A double-blinded, randomized, controlled, crossover evaluation of a zinc methionine supplement as an adjunctive treatment for canine atopic dermatitis

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Background – Zinc is important for skin health and proper immune system function.

Hypothesis/Objectives – A zinc methionine, essential fatty acids (EFA) and biotin product (Zn supplement) was compared to an EFA and biotin product (control) in canine atopic dermatitis (CAD).

Animals – Twenty seven client-owned dogs with chronic CAD receiving ciclosporin or glucocorticoids.

Methods – A 24 week, randomized, double-blinded, controlled study with crossover at week 12 and 4 week period of allergy medication reduction at weeks 8 and 20. Evaluations included Canine Atopic Dermatitis Lesion Index (CADLI), pruritus Visual Analog Scale (VAS) and cytology sampling.

Results – In dogs receiving the zinc supplement and ciclosporin for eight weeks, 44% (n = 7) had significantly decreased CADLI from 11.9 to 6.0 (P = 0.0002) with no significant change in pruritus VAS (P = 1.0). In dogs receiving the zinc supplement and glucocorticoids for eight weeks, 55% (n = 6) had significantly decreased CADLI from 10.9 to 5.0 (P = 0.0043) and pruritus VAS from 7.4 to 3.2 (P = 0.0166). For dogs receiving either steroids or ciclosporin there was a reduction in use of such medications, for at least four weeks, in 63% of dogs receiving the zinc supplement and 37% of dogs receiving the control. This difference was not significant (P = 0.1027). Seventy eight percent of dogs were diagnosed and treated for superficial skin infections during the study.

Conclusions and clinical importance – This study supports a potential benefit of adjunctive zinc methionine supplementation in CAD. Dogs receiving glucocorticoids may be more likely to benefit. Further studies are needed to substantiate these initial results.

Introduction

Canine atopic dermatitis (CAD) is a common condition requiring long-term therapy for control. Two effective therapies for CAD are glucocorticoids and ciclosporin.1 Due to known potential adverse effects of these therapies, use of combination and adjunctive treatments may enable a reduction in the amount of anti-inflammatory medications needed to control clinical signs.2

Zinc is a constituent or activator of at least 200 known enzymes, including those important for skin and wound healing, cell replication, protein synthesis and immuno-competence.3 Rapidly dividing cells, such as those of the epidermis, are particularly dependent on zinc.4 The consequences of zinc deficiency on the skin, either from reduced intake, absorption or metabolism, have been described in dogs and include impaired wound healing, erythema, alopecia, crusting and scaling.4

Zinc absorption may be improved by concomitant supplementation with essential fatty acids (EFA). This has largely been demonstrated in rodent studies.3,5 Concurrent supplementation with EFA and zinc is recommended, although not validated, for treatment of zinc-responsive dermatoses.4,6 Zinc and linoleic acid supplementation has been shown to reduce transepidermal water loss and improve skin and coat health in dogs.7 The benefits of adjunctive EFA supplementation in CAD have been reported.8,9

The exact role of zinc and the potential benefits of supplementation in atopic dermatitis (AD) in humans are largely unknown. Interestingly, serum zinc levels have been found to be lower in atopic children compared to healthy children.10-12 Another study found lower hair zinc levels in atopic children but comparable serum zinc levels between atopic and healthy individuals; the authors

**Abbreviations:** CAD, canine atopic dermatitis; CADLI, Canine Atopic Dermatitis Lesion Index; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; VAS, Visual Analog Scale; ZnS, zinc supplement.

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concluded that allergic children might be at risk for zinc deficiency.13 Atopic children with low hair zinc levels supplemented with zinc showed significant clinical improvement as compared to children not receiving zinc supplementation.14 An animal model for AD has been created by feeding mice a diet reduced in magnesium and zinc.15 A study in dogs found no significant differences between serum zinc levels in healthy, systemically ill and dogs with skin disease.16 However, serum zinc levels cannot be used to gauge epidermal zinc levels or determine if some patients with dermatological disease might benefit from zinc supplementation.16 To the best of the authors’ knowledge, there have been no published studies evaluating adjunctive therapy for CAD with zinc.

The aim of this study was to evaluate a supplement containing zinc methionine, EFA and biotin (TruCare Essentials; Zinpro Performance Minerals; Eden Prairie, MN, USA) in client-owned dogs with chronic, nonseasonal CAD. Outcome measures included the Canine Atopic Dermatitis Lesion Index (CADLI), a pruritus Visual Analog Scale (VAS) and the ability of the supplement to allow for a 50% glucocorticoid dose reduction or a reduced frequency of ciclosporin administration. We hypothesized that zinc supplementation in CAD would lead to clinical improvement with reduced CADLI and pruritus VAS, and permit control of clinical signs with a reduced need for anti-inflammatory medications.

Materials and methods

Animals
Thirty six client-owned dogs with a history of chronic, nonseasonal AD were enrolled over a period of six months from September 2014 to February 2015 at two veterinary practices. Written informed consent was obtained from the owners prior to enrolment and owners could withdraw their dogs from the study at any time; the reason for withdrawal was recorded.

