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Are Probiotics Effective in Reducing Symptoms of Atopic Dermatitis?

Samuel H. Kim, PA-S

A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

In Partial Fulfillment of the Requirements For

The Degree of Master of Science

In

Health Sciences – Physician Assistant

Department of Physician Assistant Studies
Philadelphia College of Osteopathic Medicine
Philadelphia, Pennsylvania

December 12, 2018
Abstract

OBJECTIVE: The objective of this selective EBM review is to determine whether or not probiotics are effective in reducing symptoms of atopic dermatitis.

STUDY DESIGN: Selective EBM review of three randomized, double-blind, placebo-controlled trials published after 2009, all English language.

DATA SOURCES: All three studies were published in peer-reviewed journals found on PubMed and selected based on relevance to the proposed clinical question.

OUTCOMES MEASURED: The main outcome measured was the percentage change in SCORAD index to determine severity of atopic dermatitis before and after trial through objective and subjective findings. Additional outcomes included DLQ index which was evaluated via 10 questions scored on a scale of 0-3, IDQOL and DFI questionnaires directed towards evaluating quality of life through 10 questions scored from 0-3, and frequency and amount of corticosteroid used.

RESULTS: Each study assessed the change in SCORAD when comparing the probiotic with the placebo group in those with moderate-to-severe atopic dermatitis. Gerasimov et al. found a SCORAD decrease of 33.7% in the probiotic group in comparison to a decrease of 19.4% in the placebo group and no statistically significant decrease in corticosteroid use (p=0.130). IDQOL and DFI decreased by 33% and 35.2% in the probiotic group and only by 19% and 23.8% in the placebo group, respectively. Iemoli et al. found that SCORAD and DLQ at the end of the trial was significantly reduced in the probiotic group (p = 0.001, p = 0.024, respectively). The study done by Navarro-Lopez et al. found a SCORAD change of -83% (95% CI, -95% to -70%) in the probiotic group and a change of -24% (95% CI, -36% to -11%) in the placebo group. Topical steroid use in the probiotic arm (7.7%) was significantly less compared to the placebo arm (10.8%).

CONCLUSION: This systematic review suggests that probiotics are effective only as an adjunctive therapy in the reduction of clinical symptoms and topical corticosteroid use in atopic dermatitis. However, further research is needed to assess exclusive reduction in subjective symptoms.

KEY WORDS: Atopic dermatitis, probiotics
INTRODUCTION

Atopic dermatitis (AD) is a skin disorder with a chronic, recurrent course characterized by pruritus, inflammation, and skin barrier disruption. This condition typically manifests early during childhood and often persists into adulthood. AD poses a significant impact on quality of life as the pruritus can affect sleep quality and result in symptoms that may cause emotional stress over the course of an individual’s life. Without proper care, the affected areas can harbor colonization and infection by bacteria such as *Staphylococcus aureus*.\(^1\) This condition is commonly associated with asthma and allergic rhinitis as they are all considered to be atopic disorders.

There is great potential for clinical impact in the field of AD treatments as it is a commonly diagnosed skin disorder. AD has a prevalence of approximately 3-10% in adults and 20% of children worldwide with about half of those cases being diagnosed within the first year of life.\(^2\) Beyond the scope of the individual practitioner and patient, AD also poses a sizeable portion of healthcare costs nationwide. The annual financial cost of AD is estimated to be $5.297 billion which includes direct (prescriptions, visits to the physician) and indirect costs (absenteeism, decreased quality of life).\(^3\) These costs correlate with the fact that AD comprises a great deal of healthcare visits each year. Although precise census data are not available for recent years, it is estimated that 75% of individuals with AD visited a physician at least once in the last year with AD being the prime focus of their visit.\(^3\)

The heavy burden endured by practitioners and patients in treating AD is evident. However, the exact cause of AD remains unknown. Current leading research points to a mutation in the gene that produces filaggrin, a protein that maintains the integrity of the superficial-most layer of skin.\(^2,4\) Without fully functional filaggrin, there is a greater propensity
for the entrance of allergens and microbes coupled with greater loss of moisture, resulting in skin that becomes dry easily and is more susceptible to infection.\textsuperscript{2,4} It is also thought that AD develops from an excess of T helper 2 cells relative to T helper 1 cells, leading to an increase in IgE and interleukins.\textsuperscript{2} This manifests in the patient as symptoms of dry, scaly skin, erythema, pruritus, and open, crusty, or “weepy” sores.\textsuperscript{4}

