ABSTRACT

Background: The primary objective of the study was to evaluate the efficacy and safety of oral probiotics in the treatment of atopic dermatitis (AD) using the scoring atopic dermatitis (SCORAD) index, serum IgE levels and absolute eosinophil count (AEC). The secondary objective of the study was to determine the association of oral probiotic therapy and improvement in AD using global photographs, dermoscopic images (fotofinder) and individual patient satisfaction.

Methods: This was a randomized, double-blind study conducted on 70 patients (20 adults and 50 children) with moderate to severe AD. The participants were randomized into control arm and treatment arm. The treatment arm received conventional and probiotic therapy and only conventional therapy was provided to the control arm. The research was carried out in five visits. For each visit, SCORAD was calculated and response compared using clinical and videodermoscopic images. Patient satisfaction was documented using a quality of life questionnaire during each visit.

Results: Across the treatment arm, the mean serum IgE levels were greatly decreased in contrast to the control arm over the 12 weeks period. SCORAD score was significantly lowered in the treatment arm (55.20%) compared with 18.95% in the control arm. Dermoscopic assessment, global photographic assessment and patient satisfaction in the treatment arm showed statistically significant improvement in AD compared to the control arm.

Conclusions: The decrease in SCORAD scores demonstrated strong associations with the use of probiotics in patients with AD as an adjunct to conventional therapy. Thus, in both adults and children suffering from moderate to severe AD, probiotic supplement can be administered effectively as an adjunct therapy.

Keywords: Atopic dermatitis, SCORAD, Probiotics

INTRODUCTION

Atopic dermatitis (AD) is a chronic, recurrent inflammatory skin disease that usually begins in the childhood and is characterized by variable distribution of pruritic eczematous lesions with flexural predilection; mostly in patients with personal or family history of atopic diathesis. AD has a history of relapsing with frequent exacerbations and remissions. Relapse and remission are associated with elevated levels of serum IgE. AD’s natural history is referred to as ‘atopic march’ involving typical disease progression such as food
allergy, allergic rhinitis (hay fever), and asthma. In fact, it is often clear that ‘atopic diathesis’ entails personal or family history of bronchial asthma, allergic rhinitis and conjunctivitis, and/or AD, and/or predisposition to overproduction of IgE antibodies. The cumulative incidence of AD varies from 11% to 21%. In a hospital-based survey in the North Indian population, AD was reported as the most common dermatosis with 29.9% prevalence in paediatric dermatology clinic. A typical winter exacerbation was visible in 62% of the AD population. The prevalence of AD in different population ranged from 1-3.

The pathogenesis of AD is not completely established. It has been proposed that AD arise from the complex interaction of defects in the structure of the skin barrier, immune dysregulation and environmental and infectious agents. Impaired filaggrin gene expression is apparent in AD. This gene codes structural proteins which are important for the creation of skin barriers. Colonization of Staphylococcus aureus is observed in 90% of patients with AD. Deficient innate immune response, chemokine release, and proinflammatory cytokines encourage the development of immunoglobulin E (IgE) with systemic inflammatory responses and pruritic skin inflammation in AD.

Clinical manifestations of AD can be categorized into atopic itch, atopic dryness, atopic eczema and AD’s stigmata. Acute cases show red infiltrate with oedema, vesicles, oozing, and crust; lichenification, excoriation, papules, and nodules dominate the sub-acute and chronic phase. Among infants, the lesions are often found on the face and on the extensors, whereas in children and adults there is predilection for flexors. Chronic hand eczema can be presenting feature of AD in adults. There may be atypical morphologies such as nummular (discoid), prurigo-like, follicular and seborrheic dermatitis-like.

Numerous guidelines for the diagnosis of AD have been established, including Hanifin and Rajka in 1980, which was subsequently updated by the American academy of dermatology, guidelines provided by the UK working group in 1994, and the SCORAD score of AD.

SCORAD (scoring AD) is a clinical tool that is commonly used in dermatology clinics to determine the extent and severity of eczema. This assessment method is used by dermatologists to determine the efficacy of the medication before and after treatment. It considers three elements, area of eczema (A), intensity (B), and subjective symptoms (C), respectively. The rule of nine is used to calculate the area of the eczema (A). The score is added for each region. The total area ‘A’ is 100% maximum. The criteria for intensity are redness, swelling, oozing or crust, scratch marks, lichenification and dryness that are graded as none (0), mild (1), moderate (2), or severe (3). The scores of intensities are added together to give the maximum value of ‘B’ of 18. The patient or caregiver score subjective symptoms such as itch and sleeplessness using a visual analog scale where ‘0’ is neither itch nor sleeplessness and 10 is extreme itching or sleeplessness. Those are added to give ‘C’ which has a maximum value of 20. For individuals, the cumulative SCORAD is determined using formula A/5+B/2+C.

Most cases of AD may be managed effectively with topical therapies aimed at reducing inflammation of the skin and alleviating the pruritus. Emollients, topical corticosteroids, topical calcineurin inhibitors and antimicrobial and antiseptic interventions are the most widely used topical treatments. Systemic therapies such as glucocorticoids, cyclosporine, methotrexate, mycophenolate, azathioprine, are usually intended for patients with severe and refractory AD and often cause potential adverse effects. Adjunct treatment such as probiotic therapy may be addressed where AD symptoms become uncontrolled by adequate basic therapy.