Inclusion and exclusion criteria
All dogs were diagnosed with AD using published criteria17 and through exclusion of other pruritic dermatoses. Dogs received an unchanged frequency and dose of either modified ciclosporin (Atopica®, Elanco; Greenfield, IN, USA) or systemic glucocorticoids for a minimum of one year prior to enrolment. All dogs were receiving the minimum dose and frequency of medication required for comfort as determined by the owner and the attending veterinary clinician. Dogs were excluded if they received ciclosporin concurrent with glucocorticoids on a weekly basis as part of their maintenance allergy treatment, and/or received antimicrobial therapies on a weekly basis (pulse therapy) to prevent recurrent skin infections, and/or had signs of infection at the time of study inclusion. Food-induced AD was excluded in approximately half the study population with a negative pinnal-pedal reflex and were not identified on any of the treatments to treat or prevent flares within two weeks of study evaluation.

Table 1. Concurrent or adjunctive treatments received by 27 dogs completing the study.

Study design/Treatment groups
This study was performed as a randomized, double-blinded, controlled, crossover design with each animal serving as its own control. Dogs were enrolled, evaluated and assigned to the zinc supplement (ZnS) or control (C) group at week 0. Dogs were re-evaluated at weeks 8 and 12. At Week 12, dogs were switched to the other treatment for the remainder of the study and re-evaluated at weeks 20 and 24.

Supplement/Control administration
An investigational treatment containing 30 mg elemental zinc from zinc methionine, 2 mg biotin, 128.7 mg eicosapentaenoic acid (EPA) and 85.8 mg docosahexaenoic acid (DHAl per tablet (TruCare Essentials, ZnS; Eden Prairie, MN, USA) was administered at a dose of 1 tablet/18.2 kg body weight rounded to the nearest half tablet given p.o. once daily with or without food. This dose is equivalent to 1.6 mg/kg elemental zinc, 0.1 mg/kg biotin, 7.1 mg/kg EPA and 4.7 mg/kg DHA. The control treatment contained 2 mg biotin, 128.7 mg EPA and 85.8 mg DHA per tablet, and was administered at the same dose and frequency.

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and 24. Reduction of allergy medications occurred at weeks 8 and 20.

Study protocol

1. Examination 1 (Week 0): dog started on either ZnS or C and continued either modified ciclosporin or systemic glucocorticoids at regular maintenance dose.
2. Examination 2 (Week 8): dog continued ZnS or C and allergy medication was reduced. For dogs receiving ciclosporin, the dose was kept the same but the frequency of administration was decreased as follows: daily administration was decreased to every other day, every other day administration decreased to twice weekly, and twice-weekly administration was reduced to once-weekly administration. For dogs receiving systemic glucocorticoids, the dose was decreased by 50% and the frequency was kept the same.
3. Examination 3 (Week 12 or earlier if allergy flare occurred): dog was switched to the other treatment (either ZnS or C) for the remainder of the study. Allergy medication dose and/or frequency was increased if needed to manage flare and then returned to a regular maintenance dose no later than Week 16 to avoid interfering with assessment of CADLI or pruritus VAS at Week 20.
4. Examination 4 (Week 20): repeat of protocol from Week 8 using the other treatment.
5. Examination 5 (Week 24 or earlier if allergy flare noted by owner): allergy medication dose and/or frequency was increased if needed to manage flare. As this was the final evaluation period, owners could either discontinue supplement and return to regular maintenance allergy medication dose or, if they perceived benefit in either the first or second half of the study, they had the option to continue ZnS and reduced allergy medication dose.

Clinical examination and microbiology

Complete physical examination was performed at the initial visit and full dermatological examination was conducted at every visit. Cytology samples using acetate tape impression were collected from any abnormal or pruritic areas of skin and, for dogs with clinically normal skin, samples were collected from the ventral abdomen, axillae and feet. Samples were stained with modified Wright’s stain and evaluated as described previously for the presence of bacteria, yeast and inflammatory cells. Briefly, dogs were diagnosed with infection if there were polymorphonuclear leucocytes with either intracellular bacteria or ≥2 extracellular bacteria or yeast per oil immersion field.

Efficacy outcome measures

At each clinical examination, owners assessed pruritus using a VAS consisting of a 10 cm scale where 0 cm indicated no pruritus and 10 cm indicated severe pruritus. The distance (in cm) from 0 cm to the owner’s mark was measured and recorded. Investigators assessed lesion extent and severity at each clinical examination using a previously validated scoring system, CADLI. Coat quality was additionally evaluated subjectively and recorded at each visit as normal, hypotrichotic or seborrhoeic. Seborrhoea was determined based on visible fine-scale or palpable oily coat consistency. An allergy flare was determined if an owner observed a sudden increase in their dog’s pruritus level or if the difference in pruritus VAS had increased by more than 1.5 during the four week period of allergy medication reduction.