There are various methods of treating AD with each having specific indications. One of the more common treatment modalities is the use of corticosteroids which can be administrated topically or orally, with the latter being reserved for severe cases.\textsuperscript{2} Corticosteroids are indicated for symptom reduction after an exacerbation and are not indicated for prevention of acute episodes; however, there are a variety of preventative methods to reduce the occurrence of flares. Skin hydration and emollients coupled with the avoidance of allergens and irritants are effective towards preventing acute flares of AD. Less frequently used methods to treat AD include Narrowband Ultraviolet B (UVB) Phototherapy and biologics/immunosuppressants such as dupilumab.\textsuperscript{4}

Unfortunately, there is currently no cure for AD. The treatment modalities listed above play an effective role in preventing or reducing sequelae of flares, but AD is a recurrent condition that may be a lifelong source of emotional stress on the patient. The treatment methods are also not entirely benign as corticosteroids have a variety of undesirable side effects such as stretch marks, and hypopigmentation and atrophy of skin, especially with prolonged use.\textsuperscript{4} Narrowband UVB phototherapy has a success rate of 70% in temporarily “remitting” AD, but it is primarily used for widespread or refractory AD so the application is limited.\textsuperscript{4} While biologics such as dupilumab have shown efficacy, there are a variety of barriers such as high out-of-pocket costs, requirements to fail lower forms of therapy, and the necessity of prior authorization.\textsuperscript{4}
These are only some of the many reasons why probiotics have gained a great deal of traction as an adjunctive therapy option to reduce symptoms of AD.

Probiotics have recently been targeted as a potential form of therapy in reducing AD symptoms. One of the main reasons is due to the immunological benefits of probiotics. Research has shown that AD patients tend to have a decreased innate immune response when compared with similar skin conditions such as psoriasis.\textsuperscript{1} The microflora in the human gut has a significant role in maintaining healthy immune function and as such, probiotics must be considered as a method to improve this function. This paper evaluates three double-blind, placebo-controlled, randomized controlled trials (RCTs) comparing the efficacy of various probiotic mixtures as a potential treatment option for reduction of AD symptoms.

**OBJECTIVE**

The objective of this selective EBM review is to determine whether or not probiotics are effective in reducing symptoms of atopic dermatitis.

**METHODS**

Three double-blind, placebo-controlled RCTs were used in this study. The criteria to select these studies included patients greater than 1 year of age with symptomatic moderate-to-severe atopic dermatitis. The interventions used in two of the studies were oral probiotic mixtures,\textsuperscript{2,5} while one study used a probiotic sachet.\textsuperscript{2} The treatment group receiving the probiotic mixture was compared to the control group who received a visually matched placebo.

All of the articles used in this study were published in peer-reviewed journals and selected based on patient-oriented evidence that matters (POEMs) along with relevance to the proposed clinical question. The articles were found by using the keywords “atopic dermatitis” and “probiotics” via PubMed literature search. Only studies written in English were included in
this review. The inclusion criteria included RCT, placebo-controlled, double-blind studies published after 2009. The exclusion criteria included any patients under the age of 1 and those with mild AD.

All three studies included in this systematic review used continuous data. The statistics that were reported included change in mean from baseline and p-values. The Mann-Whitney U test was used to assess Scoring of Atopic Dermatitis (SCORAD), Infant Dermatitis Quality of Life (IDQOL), and Dermatitis Family Impact (DFI) scores in one of the studies.5 Table 1 illustrates the demographics and characteristics of the reviewed studies.