Abundant evidence suggests that there are strong antipathogenic and anti-inflammatory properties in different bacterial strains chosen from the healthy gut microbiota. In AD, many targets for the probiotic approach have appeared, such as degradation/structural modification of enteral antigens, normalization of the properties of aberrant indigenous microbiota and gut barrier functions, modulation of the secretion of inflammatory mediators and promotion of immune system growth. Furthermore, the probiotic effects in AD have been attributed to the restoration of increased intestinal permeability and unbalanced intestinal microbiota, improved immunological barrier functions of the intestine, and reduced proinflammatory cytokine generation characteristic of local and systemic allergic inflammation. Therefore, alteration of the gut microbiota by probiotics, together with the immunomodulatory activity of particular probiotic strains, may be used as an approach to having a prophylactic or therapeutic effect in children and adults with atopic dermatitis. Probiotics help to control allergic hypersensitivity reactions by suppressing the Th2-mediated response that tends to balance Th1/Th2 immune responses and by increasing the Treg-mediated immune response. It was proposed that these viable microorganisms may modulate enteroocyte TLR (Toll-like receptors) and proteoglycan recognition proteins, contributing to DC (dendric cells) activation and Th1 response. A growing number of reports have studied the possible efficacy of probiotics in preventing and treating AD. Lactobacillus rhamnosus is the probiotic strain tested most commonly for the prevention of AD in children. Another research examined the effect on the treatment of allergic diseases of Bifidobacterium breve and Bifidobacterium longum administration over a span of 1 month prenatally, 6 months during infancy, and 18 months of follow up. Recent review of the role of probiotics in AD prevention suggests a beneficial impact of probiotic therapy for AD treatment.
In the current study, Lactogut and Lactogut Kidz oral probiotic supplements which were added to conventional therapy in the treatment arm were used. Considering the above background information, this clinical trial was designed with the primary objective to evaluate the efficacy and safety of oral probiotics in the treatment of atopic dermatitis (AD) using the scoring atopic dermatitis (SCORAD) index, serum IgE levels and absolute eosinophil count (AEC). The secondary objective of the study was to determine the association of oral probiotic therapy and improvement in AD using global photographs, dermoscopic images (fotofinder) and individual patient satisfaction.

METHODS

A 12 weeks randomized, double-blind assessment of the efficacy and safety of oral Lactogut and Lactogut Kidz probiotics for AD in adults and children was conducted at Cutis Academy of Cutaneous Sciences, Bangalore, Karnataka, India from March to December 2018.

This research was undertaken in compliance with the ICH harmonized tripartite guidelines for good clinical practice (GCP) adherence to the Helsinki declaration of ethical standards. The research was initiated after approval by the Cutis institutional ethics committee. The purpose of the research, the procedures to be carried out and the potential hazards that could be experienced during the study, the duration of the study and the follow-up visits were explained to subjects in non-technical terms in the language they knew, before the subjects were evaluated and enrolled in the trial. A study-specific informed consent document has been signed by all participants prior to screening. Enough time was given to read and appreciate the details presented and to ensure that participants were informed of the consequences of enrolling in the research. The informed consent was received in compliance with the ICH-GCP code of ethics.

A total of 70 patients (20 adults and 50 children) with moderate to severe AD were enrolled. Patients were recruited on the basis of the following inclusion and exclusion criteria.

### Inclusion criteria

The inclusion criteria used in this study were patients aged 0-60 years (paediatric: 0-18 years; adults: 18-60 years) with moderate to severe AD, with a SCORAD score of ≥15, subjects willing to participate in the study and those participants who consent not to alter the diet, medications or exercise routine considerably.

### Exclusion criteria

Exclusion criteria were patients using systemic corticosteroids or phototherapy in the previous 1 month, patients on systemic immunosuppressant in the previous 3 months, patients receiving probiotics during the past 4 weeks, patients on systemic antibiotics in past 8 weeks, or topical antibiotics in past 3 weeks prior to commencement of the study, subjects with concomitant skin diseases, chronic skin diseases like psoriasis, SCORAD score <20 after the initial washout period, pregnant or lactating women, subjects with a primary or acquired immunodeficiency, subjects receiving or planning to receive an investigational new drug (IND).

Figure 1: Study plan.
agent, ultraviolet light therapy, monoclonal antibodies, or systemic immunosuppressants, subjects using topical or oral complementary and alternative (CAM) agents within 4 weeks of initiation of treatment, subjects who are currently receiving or have received chemotherapy or radiation for treatment of malignancies within the previous 6 months, patients hypersensitive to any components contained in the probiotic capsules/sachets, subjects participating in a clinical research trial within 30 days prior to randomization. Individuals who are cognitively impaired and/or who are unable to give informed consent were excluded from the study.

The study was performed in five visits, namely visit 1 (day 1, T0), visit 2, (day 21, T3), visit 3 (day 42, T6), visit 4 (day 63, T9) and visit 5 (day 84, T12). 'T' refers to the number of weeks of medication. In T0, prospective patients were screened for inclusion and exclusion parameters after receiving written informed consent from the subjects. At baseline (T0), demographic information, anthropometric parameters, background of other health conditions such as diabetes mellitus, hypertension and any other chronic diseases were reported. Patients were examined during the first visit (T0) clinically as well as using fotofinder and SCORAD score was calculated. SCORAD scores greater than 15 showing moderate to severe AD were chosen for the study. Subjects were randomized to the control arm (arm 1) and the treatment arm (arm 2). The treatment arm received both conventional and probiotic therapy and the control arm conventional therapy only. 10 adults and 25 children were enrolled in each arm. Lactogut probiotic was administered to adults and Lactogut Kidz to children in the treatment arm. Conventional therapy involved moisturizers, topical steroids, topical calcineurin inhibitors, and antihistaminics. Lactogut oral probiotic supplement comprises five billion CFUs of beneficial strains of *Lactobacillus* and *Bifidobacterium*, while Lactogut Kidz oral probiotic supplement is a mixture of one billion CFUs of strains of *Lactobacillus* and *Bifidobacterium* (Table 1).