Data analysis

Data were analysed statistically with the Glimmix mixed model procedure of SAS v9.2 (SAS Institute Inc., Cary, NC, USA). The level of significance was set at $P < 0.05$. Analyses were performed on all dogs completing the study. Infrquent individual data points for CADLI and pruritus VAS ($n = 3$ for ciclosporin group, $n = 6$ for glucocorticoids group) were removed from statistical analysis when minor protocol violations occurred (owner-made adjustments in dose or frequency of allergy medication within two weeks of study examination as determined by interview at time of examination).

Fixed effects in the mixed model included sequence of treatment (ZnS followed by Control or Control followed by ZnS), allergy medication (ciclosporin or glucocorticoids), and their interaction. These were tested statistically by the random effect of the dog. Week was also included along with its interactions with the previous fixed effects of sequence and allergy medication. The use of sequence in the model generated four sets of least-squares means for each CADLI and pruritus VAS across the 24 weeks, with each set derived from a group of six to nine dogs on the same allergy medication and receiving the same sequence of treatments. Linear contrasts were used to compare ZnS and Control treatments over selected time periods during the study. The first approach was to compare linear changes in CADLI and pruritus VAS from 0 to 12 weeks and from 12 to 24 weeks, considering the unequal spacing of 0, eight and 12, and 12, 20 and 24 weeks. The second approach was to compare changes from 0 to eight weeks and 12 to 20 weeks (where allergy medication dose and frequency was stable), as well as eight to 12 weeks and 20 to 24 weeks (where allergy medication dose or frequency was reduced). These changes in adjacent periods were tested with more conservative Bonferroni t-tests due to the lack of independence among the comparisons. There were no observations discarded as outliers as all were within ±3.1 residual standard deviations from predicted and data were distributed normally.

In order to determine the effect of infection on CADLI and pruritus VAS, this was added to the sequence model for each dog at each period with the regression coefficient quantifying the change resulting from an infection. The presence of carryover effect was tested by the significance of sequence means. A carryover effect was deemed to have occurred if the overall means of the two sequences (Control followed by ZnS and ZnS followed by Control) differed. Ability to reduce allergy medication, infection frequency, influence of infection on ability to reduce allergy medication and subjective assessment of coat condition were compared using a chi-square test to evaluate differences by treatment and allergy medication at weeks 0, 8, 12, 20 and 24.

Results

Demographics

Thirty six dogs were enrolled in the study. There were 22 spayed females, 13 neutered males and one sexually intact male. Median weight was 17.3 kg (range 4.3–43.2 kg) and median age was 7.4 years (range 2–13 years). A total of 28 dogs were pure-bred, with the Labrador retriever ($n = 5$; 18%), shih tzu ($n = 4$; 14%), golden retriever ($n = 2$; 7%), French bulldog ($n = 2$; 7%) and pug ($n = 2$; 7%) being the most commonly represented breeds. Mixed breeds accounted for 22% ($n = 8$) of the study population. Twenty two dogs received modified ciclosporin and 14 dogs received systemic glucocorticoids. All dogs were housed indoors except for one dog that lived outdoors with access to a heated garage.

Study groups, completion and adverse effects

A total of 27 dogs completed the study, 16 in the ciclosporin group and 11 in the glucocorticoids group. Ciclosporin was administered daily in seven dogs, every other day in seven dogs and twice weekly in two dogs. For dogs receiving ciclosporin, seven dogs were treated with ZnS followed by Control and nine dogs were treated with Control followed by ZnS. For dogs receiving glucocorticoids, five dogs were treated with ZnS followed by Control and six dogs were treated with Control followed by ZnS.
Six dogs receiving ZnS were withdrawn within the first eight weeks of the study. Reasons for withdrawal were thought to be unrelated to investigational treatment and included: dog unwilling to consume study treatment (n = 1, ciclosporin group), owner elected withdrawal for worsening signs of AD (n = 2, ciclosporin group), discontinuation of ciclosporin mid-study (n = 1), hospitalization for pneumonia in a 12-year-old dog (n = 1, glucocorticoids group) and euthanasia following development of a large gastric tumour one week after study entry (n = 1, ciclosporin group). A single dog receiving glucocorticoids and Control treatment was withdrawn at eight weeks for failure to present for clinical examination. An additional dog receiving ciclosporin was removed at Week 13, one week after rabies vaccination and starting the Control treatment, with acute onset of severe pruritus and coalescing patches of inguinal erythema. Histopathological evaluation showed mild to moderate, perivascular to lichenoid, pyogranulomatous dermatitis without evidence of vasculitis. The dog was treated successfully with a glucocorticoid for the suspected severe allergic flare but was withdrawn from further study, because it was unethical to risk another flare. A single dog receiving glucocorticoids was removed near study completion due to numerous breaks in study protocol.

Additional adverse events that occurred during the study and did not result in withdrawal included: development of superficial pyoderma (n = 1, ciclosporin group), owner elected withdrawal for worsening signs of AD (n = 2, ciclosporin group), discontinuation of ciclosporin mid-study (n = 1), hospitalization for pneumonia in a 12-year-old dog (n = 1, glucocorticoids group) and euthanasia following development of a large gastric tumour one week after study entry (n = 1, ciclosporin group).

