

- Topics:** Evening primrose oil (EPO), omega-6 fatty acids, gamma-linolenic acid (GLA), atopic eczema, atopic dermatitis (AD), skin, delta-6-desaturase (D-6-D)
- Objective:** To determine whether EPO supplementation results in an increase in plasma GLA and its metabolite dihomo-gamma-linolenic acid (DGLA) correlate with clinical improvement of AD, assessed by the SCORing Atopic Dermatitis (SCORAD) index.
- Background:** Synthesis of the long chain omega-6 fatty acids involves alternating steps of desaturation and elongation with serial conversion of linoleic acid (LA) to GLA, dihomogammalinolenic acid (DGLA) and arachidonic acid (AA). Over twenty years ago, scientists at the Efamol Research Institute found that blood levels of LA were higher and all its metabolites were lower than normal in people with atopic eczema; a condition where skin barrier function is compromised resulting in increased trans epidermal water loss (TEWL) and epidermal hyper-proliferation. They proposed there was a defect in an enzyme called delta-6-desaturase (D-6-D) that normally converts LA to GLA that contributed to the development of atopic eczema and that supplementation with EPO, thereby providing a direct dietary source of GLA, would improve skin health. Few recent studies have investigated the association between increases GLA and DGLA status and symptom improvement following EPO supplementation. However, today the cause of atopic eczema is recognized to be multifactorial including a genetic predisposition towards disrupted skin barrier function, allergic inflammation and environmental factors. At least in a subset of patients with AD, a malfunction of D-6-D seems to play a role.
- Method:** This prospective, explorative, multi-centered, open study included 21 patients between 3-58 years with AD. Patients were supplemented with 4-6 capsules of EPOGAM (EPO) containing 80 mg of GLA per 1000 mg capsule daily for 12 weeks.
- Inclusion Criteria:** AD as defined by criteria of Hanifin and Rajka with predominant tough and fissured skin and pruritis for t least 2 months.
- Exclusion Criteria:** Pregnant or lactating women, presence of chronic dermatosis such as seborrheic dermatitis, contact dermatitis, nummular eczema, psoriasis, ichthyosis, an immune-deficiency or any immunological disorder, scabies, cutaneous fungal infection, HIV-associated skin disorders, malignant diseases, T cell-Lymphoma, Letter-Siwe disease, progressive systemic disease, serious internal diseases of the heart, liver, and/or kidneys, or diabetes, hypersensitivity towards one of the ingredients in the investigational medication, and those taking part in other studies or who have taken an investigational product during the last 4 weeks.
- Additional Criteria:** Participants were allowed to continue use of medications which they were taking prior to the study at the same dose, unless the medication could be discontinued or was listed as prohibited medication. Prohibited medications were as follows:
- 30 days prior to the study start: physical or psychological therapy, anti-inflammatory medication to treat AD and immune-modulating medications
 - 14 days prior to the study: non-steroidal anti-rheumatic drugs, systemic use of glucocorticosteroids, tansquillizers or antiemetic agents from the phenothiazine group
 - 7 days prior to start of the study: alpha- of beta-blockers, clonidine, alpha-sympathomimetic medications, azelastine, levocabastine or antidepressants.
- Assessments** before and after 4 and 12 weeks of treatment:
1. **SCORAD** – to measure symptoms of AD including redness, swelling, itching, weeping/crusting, excoriation, lichenification, dryness and total intensity.
 2. **Plasma fatty acid concentration**
 3. **Adverse events**
 4. **Hematological and clinical-chemical laboratory tests and vital signs**

Findings: A significant increase in plasma GLA and DGLA levels and a decrease in the objective SCORAD were observed 4 and 12 weeks after initiation of EPO treatment. In the per-protocol population (n = 14), a significant inverse correlation between the changes in plasma GLA levels and SCORAD was found (P = 0.008). The mean total SCORAD showed a time-dependent reduction with a statistically significant decrease after 4 weeks (P=0.019) and 12 weeks (p=0.001). At baseline, 42.9% of the patients had mild symptoms and 57.1 % had moderate symptoms. After 12 weeks treatment, 93.2% of the patients had mild symptoms, whereas only 6.8% had moderate symptoms. The concomitant use of other medications had no effect on the objective SCORAD when comparing the group that used other anti-AD medications and those that did not. There were no serious side effects. Minor ones included tiredness, impaired concentration, diarrhoea, abdominal cramps and pruritis.

Conclusion: EPO improves symptoms of atopic eczema while increasing blood levels of GLA and DGLA. In addition, clinical improvements in disease activity under EPO treatment correlate with individual increases in plasma GLA levels indicating that GLA may be responsible for the improvement and that GLA could be used as a marker to identify responders. Thus, patients without an increase in plasma GLA after 4 weeks would be regarded as non-responders and could be recommended to stop therapy while those that did have increased GLA levels could proceed and expect to achieve successful treatment. Lastly, the further improvements measured as 12 weeks support the idea that EPO should be used as a long-term therapy.