At visit 2, (day 21, T3), visit 3 (day 42, T6), visit 4 (day 63, T9) and visit 5 (day 84, T12) the decline in SCORAD was measured and response to treatment was compared using clinical and videodermoscopic images. At each visit, clinical photographs, front and lateral views were taken at a distance of 40 cm. AEC and serum IgE levels were recorded at T0 and T12. Patient satisfaction was recorded at each visit using the quality of life questionnaire. Adverse effects and serious adverse events have also been reported in compliance with the procedure.

The primary endpoints of the study were improvement from baseline in the objective SCORAD index, improvement in absolute eosinophilic count (AEC) from baseline, and change in total serum IgE levels from baseline. The secondary endpoints of the study were reduction in pruritus, reduction in AD severity (photographic assessment) and improvement in patient satisfaction of skin condition at each visit using quality of life questionnaire.

| Lactogut Kidz | Lactogut |
|---------------|----------|
| Each gm sachet contains proprietary probiotic blend of 1 billion CFU containing Bacillus coagulans unique IS-2 | Each gelatine capsule contains proprietary probiotic blend of 5 billion CFU containing Bacillus coagulans unique IS-2 |
| *Lactobacillus rhamnosus* UBLR-58 | *Lactobacillus rhamnosus* UBLR-58 |
| *Bifidobacterium longum* UBBL-64 | *Bifidobacterium longum* UBBL-64 |
| *Bifidobacterium bifidum* UBBB-55 | *Bifidobacterium bifidum* UBBB-55 |
| *Bifidobacterium infantis* UBBI-01 | |
| *Saccharomyces boulardii* unique 28 | *Saccharomyces boulardii* unique 28 |
| *Streptococcus thermophilus* UBST-50 | *Streptococcus thermophilus* UBST-50 |
| Elemental zinc (as zinc lactate) 10 mg | |
| Fructooligosaccharides 20 mg | Fructooligosaccharides 20 mg |
| Lactitol 10 mg | Lactitol 10mg |

**Ethical approval**

Ethics approval of the study has been obtained from Institutional Ethics Committee of Cutaneous Sciences, Bengaluru, Karnataka, India.

**RESULTS**

A total of 70 patients were enrolled in the study which includes 20 adults and 50 children. In treatment arm, adult subjects received Lactogut and children received Lactogut Kidz along with conventional therapy and controls received only conventional therapy. 10 adults and 25 children were enrolled in each arm. Demographic details are presented in (Table 2).

**Assessment of SCORAD score, IgE levels and AEC values**

**Children group**

The independent ‘t’ test was used to evaluate the outcomes between the control arm and the treatment arm. The mean age in the control arm was 5.76 years with a standard deviation of 3.76 years, while it was 5.28 years.
with the standard deviation of 3.85 years in the treatment arm, which is statistically not significant. SCORAD in control arm at T0 is 32.46 with standard deviation of 11.79 while in treatment arm it is 32.23 with SD of 11.66. With ‘t’ value of -0.233 this difference is statistically not significant. SCORAD score between the control arm and the treatment arm is also statistically not significant at T3 and T6. SCORAD scores at T9 and T12 demonstrate statistically significant differences between the two groups with a ‘t’ value of 2.24 and 3.225 respectively and the p value of 0.031 and 0.003.

Table 2: Demographic data.

| Characteristics                  | Treatment arm | Control arm |
|----------------------------------|---------------|-------------|
|                                  | Adults        | Children    | Adults | Children |
| Total number of patients enrolled| 10            | 25          | 10     | 25       |
| Completed study                  | 9             | 23          | 8      | 22       |
| Male patients                    | 4             | 9           | 4      | 9        |
| Female patients                  | 5             | 14          | 4      | 13       |
| Mean age of male patients        | 29            | 7.88        | 26.75  | 7.55     |
| Mean age of female patients      | 22.4          | 3.57        | 35     | 5        |

Table 3: Independent ‘t’ test values of both groups (children and adults) to compare between control arm and treatment arm.

| Variable                          | Control group (n=25) | Treatment group (n=25) | t     | P value |
|-----------------------------------|----------------------|------------------------|-------|---------|
| Age                               | Mean±SD              | Mean±SD                |       |         |
| SCORAD T0                         | 32.4±11.79           | 33.23±11.66            | -0.233| 0.816   |
| SCORAD T3                         | 30.83±11.45          | 28.83±10.59            | 0.634 | 0.529   |
| SCORAD T6                         | 29.46±12.15          | 23.85±9.27             | 1.782 | 0.081   |
| SCORAD T9                         | 26.71±12.14          | 19.63±8.89             | 2.24  | 0.031   |
| SCORAD T12                        | 24.57±12.27          | 14.72±7.57             | 3.225 | 0.003   |
| SCORAD difference between baseline and T3 | 1.63±2.41          | 4.62±2.6               | -4.176| <0.001  |
| SCORAD difference between baseline and T6 | 2.91±2.77          | 9.59±4.73              | -5.946| <0.001  |
| SCORAD difference between baseline and T9 | 4.76±4.24          | 13.82±5.38             | -6.302| <0.001  |
| SCORAD difference between baseline and T12 | 6.9±5.14           | 18.14±7.21             | -5.998| <0.001  |
| IgE T0                            | 563.19±607.94       | 273.19±505.4           | 1.834 | 0.073   |
| IgE T12                           | 559.63±570.19       | 315.94±696.65          | 1.281 | 0.207   |
| IgE T0-T12                        | 61±366.2            | -30.61±186.73          | 1.064 | 0.293   |
| AEC T0                            | 709.96±399.76       | 432.84±201.09          | 3.096 | 0.004   |
| AEC T12                           | 556.73±268.67       | 346.43±224.19          | 2.856 | 0.007   |
| AEC T0-T12                        | 192.55±273.51       | 88.04±109.66           | 1.696 | 0.097   |