Assessment of efficacy
At Week 0, CADLI averaged 9.9 (4.0 SD) and pruritus VAS averaged 3.2 (2.1 SD) across all treatment groups.

Zinc supplement and ciclosporin CADLI and pruritus VAS
For dogs receiving ZnS and ciclosporin for a total of eight weeks, 44% (n = 7) had a significant reduction in CADLI from 11.9 to 6.0 (P = 0.0002) and the remaining 56% (n = 9) had no statistically significant change in CADLI. There was no statistically significant change in pruritus VAS for either group. For dogs receiving Control and glucocorticoids, there was no statistically significant change in CADLI or pruritus VAS at any time point (Figure 1).

Zinc supplement and ciclosporin medication reduction
Sixty nine percent (n = 11) of dogs receiving ZnS had their ciclosporin frequency reduced for four weeks without incurring an allergy flare. Within this group, for three dogs it was not possible to reduce their ciclosporin frequency when receiving Control. Sixty three percent (n = 10) of dogs receiving Control had their dose reduced for their ciclosporin frequency for four weeks without incurring an allergy flare. Within this group, for two dogs it was not possible to reduce their ciclosporin frequency when receiving ZnS. For three dogs it was not possible to reduce their ciclosporin frequency with either ZnS or Control. There was no statistical difference between ZnS and Control in allowing reduction of frequency of administration of ciclosporin.

Zinc supplement and glucocorticoids CADLI and pruritus VAS
In dogs receiving ZnS and glucocorticoids for a total of eight weeks, 55% (n = 6) of dogs had significantly reduced CADLI scores from 10.9 to 5.0 (P = 0.0043) and pruritus VAS from 7.4 to 3.2 (P = 0.0166). The remaining five dogs (45%) in the ZnS and glucocorticoids group had no statistically significant change in CADLI or pruritus VAS. For dogs receiving Control and glucocorticoids, there was no statistically significant change in CADLI or pruritus VAS at any time point (Figure 2).

Figure 1. Mean Canine Atopic Dermatitis Lesion Index (CADLI) score by week of study evaluation for dogs receiving ciclosporin. Circles represent a treatment group of nine dogs and squares represent a treatment group of seven dogs. The black line represents Zinc supplementation and the grey line represents Control treatment. Frequency of ciclosporin administration was decreased at Week 8, returned to maintenance at Week 12 and was again decreased at Week 20. n number of dogs, ZnS zinc supplement.

Figure 2. Mean Canine Atopic Dermatitis Lesion Index (CADLI) score by week of study evaluation for dogs receiving glucocorticoids. Circles represent a treatment group of six dogs and squares represent a treatment group of five dogs. The black line represents Zinc supplementation and the grey line represents Control treatment. Glucocorticoid dose was decreased by 50% at Week 8, returned to maintenance at Week 12 and was again decreased at Week 20. n number of dogs, ZnS zinc supplement.
Zinc supplement and glucocorticoid medication reduction
Fifty five percent \((n = 6)\) of dogs receiving ZnS had their glucocorticoid dose reduced by half for four weeks without incurring an allergy flare. Within this group, four dogs could not have their glucocorticoid dose reduced when receiving Control. Eighteen percent \((n = 2)\) of dogs receiving Control had their glucocorticoid dose reduced by half for four weeks without incurring an allergy flare. Forty five percent \((n = 5)\) of dogs did not have their glucocorticoid dose reduced when receiving either ZnS or Control. There was a trend between ZnS and Control in glucocorticoid dose reduced when receiving either ZnS or Control. Eighteen percent \((n = 18)\) of dogs receiving Control could not have their glucocorticoid dose reduced when receiving either ZnS or Control. Table 2. Summary of Canine Atopic Dermatitis Lesion Index (CADLI) and pruritus Visual Analog Scale (VAS) in dogs where allergy medication was reduced for at least four weeks without an allergy flare.

<table>
<thead>
<tr>
<th>ZnS or control + allergy medication (ciclosporin or glucocorticoids)</th>
<th>Dogs with statistically significant reduction in CADLI, n/total number</th>
<th>Dogs with statistically significant reduction in pruritus VAS, n/total number</th>
<th>Dogs for which allergen medication was reduced for at least four weeks, n/total number</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZnS + ciclosporin</td>
<td>44, seven of 16</td>
<td>0, 0 of 16</td>
<td>69, 11 of 16</td>
</tr>
<tr>
<td>ZnS + glucocorticoids</td>
<td>55, six of 11</td>
<td>55, six of 11</td>
<td>55, six of 11</td>
</tr>
<tr>
<td>Control + ciclosporin</td>
<td>0, 0 of 16</td>
<td>0, 0 of 16</td>
<td>63, 10 of 16</td>
</tr>
<tr>
<td>Control + glucocorticoids</td>
<td>0, 0 of 11</td>
<td>0, 0 of 11</td>
<td>18, two of 11</td>
</tr>
</tbody>
</table>

Dogs received either ciclosporin (16 dogs) or glucocorticoids (11 dogs) for the duration of the study. Dogs also received the investigational zinc supplement (ZnS) for 12 weeks followed or preceded by the Control for 12 weeks. There was a four week allergy medication reduction during the final four weeks of each 12 week period. The difference between ZnS versus control in relation to reduction in allergy medication was not statistically significant for either ciclosporin or glucocorticoids.