Relevance to: Efamol Evening Primrose Oil

Reference: Gamma-Linolenic Acid Levels Simon D, Eng PA, Borelli S, Kägi R, Zimmermann C, Zahner C, Drewe J, Hess L, Ferrari G, Lautenschlager S, Wüthrich B, Schmid-Grendelmeier P. Correlate with Clinical Efficacy of Evening Primrose Oil in Patients with Atopic Dermatitis. *Adv Ther.* 2014 Jan 17. [Epub ahead of print]

PRESS RELEASE**Independent Studies Proving Once Again that EPO Significantly Improves Symptoms of Atopic Eczema ¹.**

The latest multi-centered, open clinical trial of EPO for the treatment of atopic eczema/dermatitis (AD) has confirmed findings of Efamol scientists nearly 3 decades earlier – EPO is an effective treatment for this debilitating skin condition. The collaboration among the University Hospital of Bern, Children's Hospitals Aarau, Children's Hospitals Lucerne, Pediatric Practice at Rigiplatz, MaxZeller Söhne, Brunner & Hess Software AG, University Hospital of Zurich and Hospital Zollikerberg, Switzerland, included 21 patients between 3-58 years with AD supplemented with 4-6 capsules of EPOGAM (previously the prescription drug format of Efamol EPO) containing 80 mg of GLA per 1000 mg capsule daily for 12 weeks. Before and after 4 and 12 weeks of treatment, each patient supplied a blood sample to determine their gamma-linolenic acid (GLA) and dihomo-gammalinolenic acid (DGLA) status. These two fatty acids are lower than normal in many people with AD and EPO treatment can increase the concentration of these two fatty acids to normal. In addition, the AD scoring index (SCORAD) was used to measure symptoms of AD at baseline and 4 and 12 weeks following treatment including redness, swelling, itching, weeping/crusting, excoriation, lichenification, dryness and total intensity.

The results showed that EPO improves symptoms of atopic eczema while increasing blood levels of GLA and DGLA. At baseline, 42.9% of the patients had mild symptoms and 57.1% had moderate symptoms. After 12 weeks treatment, 93.2% of the patients had mild symptoms, whereas only 6.8% had moderate symptoms. The clinical improvements in disease activity under EPO treatment correlated with individual increases in plasma GLA levels indicating that GLA may be responsible for the improvement and that GLA could be used as a marker to identify responders. Thus, patients without an increase in plasma GLA after 4 weeks would be regarded as non-responders and could be recommended to stop therapy while those that did have increased GLA levels could proceed and expect to achieve successful treatment.

A study last year reported similar results where symptoms including redness, skin thickness, itching and lichenification improved significantly and in a dose dependent manner following supplementation with eight 500 mg capsules of EPO for 8 weeks². In addition, there was a dose dependent improvement in symptoms and in the concentration of serum GLA and AA (arachidonic acid), showing that EPO supplementation was responsible for the benefits. That randomised, parallel trial included 40 children and adolescents aged between 2 and 15 years having had eczema for about 8.6 months. There were no side effects associated with EPO treatment.

Atopic eczema is a skin condition affecting up to 30% of children in Westernized countries³, up to 10% of adults¹ and is a non-infectious, chronically relapsing inflammatory condition causing scaliness, dryness, redness, cracks, sores and severe itching, which from the patient's perspective is the most troublesome symptom. It starts in infancy or early childhood, continues throughout life and runs in families. An associated abnormality in fatty acid metabolism was first proposed in the early 1930s and a study at the Efamol Research Institute in the early 1980s confirmed that people with atopic eczema had lower than normal blood levels of linoleic acid (LA) metabolites including GLA and other fatty acids derived from it including DGLA and AA^{4,5}.

In 2008, a group of researchers in Taipei looked at the relationship between omega-6 fatty acid deficiency, water loss through the skin (TEWL) and immune response in children with atopic disorders⁶. The study included 35 children with atopic eczema, 35 age matched children with allergic rhinitis, asthma or both and 31 nonatopic controls. Results showed that atopic children had higher levels of LA and lower levels of its metabolites including GLA, DGLA and AA. Furthermore, it showed that the more deficient they were in GLA, DGLA and AA, the more severe was their atopic dermatitis and the greater was the loss of water through their skin. Those with the highest LA had the worst TEWL and atopic eczema.

Dietary GLA supplementation can partially correct the deficiency of GLA, DGLA and AA in people with atopic eczema⁴. A study in India reported a 96% response rate using EPO as a source of GLA to treat atopic eczema in an East Indian population⁷. Results of this study also agree with those of two meta-analyses using Efamol EPO as the active ingredient reported in 1989 and 2007. The 1989 investigation including 10 clinical studies showed that EPO was particularly effective for relieving itch and those patients who had the greatest increase in their blood levels of GLA, DGLA and AA also had the greatest improvement in their skin condition⁸. The 2007 meta-analysis including 26 studies with more than 1200 patients confirmed that Efamol EPO is a safe and effective remedy for symptomatic relief of atopic eczema with simultaneous benefits on itch, crusting, swelling and redness that become apparent between 4 and 8 weeks after treatment is initiated⁹.

Results of this latest independent study reflect those of the previously mentioned studies which further substantiates the use of GLA supplementation for skin health and in particular for the treatment of atopic eczema. In addition, it helps to explain why some people in previous studies have not achieved improvements following EPO supplementation.

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