Table 3: Independent ‘t’ test values of both groups (children and adults) to compare between control arm and treatment arm.
Table 4: Intra group comparison of the SCORAD score, IgE levels and AEC values using paired ‘t’ test in children.

| Groups                  | N  | Mean±SD     | Mean difference ±SD | t value | P value |
|-------------------------|----|-------------|---------------------|---------|---------|
| **Children control arm**|    |             |                     |         |         |
| Pair 1                  | 25 | 32.46±11.79 | 1.63±2.41           | 3.38    | 0.002   |
| Pair 2                  | 23 | 32.37±12.23 | 2.91±2.77           | 5.04    | <0.001  |
| Pair 3                  | 22 | 31.47±11.73 | 4.76±4.24           | 5.27    | <0.001  |
| Pair 4                  | 22 | 31.47±11.73 | 6.9±5.14            | 6.30    | <0.001  |
| Pair 5                  | 22 | 559.63±570.19 | 61.3±66.2   | 0.78    | 0.443   |
| **Children treatment arm**| | | | | |
| Pair 1                  | 24 | 33.45±11.86 | 4.62±2.6            | 8.69    | <0.001  |
| Pair 2                  | 24 | 33.45±11.86 | 9.59±4.73           | 9.94    | <0.001  |
| Pair 3                  | 24 | 33.45±11.86 | 13.82±5.38          | 12.59   | <0.001  |
| Pair 4                  | 23 | 32.86±11.76 | 18.14±7.21          | 12.07   | <0.001  |
| Pair 5                  | 23 | 285.34±525.69 | -30.61±186.73 | -0.79   | 0.44    |
| Pair 6                  | 23 | 315.94±696.65 | 88.04±109.66 | 3.85    | 0.001   |

Mean SCORAD in the T9 and T12 treatment arm is 19.63±8.89 and 14.72±7.57, in contrast with 26.71±12.14 and 24.57±12.27 in the T9 and T12 control arm respectively. The SCORAD difference between the control and treatment arm from baseline to T3, T6, T9 and T12 indicates statistically significant difference in treatment arm with reduced SCORAD score. The T0 and T12 IgE levels between the control and treatment arm indicate no statistically significant difference. However, AEC at T0 and T12 between the control and treatment arm indicates statistically significant difference in treatment arm with reduced AEC count.

Statistical measures are mentioned in (Table 3). The paired ‘t’ test was used for intragroup comparison of mean SCORAD score, IgE levels, and AEC between control arm and treatment arm. The findings of the paired ‘t’ test for both the control and the treatment arm are statistically significant for SCORAD score and AEC between T0 and T12 visit. Mean IgE levels for both the control and treatment arm before and after treatment do not indicate statistically significant difference. In Table 4, results of the paired ‘t’ test for intra group comparison in children is given.

**Adult group**

Mean age was 32.4±10.32 years for the control arm and 24.6±6.79 years for the treatment arm, which is not statistically significant. Mean SCORAD score does not indicate statistically significant difference between control and treatment arm for all 5 visits. However, the mean SCORAD score between the control and treatment arm from baseline to T3, T6, T9 and T12 indicates a statistically significant difference, as seen in Table 5. Mean levels of IgE at T0 and T12 between the control and treatment arm indicate statistically significant difference in treatment arm with lower levels of IgE being apparent. Mean AEC between control arm and treatment arm indicates no statistically significant difference; however, comparison between baseline and T12 reveals statistically significant difference. Adult group statistical results are clarified in (Table 3).
Table 5: Intra group comparison of the SCORAD score, IgE levels and AEC values using paired ‘t’ test in adults.