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completion at Week 24. Neither owner had been able to discontinue glucocorticoids previously.

After eight weeks of supplementation with either ZnS or Control, we attempted to reduce the frequency of ciclosporin or dose of glucocorticoids by half. When combining results for the two allergy medications, 63% of dogs receiving ZnS and 37% of dogs receiving Control had their allergy medication reduced for at least four weeks without experiencing an allergy flare. This difference was not significant (P = 0.1027). Fifty five percent of dogs receiving glucocorticoids and ZnS could have their glucocorticoid dose reduced to control pruritus by half. Four of these eleven dogs responded to ZnS and not to Control. The difference between ZnS and Control to successfully permit glucocorticoid dose reduction was nearly significant (P = 0.076). The authors suspect that statistical significance could be achieved if a larger study population were evaluated.

A surprising outcome of this study was the marked difference in the response to ZnS between dogs receiving ciclosporin compared with dogs receiving glucocorticoids. This led the study to being unexpectedly underpowered. Dogs receiving glucocorticoids were more likely to benefit from therapy with ZnS. It is assumed that glucocorticoids enhance the absorption of zinc in dogs and perhaps this explains why dogs receiving glucocorticoids seemed to receive more benefit from ZnS than dogs receiving ciclosporin.4

Several dogs could have the frequency of ciclosporin administered or the dose of glucocorticoid administered decreased for four weeks without incurring an allergy flare while receiving ZnS and also while receiving Control. It is possible these dogs could have had the dose of glucocorticoid or frequency of ciclosporin reduced by the owner prior to being enrolled in the study, although the owners and attending veterinarians thought the dogs were receiving the lowest effective dose.

Individual variation occurred with the effect of ZnS on coat condition. Subjective assessments of coat condition did not reveal a significant difference between ZnS versus Control for either treatment group. One dog receiving ciclosporin and one dog receiving glucocorticoid each had dramatic hair growth during eight weeks of treatment with ZnS. The change in hair was not associated with development or resolution of skin infections because both dogs had no evidence of infection based on examination of cytological samples at study entry.

The investigational treatment, ZnS, contained 30 mg zinc from zinc methionine, 2 mg biotin, 128.7 mg EPA and 85.8 mg DHA per tablet administered as 1 tablet per 18.2 kg body weight. A zinc dose of 10–20 mg per day has been suggested for initial supplementation of zinc-deficient human patients with AD.14 Dogs with zinc-responsive dermatoses are often empirically dosed initially at 2 mg/kg per day of elemental zinc.21 The 1.6 mg/kg zinc provided by ZnS is just below this recommended dose. The amount of EFA in ZnS is 7.1 mg/kg EPA and 4.7 mg/kg DHA. This is much lower than the commonly recommended dose of 40 mg/kg EPA and 26 mg/kg DHA for dogs with pruritic skin disease,8 and therefore the EFA in ZnS is unlikely to have been responsible for the clinical benefit. A weakness of our study is the uncontrolled EFA amounts received through the dogs’ diets and through a concurrent EFA supplement in four dogs. The amount of biotin in ZnS is 0.1 mg/kg and is much lower than the 0.5 mg/kg dose used in a study which purported to show a favourable effect of biotin on skin condition in dogs.22 ZnS should be viewed as a supplement and not a total replacement to meet the daily EFA and biotin needs of dogs.

A major limitation to this study is the small sample size. Particularly with the noted differences between dogs receiving ciclosporin and those receiving glucocorticoids, larger groups of dogs receiving each of these allergy medications are clearly needed to further define the role of zinc methionine in CAD. It would also be helpful to evaluate the adjunctive use of zinc methionine in dogs receiving other immune modulating therapies for CAD.

A crossover design allowed each patient to serve as its own control. Although there was no washout period between the treatments, as we were studying the adjunctive effect of zinc in CAD, the only difference between the two supplements was the presence or absence of zinc. To minimize the possibility of carryover effect, dogs were evaluated no sooner than eight weeks after the crossover. Additionally, all patients were required to be returned by their owners to their maintenance allergy therapies no later than four weeks prior to study evaluation at Week 20. We tested the possibility of a carryover effect and determined there was no evidence of a significant carryover effect on either CADLI or pruritus VAS. Thus, the data from the two periods were combined and analysed. Despite the lack of a significant carryover effect, the inherent potential bias of the cross-over design is a potential weakness of this study.

Another limitation was our decision to include only dogs well controlled on their current allergy treatments. This resulted in narrow ranges over which scores varied. At Week 0, CADLI scores averaged 9.8 (with a maximum score of 50), placing most dogs in the “mild” category with a few dogs falling into the “moderate” category. Throughout the study, pruritus VAS scores for dogs receiving ciclosporin ranged from two to five of 10, and most dogs were well controlled throughout the study. The owners, however, likely recalling their dog’s previous history of severe pruritus, were very sensitive to even small increases in pruritus level. It has been observed elsewhere that owners may tend to overestimate their dog’s level of pruritus.19 Additional studies with larger populations of dogs, particularly those with more severe signs of CAD, are needed.