**Table 1: Demographics and Characteristics of Included Studies.**

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th># Pts</th>
<th>Age (yrs)</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>W/D</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gerasimov5 (2010)</td>
<td>Double blind RCT</td>
<td>90</td>
<td>1-3</td>
<td>-Patients aged 1-3 years old with moderate to severe AD</td>
<td>-Mild AD</td>
<td>6</td>
<td>Probiotic mixture (Lactobacillus acidophilus DDS-1 and Bifidobacterium lactis UABLA-12 with fructo-oligosaccharide in a rice maltodextrin powder) 1 g BID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Parent or legal guardian must comprehend study requirements and provide informed consent</td>
<td>-Clinically evident bacterial lesions</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Direct telephone access</td>
<td>-Use of systemic corticosteroids</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Food allergy besides egg or cow’s milk</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Concomitant disease requiring immunosuppressants or allergic reactions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Design</td>
<td>Sample Size</td>
<td>Eligibility</td>
<td>Probiotics</td>
<td>OUTCOMES MEASURED</td>
<td></td>
<td></td>
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<tr>
<td>------------------</td>
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<td>-------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>------------------------------------------------------------------------------------------------</td>
<td>----------------------------------------------------------------------------------------------------------</td>
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<td></td>
</tr>
</tbody>
</table>
| Iemoli et al. (2012) | Double blind RCT | 48          | -Adult men and women with moderate to severe AD                                                   -Probiotic, antibiotic, or immune modulating agent usage 6 months before the study  
-Oral steroid treatment usage 1 month before enrollment | Probiotic mixture (Lactobacillus salivarius and Bifidobacterium breve combination) matched for size, shape, and volume - BID |
| Navarro-Lopez (2018) | Double blind RCT | 50          | -AD meeting the Hanifin and Rajka criteria and moderate SCORAD index who had been prescribed topical steroids  
-Current diet with a Mediterranean Diet Quality Index (KIDMED) score >7  
-Written informed consent from parents or a legal representative (and the child if >12 years) | Systemic corticosteroid, methotrexate, cyclosporine, or anti-TNF drug use in the past 3 months, antibiotics in the past 2 weeks, or concomitant diagnosis of gluten and/or lactose intolerance or bacterial infection. | Each of the three studies assessed changes in objective and subjective findings between the probiotic and placebo group using the SCORAD index which was calculated with the following formula: A/5 + 7B/2 + C. Objective findings included characteristics such as extent and intensity of AD, while subjective symptoms included elements such as pruritus and sleep loss. The SCORAD index questionnaire assessed the severity of AD, categorizing them as mild, moderate, or severe. Each study had differing values indicating the severity of AD. For instance, Gerasimov et al. categorized any score between 25-50 as moderate AD, while a score above 50 indicated severe AD. This study also implemented IDQOL and DFI questionnaires for the test |
subjects to complete. These questionnaires included ten questions specific to the infant or family activity over the course of the previous week with each answer being graded from 0-3. A minimum score of 0 and a maximum score of 30 is possible with the maximum score indicating the worst quality of life or the greatest family impact. Lastly, corticosteroid use was documented by the participants.

In the Lopez et al. study, the SCORAD index was assessed with a score of 20-40 indicating moderate AD. These were measured at the time of inclusion and every 4 weeks until the end of follow-up period at week 12. As it was performed in the study by Gerosimov et al., this study measured the proportion of days that a topical steroid was used during flares within the same 12 weeks of follow-up. A flare was defined as the use of a corticosteroid for at least 3 consecutive days and any corticosteroid use occurring less than 3 days was not included.

In the Iemoli et al. study, the SCORAD index was scored as follows: 0-15 indicated mild AD, 16-40 indicated moderate AD, and any score above 40 indicated severe AD. Another outcome that was assessed was the Dermatology Quality of Life (DLQ) index which was performed by the patient. The DLQ index has a minimum score of 0 and a maximum score of 30. It is a 4-point scale ranging from 0-3 in which 0 indicates not at all, 1 indicates a little, 2 indicates a lot, and 3 indicates very much.

RESULTS

All three RCT studies evaluated the effectiveness of various probiotic mixtures compared to placebo on individuals with moderate-to-severe AD. Placebos in these studies were identical to the probiotic in characteristics such as taste, smell, and/or visual appearance. Patients were excluded if they had previously used antibiotics, immunomodulators, or systemic corticosteroids in any of these studies. Continuous data were used for all three experiments and not
convertible to dichotomous format. Each study determined data to be statistically significant if the p-value was <0.05.

Two trials mentioned compliance with only one of those studies providing statistical evidence. Gerasimov et al. reported that the placebo and probiotic group were 95% and 92% compliant, respectively, with both groups receiving more than 90% of available doses (p=0.723). This statistic was calculated through parental report and by measuring the probiotic and placebo powder which remained at the end of the trial. Ieomoli et al. reported that compliance was evaluated through a dose count but omitted results of such findings. Two trials were in children over the age of 1, while one trial exclusively included adults.