| Groups                  | N  | Mean±SD        | Mean difference ±SD | t value | P value |
|-------------------------|----|----------------|---------------------|---------|---------|
| **Adult control arm**   |    |                |                     |         |         |
| Pair 1                  | 9  | 28.89±11.55    | -0.44±2.35          | -0.57   | 0.586   |
| SCORAD T0               | 9  | 29.33±11.35    |                     |         |         |
| SCORAD T3               | 8  | 29±12.34       | 0.63±2.5            | 0.71    | 0.503   |
| Pair 2                  | 8  | 28.38±12.83    | 2±2.56              | 2.21    | 0.063   |
| SCORAD T0               | 8  | 29±12.34       |                     |         |         |
| SCORAD T6               | 8  | 27±12.59       |                     |         |         |
| Pair 3                  | 8  | 29±12.34       | 4.5±1.93            | 6.60    | <0.001  |
| SCORAD T0               | 8  | 24.5±11.81     |                     |         |         |
| SCORAD T12              | 8  |                |                     |         |         |
| Pair 4                  | 8  | 220.64±71.86   | 1.88                | 0.102   |         |
| IgE T0                  | 8  | 174.63±60.43   |                     |         |         |
| IgE T12                 | 8  |                |                     |         |         |
| Pair 5                  | 8  | 422.38±193.01  | 12.89±3.37          | 11.47   | <0.001  |
| AEC T0                  | 8  | 394.56±131.51  | 17.78±4.89          | 10.90   | <0.001  |
| AEC T12                 | 8  |                |                     |         |         |
| **Adult treatment arm** |    |                |                     |         |         |
| Pair 1                  | 9  | 38.33±11.2     | 4.22±1.3            | 9.73    | <0.001  |
| SCORAD T0               | 9  | 34.11±10.42    |                     |         |         |
| SCORAD T3               | 9  | 30±10.42       | 8.33±2.74           | 9.13    | <0.001  |
| Pair 2                  | 9  | 38.33±11.12    | 12.89±3.37          | 11.47   | <0.001  |
| SCORAD T0               | 9  | 25.44±10.17    |                     |         |         |
| SCORAD T6               | 9  |                |                     |         |         |
| Pair 3                  | 9  | 38.33±11.2     | 17.78±4.89          | 10.90   | <0.001  |
| SCORAD T0               | 9  | 20.56±9.18     |                     |         |         |
| SCORAD T12              | 9  |                |                     |         |         |
| Pair 4                  | 9  | 110.59±47.44   | 39.12±30            | 3.91    | 0.004   |
| IgE T0                  | 9  | 71.47±21.2     |                     |         |         |
| IgE T12                 | 9  |                |                     |         |         |
| Pair 5                  | 9  | 394.56±131.51  | 132.22±81.11        | 4.89    | 0.001   |
| AEC T0                  | 9  | 262.33±103.51  |                     |         |         |
| AEC T12                 | 9  |                |                     |         |         |

A paired ‘t’ test was used for intragroup comparison of mean SCORAD score, IgE levels, and AEC between control arm and treatment arm. The findings of the paired ‘t’ test are statistically significant for SCORAD score for only T0-T12 pair of the control arm, but mean SCORAD score for treatment arm is statistically significant for all pairs (T0-T3, T0-T6, T0-T9, and T0-T12). Mean control arm IgE levels do not demonstrate statistically significant difference for the T0-T12 pair, while mean treatment arm IgE levels display statistically significant difference for the T0-T12 pair. The mean AEC value indicates statistically significant difference for both the control and the treatment arm between the T0-T12 pairs. In Table 5, results of the paired ‘t’ test for intra-group comparison of adult group are seen.

Figure 2 demonstrates the treatment arm SCORAD index versus control arm. This was 32.86 on day 0 in the treatment arm, and 14.72 on day 84 at the end of the study. Thus, the SCORAD index significantly decreased in moderate to severe AD, with a drop of 55.20%.

Table 6: Photographic assessment of AD lesions using independent ‘t’ test.

| Groups                  | N  | Mean SD     | T value | df  | P value |
|-------------------------|----|-------------|---------|-----|---------|
| **Children**            |    |             |         |     |         |
| Photographic assessment | 22 | 18.180      | 13.052  | -8.834 | 43 | <0.001 |
| Control arm             | 23 | 56.960      | 16.148  |       |       |       |
| Treatment arm           | 32 | 17.330      | 11.651  | -11.78 | 60 | <0.001 |
| **Adult**               |    |             |         |     |         |
| Photographic assessment | 8  | 15<0.001    | 6.547   | -10.64 | 15 | <0.001 |
| Control arm             | 9  | 55.560      | 8.819   |       |       |       |
| Treatment arm           | 31 | 17.330      | 11.651  | -11.78 | 60 | <0.001 |
Table 7: Patient satisfaction before and after treatment using chi-square test.

| Child/adult | Group | Control | Treatment | Total |
|------------|-------|---------|-----------|-------|
| Moderate   | Count | 15      | 3         | 18    |
|            | % within group | 68.2    | 13.0      | 40.0  |
| Good       | Count | 7       | 9         | 16    |
|            | % within group | 31.8    | 39.1      | 35.6  |
| Very good  | Count | 0       | 6         | 6     |
|            | % within group | 0.0     | 26.1      | 13.3  |
| Excellent  | Count | 0       | 5         | 5     |
|            | % within group | 0.0     | 21.7      | 11.1  |
| Total      | Count | 22      | 23        | 45    |
|            | % within group | 100.0   | 100.0     | 100.0 |

| Child/adult | Group | Control | Treatment | Total |
|------------|-------|---------|-----------|-------|
| Moderate   | Count | 5       | 0         | 5     |
|            | % within group | 62.5    | 0.0       | 29.4  |
| Good       | Count | 3       | 5         | 8     |
|            | % within group | 37.5    | 55.6      | 47.1  |
| Very good  | Count | 0       | 3         | 3     |
|            | % within group | 0.0     | 33.3      | 17.6  |
| Excellent  | Count | 0       | 1         | 1     |
|            | % within group | 0.0     | 11.1      | 5.9   |
| Total      | Count | 8       | 9         | 17    |
|            | % within group | 100.0   | 100.0     | 100.0 |

| Child/adult | Group | Control | Treatment | Total |
|------------|-------|---------|-----------|-------|
| Moderate   | Count | 20      | 3         | 23    |
|            | % within group | 66.7    | 9.4       | 37.1  |
| Good       | Count | 10      | 14        | 24    |
|            | % within group | 33.3    | 43.8      | 38.7  |
| Very good  | Count | 0       | 9         | 9     |
|            | % within group | 0.0     | 28.1      | 14.5  |
| Excellent  | Count | 0       | 6         | 6     |
|            | % within group | 0.0     | 18.8      | 9.7   |
| Total      | Count | 30      | 32        | 62    |
|            | % within group | 100.0   | 100.0     | 100.0 |