Although these dogs were well-controlled on their current allergy medication regimen, allergy flares occurred over this 24 week study period. These flares occurred independent of study treatment and, at times, without adjustment to maintenance allergy medication. These flares likely occurred secondary to fluctuations in pollen levels, mould or dust exposure. The authors attempted to minimize seasonal influences on allergy flares by staggering study entry so the study covered the entire calendar year. Owners were instructed to present for examination any dog believed to have worsening allergy signs prior to adjusting allergy medication dose or frequency. However, many owners were adept at adjusting their dog’s allergy...
treatments based on the dog’s clinical signs despite this practice being discouraged during the study. Owners were interviewed at each study evaluation to determine if changes had been made to maintenance therapies within the preceding two weeks. We removed from statistical analysis individual data points for CADLI or pruritus VAS when such owner-made adjustments happened, but it is possible that such adjustments were not always known to have occurred. Inclusion of these data may have affected the overall study results.

Infections occurred during this study at a surprisingly high rate in both allergy medication groups and in both treatment groups. ZnS was not found to reduce infection occurrence over Control. Although dogs were screened for and infections were treated prior to study enrolment, 78% of the dogs developed infection at least once during the study period. It is possible that the high rate of infection found in this study was impacted by our narrow definition of what constituted infection. However, failure to treat infections may have adversely affected patient comfort or led to a high attrition rate for the study. Infection treatment during the study was instituted to improve patient wellbeing, simulate actual clinical practice and allow for a better evaluation of the study treatments and their effect on allergic pruritus and skin lesions. Treatment of infections minimally impacted the overall study results. Although treatment of infections can improve CADLI,20 our results did not find a significant association between infection treatment and CADLI. Though reduced pruritus is an expected outcome of eliminating infectious organisms from the skin, we found a significant association between infection treatment and reduced pruritus VAS only for study Week 20. For all other study evaluations, treatment of infection did not significantly affect pruritus VAS. Many dogs could have a reduction in allergy medication with ZnS without receiving antimicrobial therapy. Conversely, many dogs on Control could not have a reduction in allergy medication even with antimicrobial therapies. For dogs receiving ZnS, those receiving an antimicrobial were no more likely to have their allergy medication reduced without experiencing an allergy flare than those not receiving an antimicrobial. For dogs receiving Control, those receiving ciclosporin were less likely to have a reduction made in their allergy medication while receiving an antimicrobial. The reasons for this are unknown.

As fluconazole and ketoconazole increase ciclosporin blood levels,25 there may have been additional effects on the clinical signs of AD when treating this population of dogs for Malassezia yeast dermatitis. Four dogs received ciclosporin and fluconazole concurrently for two weeks during the study period. Any influence on study outcome was minimized by discontinuing fluconazole a minimum of two weeks prior to evaluation of CADLI and pruritus VAS. However, a possible consequence on the overall efficacy outcomes must be considered for these three dogs.

In summary, this study provides evidence supporting a potential benefit of adjunctive zinc methionine supplementation in dogs with mild to moderate, chronic, non-seasonal CAD. Dogs receiving glucocorticoids may be more likely to benefit from zinc methionine supplementation. Additional studies are needed to better clarify the role of adjunctive zinc methionine in the treatment of CAD.

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References

Résumé

Contexte – Le zinc est important pour la santé de la peau et pour une bonne fonction du système immunitaire.

Hypothèses/Objectifs – Le méthylium de zinc, les acides gras essentiels (EFA) et les produits de biotine (supplément en Zn) ont été comparé à EFA et produit de biotine (contrôle) dans la dermatite atopique canine (CAD).

Sujets – Vingt sept chiens de propriétaires atteints de CAD chronique recevant de la ciclosporine ou des corticoïdes.

Méthodes – Une étude contrôlée, en double aveugle, randomisée de 24 semaines avec crossoverse à semaine 12 et avec 4 semaines de diminution des traitements allergiques aux semaines 8 et 20. Les évaluations ont compris un CADLI (Canine Atopic Dermatitis Lesion Index), une VAS (pruritus Visual Analog Scale) et des cytologies.

Résultats – Les chiens recevant la supplémentation en zinc et la ciclosporine pendant huit semaines, 44% (n = 7) avaient un CADLI diminué significativement de 10.9 à 5.0 (P = 0.0043) et une VAS de prurit de 7.4 à 3.2 (P = 0.0166). Pour les chiens recevant soit des corticoïdes soit de la ciclosporine, il n’y avait pas de diminution dans l’utilisation de ces traitements, et au moins pour quatre semaines, dans 63% des chiens recevant la supplémentation en zinc et 37% des chiens recevant le contrôle. Cette différence n’était pas significative (P = 0.1027). Au cours de l’Étude 78% des chiens ont été diagnostiqués et traitées pour une infection cutanée superficielle.

