腋窝、胸侧、前臂侧面、耳廓凹面、面颊和鼻梁。

**结果** – 耳廓( $r = 0.59$ ),鼻梁( $r = 0.62$ ),指间( $r = 0.47$ ) TEWL和总CADESI正相关。腋窝 ( $r = 0.73$ ),腹股沟( $r = 0.55$ )和指间( $r = 0.77$ ) TEWL 和局部CADESI成正相关。

**总结与临床意义** – 结果显示有可能使用TEWL方法来评估皮肤病变的严重程度,但10个部位中只有5个呈正相关。