### Chi-square tests

| Child/adult | Value  | df | P value (<0.05) |
|------------|--------|----|----------------|
| Children   | Pearson chi-square | 19.237 | 3 | <0.001  |
| Number of valid cases | 45      |    |                |
| Adult      | Pearson chi-square | 9.474  | 3 | 0.024   |
| Number of valid cases | 17      |    |                |
| Total      | Pearson chi-square | 28.197 | 3 | <0.001  |
| Number of valid cases | 62      |    |                |

*Comparison by photographic assessment*

Based on the blind assessment of the global photographs (Figure 5) and the dermoscopic assessment using fotofinder images (Figure 6), patients were graded by two independent dermatologists as grade 1 <25% reduction; grade 2 26-50% reduction; grade 3 51-75% reduction; grade 4 >76% reduction. In the treatment arm of dermoscopic assessment using fotofinder, 15.63% had an improvement of grade 4, 34.38% had an improvement of grade 3, 50.00 % had an improvement of grade 2 and none had an improvement of grade 1 while in the control...
arm none had an improvement of grade 4 or grade 3, 16.67% had an improvement of grade 2 and 83.33% had an improvement of grade 1. Figure 4 indicates the overall percentage improvement in the treatment arm, based on the assessment of global photographs.

Global photographic assessment in the treatment arm showed grade 4 improvement in 9.38% of patients, an improvement of grade 3 in 40.63% of patients and an improvement of grade 2 in 50.00% of patients. In the control arm none had an improvement of grade 4 or grade 3, 13.33% had an improvement of grade 2 and 86.67% had grade 1 improvement. In the control and treatment arms of children and adult groups, independent ‘t’ test was used to compare the photographic assessment of AD lesions. Mean scores of photographic assessments was statistically significant across arms of control and treatment in both children and adult groups. Table 6 sums up the methodological results.

Figure 2: SCORAD index comparison in both groups.

Figure 3: Dermoscopic assessment using fotofinder (overall improvement in both groups).

Assessment of patient satisfaction

Categorical variable 'patient satisfaction' was compared using chi-square test. Scores of patient satisfaction with pre and post treatment demonstrated statistically significant difference in the application of chi-square testing. The statistical results are discussed in depth in (Table 7).

There was overall percentage increase in patient satisfaction in the treatment arm at the end of the therapy. In total it was rated as excellent by 18.75% of patients, 28.13% of patients graded it as very good, 73.75% of patients graded it as good and 9.38% of patients considered it moderate in the treatment arm. In the control arm, none called it excellent or very good although 33.33% of patients thought it good and 66.67% of patients deemed it moderate.

Three children and two adult volunteers in the control arm and two children and one adult volunteer in the treatment arm were among the dropouts from the study.

Adverse events

The therapy was not associated with any relevant adverse events, either in the treatment arm or the control arm.

DISCUSSION

AD or atopic eczema is a chronic, recurring, pruritic, inflammatory skin condition with a prevalence of up to 20% in children and 1-2% in adults in both developed and developing countries. AD is a prevalent disease, especially in childhood, but can continue or begin in adulthood. At sites of typical predilection, acute flare-ups and exacerbations as well as chronic eczematous skin lesions on dry skin, such as flexural folds accompanied by intense pruritus, characterize the disease and are quite homogenous, but the disease's trigger factors are diverse and the pathophysiological network involved is complex. The effect of pruritus and the noticeable presence of AD-
related effects has a substantial adverse influence on the quality of life of patients and their families, which may vary from physical and emotional wellbeing loss to impaired social activity. AD’s fundamental mechanism and etiology are uncertain, but are suspected to be multifactorial in nature, including hereditary, socio-economic, environmental, and immunological influences culminating in AD being triggered and advanced. Using uniform standards and scoring systems, AD can range from mild to moderate to severe forms and diagnosis, as well as severity may be defined.1,4

AD patients are treated effectively using topical therapies that involve topical corticosteroids, emollients, and antihistaminics. Additional immunosuppressants are given in refractory cases. Corticosteroids and immunosuppressants can cause adverse effects. Probiotics are used as adjunct therapy. Probiotics include live microorganisms that transmit beneficial results and improve immunity. Probiotics have strong anti-inflammatory and antipathogenic capabilities.4,5

In our research, 12 weeks, randomized, double-blind study of the efficacy of Lactogut and Lactogut Kidz probiotics oral supplement on AD in adults and children was conducted, respectively. The research was performed on a total of 70 patients (20 adults and 50 children) with moderate to severe AD over duration of 12 weeks per case. Subjects were double-blindly randomized and obtained a conventional therapy plus study supplement in treatment arm and just conventional therapy in control arm. Subjects were instructed to take two probiotic capsules/sachets (Lactogut/Lactogut Kidz) every day during this study. In the following visits, the study was conducted: visit 1 (day 0, T0), visit 2, (day 21, T3), visit 3 (day 42, T6), visit 4 (day 63, T9) and visit 5 (day 84, T12).