Conclusions et importance clinique – Cette étude montre un effet potentiel bénéfique d’une supplémentation en méthylium de zinc dans la CAD. Les chiens recevant les corticoïdes peuvent être plus susceptibles d’en bénéficier. Des études supplémentaires sont nécessaires pour étayer ces premiers résultats.

Resumen

Introducción – El zinc es importante para la salud de la piel y la función adecuada del sistema inmunológico.

Hipótesis /Objetivos – Se comparó un suplemento de metionina de zinc, ácidos grasos esenciales (EFA) y biotina (suplemento de Zn) con un producto de EFA y biotina (control) para la dermatitis atópica canina (CAD).

Animales – Vinteisiete perros de propietarios privados con CAD crónica que recibían ciclosporina o glucocorticoides.

Métodos – Un estudio controlado, doble ciego, al azar, de 24 semanas con cruzamiento en la semana 12 y con un período de 4 semanas de reducción de la medicación alérgica a las semanas 8 y 20. Las evaluaciones incluyeron el índice de lesiones de dermatitis atópica canina (CADLI), escala visual análoga de prurito (VAS) y muestreo citológico.

Resultados – En perros que recibieron el suplemento de zinc y la ciclosporina durante ocho semanas, el 44% (n = 7) presentaron disminución significativa del CADLI de 11.9 a 6.0 (P = 0.0002) sin cambio significativo en el VAS de prurito (P = 1.0). En los perros que recibieron el suplemento de zinc y los glucocorticoides durante ocho semanas, el 55% (n = 6) presentaron disminución significativa del CADLI de 10.9 a 5.0 (P = 0.0043) y el prurito VAS de 7.4 a 3.2 (P = 0.0166). Para perros que recibieron esteroides o ciclosporina hubo una reducción en el uso de estos medicamentos, durante al menos cuatro semanas, en el 63% de los perros que recibieron el suplemento de zinc y el 37% de los perros que recibieron el control. Esta diferencia no fue significativa (P = 0.1027). Setenta y ocho por ciento de los perros fueron diagnosticados y tratados por infecciones cutáneas superficiales durante el estudio.

Conclusiones y importancia clínica – Este estudio indica un efecto potencialmente beneficioso de la suplementación con metionina de zinc en CAD. Los perros que reciben glucocorticoides pueden ser más propensos a beneficiarse. Se necesitan más estudios para apoyar estos resultados iniciales.

Zusammenfassung

Hintergrund – Zink ist wichtig für die Hautgesundheit und eine gute Funktion des Immunsystems.

Hypothese/Ziele – Es wurde ein Produkt bestehend aus Zinkmethionin, essentiellen Fettsäuren (EFA) und
Zinc as adjunctive therapy for CAD

Biotin (Zn Supplement) mit EFA und einem Biotinprodukt (Kontrolle) zur Behandlung der atopischen Dermatitis (CAD) des Hundes verglichen.

**Tiere** – Siebenundzwanzig Hunde in Privatbesitz mit chronischer CAD erhielten Cyclosporin oder Glukokortikoide.


**Ergebnisse** – Bei den Hunden, die das Zinksupplement und Cyclosporin acht Wochen lang erhielten zeigten 44% (n = 7) eine signifikante Verminderung der CADLI Werte von 11,9 auf 6,0 (P = 0,0002) ohne einen signifikanten Unterschied bei den Pruritus VAS Werten (P = 1,0). Bei Hunden, die das Zinksupplement und Glukokortikoide acht Wochen lang erhielten, zeigten 55% (n = 6) signifikante CADLI Werte von 10,9 auf 5,0 (P = 0,0043) und Pruritus VAS von 7,4 auf 3,2 (P = 0,0166). Bei Hunden, die entweder Steroide oder Cyclosporin erhielten, konnten bei 63% der Hunde, die Zinksupplement erhielten und bei 37% der Hunde, die die Kontrollprodukten erhielten, diese Medikamente für mindestens vier Wochen reduziert werden. Der Unterschied war nicht signifikant (P = 0,1027). Bei achtundseidzig Prozent der Hunde wurde während der Studie eine superfizielle bakterielle Infektion diag nostiziert und behandelt.

**Schlussfolgerungen und klinische Bedeutung** – Diese Studie stützt den potentiellen Nutzen einer zusätzlichen Zinkmethionin Supplementierung bei CAD. Hunde, die Glukokortikoide erhielten konnten davon mehr profitieren. Es sind weitere Studien nötig, um diese ersten Ergebnisse zu festigen.