The Gerasimov et al. study included children between the age of 1-3 with moderate-to-severe AD. Direct telephone and informed consent from a parent or legal guardian were also part of the inclusion criteria as the participants were too young to provide consent on their own. Individuals excluded from this study included those with mild AD, bacterial lesions that were clinically evident, food allergies excluding egg or cow’s milk, current systemic disease or cancer, and immunodeficiencies.

The beginning of the experiment included 96 participants, however, by the week 8 mark, 5 were lost to follow-up in the experimental group while 1 was lost in the control group. The experimental group of 43 patients received a probiotic mixture (DDS-1, UABLA-12 with fructo-oligosaccharide) twice a day for 8 weeks while the control group of 47 patients received a placebo twice a day for 8 weeks. SCORAD, IDQOL, DFI, and corticosteroid use were documented to evaluate the effectiveness of the probiotic in reducing symptoms of AD. Statistical significance was observed when comparing SCORAD, IDQOL, and DFI at baseline and week 8 of the trial (p=0.001, p=0.013, and p=0.010, respectively). This study found a
statistically significant reduction in SCORAD at the end of the trial when assessing exclusively subjective symptoms (pruritus, sleep loss). These findings fall in line with the overall SCORAD decrease of 33.7% and 19.4% in the probiotic and placebo group, respectively. However, there was no statistical significance with corticosteroid use per week (p=0.130) when comparing baseline and week 8 findings. These findings are illustrated in Table 2 below.

**Table 2: Change in mean at baseline and week 8 (Gerosimov et al.)**

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Probiotic (SD)</th>
<th>Placebo (SD)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SCORAD</strong>*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>8.7 (2.9)</td>
<td>8.0 (2.4)</td>
<td>0.001</td>
</tr>
<tr>
<td>Week 8</td>
<td>-3.0 (2.7)</td>
<td>-1.4 (2.0)</td>
<td></td>
</tr>
<tr>
<td><strong>IDQOL</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>11.2 (4.4)</td>
<td>12.1 (3.6)</td>
<td>0.013</td>
</tr>
<tr>
<td>Week 8</td>
<td>-3.7 (3.3)</td>
<td>-2.3 (1.6)</td>
<td></td>
</tr>
<tr>
<td><strong>DFI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.2 (4.0)</td>
<td>12.6 (4.7)</td>
<td>0.010</td>
</tr>
<tr>
<td>Week 8</td>
<td>-4.3 (1.7)</td>
<td>-3.0 (2.7)</td>
<td></td>
</tr>
<tr>
<td><strong>Corticosteroid use</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>1.9</td>
<td>1.7</td>
<td>0.130</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.8</td>
<td>1.2</td>
<td></td>
</tr>
</tbody>
</table>

*Assessing subjective symptoms (pruritus, sleep loss)

SD = standard deviation

The Iemoli et al. study included adult men and women with moderate-to-severe AD in the setting of a hospital allergy unit. Individuals were excluded from the study if they had used probiotics 6 months prior to the trial. A total of 48 patients were enrolled in the study and separated into a probiotic and placebo group in a 2:1 ratio. A single patient was lost from each group. The experimental group of 32 patients were administered with a probiotic mixture (LS01 and BR03 strains) taken twice daily for 12 weeks. The control group of 16 patients took a placebo (maltodextrin) with the same regimen.

The SCORAD and DLQ questionnaire were addressed in this study with changes noted in the probiotic and placebo group when compared at baseline to week 12 of the study. The SCORAD at baseline for the probiotic group (46.25 +/- 3.70) and placebo group (45.00 +/- 2.60) were decreased at week 12 to 29.45 +/- 2.01 and 40.21 +/- 1.53, respectively. The probiotic
group had significant decreases in SCORAD and DLQ at the end of treatment (p = 0.001, p = 0.024, respectively) and even 2 months after treatment (p = 0.006, p = 0.001, respectively). The placebo group had no significant differences.

The Lopez et al. study was performed in an outpatient hospital and included children between age 4-17 years old with moderate AD. It was required for participants to be currently on a high-quality Mediterranean diet validated through the Mediterranean Diet Quality Index (KIDMED). As with the previous study, participants required written consent from the parent or legal representative due to age. Those excluded from the study included intolerance to gluten or lactose as well as signs of bacterial infection.