Mean SCORAD score at T9 and T12 in the children’s group demonstrated statistically significant difference between the control arm and the treatment arm with lower mean SCORAD score in the treatment arm. IgE levels of the children’s group’s control and treatment arm indicate little statistically significant difference, yet AEC demonstrated a statistically significant difference between the control arm and the treatment arm. It suggests that probiotic supplements was dramatically effective in lowering AD severity by reducing the T9 and T12 SCORAD score relative to the control arm. Children's group's patient satisfaction score was ranked very good in 26% and excellent in the treatment arm’s 21% subjects as opposed to 0% in control arm subjects. This suggests a significant increase in the patient satisfaction score in the group of children in whom oral probiotic supplements are added to conventional therapy. The research performed by Wu et al indicated that supplementing the species Lactobacillus and Bifidobacterium was substantially helpful in decreasing AD severity in a 1 to 3 years age range of children. Their research also shows a substantial decline in the scores of SCORAD, infant dermatitis quality of life and dermatitis family impact scores.10 In 1-3 years old children, the supplement of Lactobacillus salivarius, Lactobacillus casei, Lactobacillus acidophilus and Bifidobacterium bifidum showed prevailing decreases in SCORAD, IgE, IL-6, IL-5 and IFN gamma levels.11 Another study found that the presence of Lactobacillus fermentum alone, Lactobacillus paracasei alone and combining of both strains for 12 weeks improved SCORAD, infant dermatology quality of life index and family dermatology quality of life index scoring, urinary 8-oso-2-deoxyguanosine and eosinophil protein X, serum IgE and TNF alfa levels in AD subjects.12 The study performed by Woo SI with Lactobacillus fermentum species in infants aged 6-18 months reported a significant reduction in SCORAD and severity of AD.13 Lactobacillus sakei (in children aged 2-10 years) and Lactobacillus plantarum (in children aged 1-13 years) showed a significant reduction in SODCRA score over a 12 weeks span.14 The treatment of children 1 of 3 years old of Lactobacillus acidophilus, DDS-1, Bifidobacterium lactis, UABLA-12 and fructo-oligosaccharide reported a 33% reduction in SCORAD. Gerasimov et al showed a quality of life score for child dermatitis of 33% and a dermatitis family impact of 35.2%.15

Figure 5: Global photographs of subjects in the treatment arm (before and after treatment).

In our study, SCORAD score in adult group shows no significant difference between control arm and treatment arm. However, a statistically significant difference between baseline SCORAD score at T0 versus mean SCORAD score at T3, T6, T9 and T12 is noted. In addition, a statistically significant difference between mean IgE levels of control arm and treatment arm was observed. AEC values do not indicate any significant difference between the control arm and the treatment arm. Adult patient satisfaction score was very good in 33.3% and excellent in 11.1% for subjects in the treatment group relative to 0% in subjects in the control group. This suggests a significant decrease in SCORAD index and
observed the clinical and immunological impact of a mixture of seven strains of probiotic bacteria (Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium infantis, Lactobacillus bulgaricus) and fructo olig saccharide in infants and children (3 months to 6 years) with mild to severe AD for 8 weeks, and showed a significantly greater reduction in SCORAD in the symbiotic group than in the placebo group.22 In another study, the intake of a mixture of oral probiotics (Bifidobacterium lactis, B. longum, and Lactobacillus casei) by children aged 4 to 17 years with moderate atopic dermatitis demonstrated statistically significant reduction of SCORAD coupled with decrease in the usage of topical corticosteroids in the treatment group at the end of 12 weeks relative to the placebo group.23 Some trials struggled to demonstrate the efficacy of probiotics or symbiotic in the treatment of AD.24-26 Michail et al collected evidence from 10 trials (n=678) to assess if probiotics were successful in the treatment of AD which indicated an overall statistically significant difference in favour of probiotics compared to placebo in reducing the SCORAD score.26 In the current study, our group used special combinations of bacterial strains of oral probiotic (Table 1) to test the efficacy of oral probiotics in treating AD, to assess the correlation of SCORAD score, serum IgE, AEC, global photography assessment, dermoscopy assessment using fotofinder and patient satisfaction score with probiotic therapy in AD. Thus, this study has explored the association of oral probiotic supplements and various criteria of AD management.

CONCLUSION

The findings of the study concluded that added conventional therapy with Lactogut Kidz supplements demonstrated effective control of SCORAD score and AEC levels in children suffering from AD. For children with both conventional and conventional and probiotic therapy, IgE levels between baseline and at 12 weeks demonstrated effective reduction. Adding to conventional therapy, the Lactogut supplement in adults showed effective control of SCORAD score, serum IgE, AEC, global photography assessment, dermoscopy assessment using fotofinder and patient satisfaction score with probiotic therapy in AD.

Funding: The study was funded by Tenshi Life Care Private Limited, Bengaluru, Karnataka, India
Conflict of interest: None declared
Ethical approval: The study was approved by the institutional ethics committee
REFERENCES

1. Rajagopalan M, De A, Godse K, Shankar KDS, Zawar V, Sharma N, et al. Guidelines on management of atopic dermatitis in India: an evidence-based review and an expert consensus. Indian J Dermatol. 2019;64:166-81.

2. Kanwar AJ. Adult-onset atopic dermatitis. Indian J Dermatol. 2016;61:662-3.

3. Kapur S, Watson W, Carr S. Atopic dermatitis. Allergy Asthma Clin Immunol. 2018;14(2):43-52.

4. Pedersen TK. Clinical aspects of atopic dermatitis. Clin Exp Dermatol. 2000;25(7):535-43.

5. Thomsen SF. Atopic dermatitis: Natural history, diagnosis and treatment: Review article. ISRN Allergy. 2014;354250:1-7.

6. Stalder JF, Taieb A, Atherton DJ, Bieber T, Bonifazi E, Broger A, et al. Severity scoring of atopic dermatitis: the SCORAD index. Consensus report of the European Task Force on Atopic Dermatitis. Dermatology. 1993;186:23-31.