**要約**

**背景** – 塩鉄は皮膚の健康と適切な免疫機能にとって重要である。

**仮設/目的** – 大アトピー性皮膚炎(CAD)に対する、塩鉄メチオニン、必須脂肪酸(EFA)およびビオチンの製品(塩鉄サプリメント)とEFAおよびビオチンのみの製品(コントロール)の効果を比較した。

**供与動物** – シクロスポリンまたはグロコールチオイルを服用している慢性CADに罹患した27頭の対象犬。

**方法** – 本研究は、24週間の無作為化二重盲検対照研究で、12週目にクロスオーバーを行い、8週目および20週目52間のアレルギー薬の減量を行った。評価には、犬アトピー性皮膚炎変数指数(CADLI)、スンミのVisual Analog Scale(VAS)および細胞診を用いた。

**結果** – 塩鉄サプリメントとシクロスポリンを8週間投与された犬の44% (n = 7)でCADLIが11,9から6,0へと有意に減少した(P = 0,0002)が、スンミVASに有意な変化は認められなかった(P = 1,0)。塩鉄サプリメントとグロコールチオイルを8週間投与された犬の55% (n = 6)でCADLIが10,9から5,0へと(P = 0,0043)およびスンミVASが7,4から3,2へと有意に減少した(P = 0,0166)。ステロイドまたはシクロスポリンを投与された犬では、塩鉄サプリメント群の63%およびコントロール群の37%において、少なくとも4週間の薬剤減量が行われたが、有意差は認められなかった(P = 0,1027)。78%の犬が、治療中に表在性膿皮症と診断され、治療を受けた。

**結論および臨床的な重要性** – 本研究は、CADにおける塩鉄メチオニンサプリメントの補助的効果の可能性を支持している。グロコールチオイルを投与された犬ではより効果がある可能性がある。これらの初期結果を実証するためにはさらなる研究が必要である。

**摘要**

**背景** – 塩鉄を皮膚健康と維持正常免疫機能具有重要作用。

**仮説/目的** – 一种含锌氨基酸，必需脂肪酸(EFA)和生物素的产品(锌补充剂)，应用于犬异位性皮炎(CAD)，同时以不含EFA和生物素的产品作为对照进行比较。

**动物** – 27只家犬接受受环境因素和或皮质激素治疗的慢性CAD患犬。

**方法** – 采用持续24周的随机、双盲、对照研究。在服药8周和20周时，开始减少过敏药物用量，持续4周。在第12周进行交换。评价指标包括犬异位性皮炎变数指数(CADLI)、瘙痒视觉模拟能量表(VAS)和细胞学采样。

**结果** – 在接受环境因素和锌补充剂治疗达8周的犬中，44%(n = 7)的CADLI值从11,9降到6,0 (P = 0,0002)，但瘙痒VAS值变化不显著(P = 1,0)。在接接受皮质激素和锌辅助治疗达8周的犬中，55%(n = 6)的CADLI值从10,9降到5,0 (P = 0,0043)。受试者VAS值从7,4降到3,2 (P = 0,0166)。不论服用皮质激素还是是锌补充剂，至少在4周的减量过程中，有63%的犬接受锌补充剂治疗，37%的犬接受对照药物治疗。其差异不显著(P = 0,1027)。在研究期间，有78%的犬发生了线表皮肤感染，并接受相应治疗。

**结论和临床意义** – 这项研究表明，治疗犬异位性皮炎时，补充锌氨酸锌具有潜在的价值。病犬同时接受皮质激素素治疗可能效果更好，这些初步结果还需要进一步研究论证。

**Resumo**

**Contexto** – O zinco é importante para a saúde da pele e para o bom funcionamento do sistema imune.

**Hipótese/Objetivos** – Um suplemento contendo zinco metionina, ácidos graxos essenciais (EFA) e biotina (suplemento Zn) foi comparado a um suplemento com EFA e biotina (controle) em animais com dermatite atópica canina (DAC).
Animais – Vinte e sete cães de proprietários com DAC crônica tratados com ciclosporina ou glicocorticóide.

Métodos – Um estudo duplo-cego controlado e randomizado de 24 semanas, com configuração cruzada na semana 12 e um período de 4 semanas de redução da medicação antialérgica nas semanas 8 e 20. As avaliações incluíram o Canine Atopic Dermatitis Lesion Index (CADLI), pruritus visual analogue scale (VAS) e análises citológicas.

Resultados – Dos cães que receberam o suplemento com zinco e ciclosporina por oito semanas, 44% (n = 7) tiveram uma redução significativa no CADLI de 11.9 para 6.0 (P = 0.0002) sem redução significativa no prurido VAS (P = 1.0). Dos cães recebendo suplemento com zinco e glicocorticoides por oito semanas, 55% (n = 6) tiveram redução significativa no CADLI de 10.9 para 5.0 (P = 0.0043) e no prurido VAS de 7.4 para 3.2 (P = 0.0166). Houve uma redução no uso de medicação tanto nos cães recebendo glicocorticoides ou ciclosporina, por ao menos 4 semanas, em 63% dos cães recebendo o suplemento com zinco e 37% nos cães recebendo o controle. Esta diferença não foi significativa (P = 0.1027). Setenta e oito porcento dos cães foram diagnosticados e tratados para infecções bacterianas superficiais durante o estudo.

Conclusões e importância clínica – Este estudo corrobora com o potencial benefício adjuvante da suplementação com zinco metionina em DAC. Cães tratados com glicocorticoides foram mais predispostos aos benefícios da suplementação. São necessários mais estudos para substanciar estes resultados iniciais.