The study began with 50 participants, however, 2 were lost to follow-up at the 8-week mark, while 1 was lost at the 12-week follow-up in the experiment group. This study examined the change in SCORAD score and corticosteroid use between the experimental and control group. The experimental group of 26 patients were instructed to take a probiotic (CECT 8145, CECT 7347, and CECT 9104) once daily for 12 weeks. The control group of 24 patients took a placebo (maltodextrin) once daily for the same amount of time and was matched in appearance and route of administration to the probiotic. Lopez et al. reported a significant improvement in the total SCORAD score among the probiotic group when compared to the placebo group. The total SCORAD combined objective findings (intensity and spread of eczema) and subjective symptoms (pruritus, sleep loss) in the report. However, subjective symptoms are the only factor of statistical importance in this review. There was an insufficient amount of data provided in this study as the only conclusive finding was a report of no statistically significant difference in subjective symptoms between the probiotic and placebo group.
Lopez et al. found a statistically significant reduction in the use of corticosteroids during flares among the probiotic group. An adjusted logistic regression model was used to calculate the odds ratio (OR) to be 0.63 with a confidence interval (CI) of 95% [0.51 to 0.78]. The data favored probiotics even when a sensitivity analysis was performed to account for steroid use which included non-flare scenarios (defined as less than 3 consecutive days of corticosteroid use). In this situation, the placebo and probiotic arm had 336 (16.5%) and 291 (14.0%) days of steroid use, respectively. In this case, the OR was 0.77 with a CI of 95% [0.65 to 0.91] and p-value <0.003. The findings are illustrated in Table 3 below.

**Table 3**: Corticosteroid use in a flare (Lopez et al.)

<table>
<thead>
<tr>
<th></th>
<th>Patient-days of observation</th>
<th>Days of steroid use to treat flares</th>
<th>Odds Ratio; [CI 95%]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Probiotic</strong></td>
<td>2084</td>
<td>161 (7.7%)</td>
<td>0.63 [0.51 to 0.78]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>2032</td>
<td>220 (10.8%)</td>
<td></td>
<td></td>
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</tbody>
</table>

**DISCUSSION**

Probiotics offer a safe option in reducing symptoms of AD as they have an extensive history of being safe to use in healthy individuals. In fact, of the three studies in this review, only one mentioned adverse effects such as diarrhea, constipation, and upper respiratory infection with none of these being linked to the probiotics used in the study. The exception to safe probiotic use is with severely ill and immunocompromised individuals who may experience greater side effects.

In the review of these studies, a major limitation was in the assessment of the SCORAD index. The SCORAD evaluates objective findings, or disease-oriented outcomes, in addition to subjective symptoms, patient-oriented outcomes. For the purpose of this review paper, the latter is the focus which includes effects on pruritus and sleep loss. The combination of both categories
of symptoms makes it difficult to assess whether subjective, patient-oriented outcomes are truly being improved with the use of probiotics. Only two of the three studies in this review separated subjective and objective elements of the SCORAD with one of those studies finding statistically significant reduction in subjective symptoms,\(^5\) and the other noting insignificant symptom reduction between the probiotic and placebo group.\(^2\)

It is important for studies to control outside factors that can influence the results of a study. This was seen in the Lopez et al. study which mandated a high-quality Mediterranean diet. However, the data could have been more accurate with diary documentation of additional habits that may influence the course of AD such as exercise, brand of laundry detergent or soaps, and even moisturizing routine. These are all precipitating factors that have been proven to cause acute exacerbations of AD.\(^4\) It is apparent that these controls would be more difficult in studies exclusively involving children as it would require a great deal of compliance and responsibility in the hands of both the participant and the parent or legal representative.

**CONCLUSION**

These studies provide evidence that probiotics can be used as an effective adjunctive therapy in those with moderate-to-severe AD. While it will not have efficacy as monotherapy, the studies in this review have demonstrated a reduction of symptoms when taken along with other standard medications such as topical corticosteroids. In addition to being effective in reducing symptoms, it was also shown to significantly reduce the need for corticosteroid use in two of the studies.\(^2,5\) While all three of these studies found improvement in SCORAD overall, more research must be done focusing strictly on subjective symptoms given that this index also factors in objective signs.
References