7. Kachagia M, Basoulis D, Konstantopoulou S, Dimitriadi D, Gyftopoulou K, Skarmoutsou N, et al. Health benefits of probiotics: a review. ISRN Nutrition. 2013;481651:1-7.

8. Gill HS, Guarnier F. Probiotics and human health: a clinical perspective. Postgrad Med J. 2004;80:516-26.

9. Huang R, Ning H, Minxue S, Li j, Zhang J, Chen X. Probiotics for the treatment of Atopic Dermatitis in Children: a systematic review and meta-analysis of randomized controlled trials. Front Cell Infect Microbiol. 2017;7(391):1-11.

10. Wu KG, Li TH, Peng HJ. Lactobacillus salivarius plus fructooligosaccharide is superior to fructooligosaccharide alone for treating children with moderate to severe atopic dermatitis: a double-blind, randomized, clinical trial of efficacy and safety. Br J Dermatol. 2012;166(1):129-36.

11. Yesilova Y, Calka O, Akdeniz N, Berktaş M. Effect of probiotics on the treatment of children with atopic dermatitis. Ann Dermatol. 2012;24(2):189-93.

12. Wang JJ, Wang JY. Children with atopic dermatitis show clinical improvement after Lactobacillus exposure. Clin Exp Allergy. 2015;45(4):779-87.

13. Woo SI, Kim JY, Lee YJ, Kim NS, Hahn YS. Effect of Lactobacillus sakei supplementation in children with atopic eczema-dermatitis syndrome. Ann Allergy Asthma Immunol. 2010;104(4):343-8.

14. Han Y, Kim B, Ban J, Lee J, Kim BJ, Choi BS, et al. A randomized trial of Lactobacillus plantarum CJLP133 for the treatment of atopic dermatitis. Pediatr Allergy Immunol. 2012;23(7):667-73.

15. Gerasimov SV, Vasjuta VV, Mykhovych OO, Bondarchuk LI. Probiotic supplement reduces atopic dermatitis in preschool children: a randomized, double-blind, placebo-controlled, clinical trial. Am J Clin Dermatol. 2010;11(5):351-61.

16. Drago L, Iemoli E, Rodighiero V, Nicola L, Vecchi DE, Piconi S. Effects of Lactobacillus salivarius LS01 (DSM 22775) treatment on adult atopic dermatitis: a randomized placebo-controlled study. Int J Immunopathol Pharmacol. 2011;24(4):1037-48.

17. Drago L, Toscano M, Vecchi DE, Piconi S, Iemoli E. Changing of fecal flora and clinical effect of L. salivarius LS01 in adults with atopic dermatitis. J Clin Gastroenterol. 2012;46:56-63.

18. Matsumoto M, Ebata T, Hirooka J, Hosoya R, Inoue N, Itami S, et al. Antipruritic effects of the probiotic strain LKM512 in adults with atopic dermatitis. Ann Allergy Asthma Immunol. 2014;113(2):209-16.

19. Rather IA, Bajpai VK, Kumar S, Lim J, Paek WK, Park YH. Probiotics and Atopic Dermatitis: An Overview. Frontiers in Microbiol. 2016;7:507.

20. Frei R, Akdis M, Mahony OL. Prebiotics, probiotics, symbiotic, and the immune system: experimental data and clinical evidence. Curr Opin Gastroenterol. 2015;31(2):153-8.

21. Enomoto T, Sowa M, Nishimori K, Shimazu S, Yoshida A, Yamada K, et al. Effects of bifidobacterial supplementation to pregnant women and infants in the prevention of allergy development in infants and on fecal microbiota. Allergol Int. 2014;63(4):575-85.

22. Farid R, Ahanchian H, Jabbari F, Moghimian T. Effect of a new symbiotic mixture on atopic dermatitis in children: a randomized-controlled trial. Iranian J Pediatrics. 2011;21(2):225-30.

23. Lopez NV, Bosca RA, Vidal RD, Costas RB, Martinez GS, Cuadros CE, et al. Effect of Oral Administration of a Mixture of Probiotic Strains on SCORAD Index and Use of Topical Steroids in Young Patients with Moderate Atopic Dermatitis: A Randomized Clinical Trial. JAMA Dermatol. 2018;154(1):37-43.

24. Boyle RJ, Hextall BFJ, Bee LJ, Murrell DF, Tang ML. Probiotics for the treatment of eczema: a systematic review. Clin Exp Allergy. 2009;39(8):1117-27.

25. Kopp MV, Safied P. Probiotics and prevention of allergic disease. Curr Opin Clin Nutr Metab Care. 2009;12(3):298-303.

26. Van DALB, Heymans HS, Aalderen VVM, Smitt SJH, Knol J, Amor BK, et al. The Synbad Study Group. Effect of a new symbiotic mixture on atopic dermatitis in infants: a randomized–controlled trial. Clin Exp Allergy. 2010;40(5):795-804.

27. Michail SK, Stolfi A, Johnson T, Onady GM. Efficacy of probiotics in the treatment of pediatric atopic dermatitis: a meta-analysis of randomized controlled trials. Ann Allergy Asthma Immunol. 2008;101(5):508-16.

Cite this article as: Chandrashekar BS, Agarwal R, Nayak PB, Vijayaraghavan S, Deshmukh AA. A 12 weeks, randomized and double-blind evaluation of the efficacy of oral supplements of probiotics (Lactogut and Lactogut Kidz) on atopic dermatitis in adults and children. Int J Res Dermatol 2020;6:604-15.