Prevention of polymorphic light eruption by oral administration of a nutritional supplement containing lycopene, β-carotene, and Lactobacillus johnsonii: results from a randomized, placebo-controlled, double-blinded study

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SUMMARY

Background
Polymorphic light eruption (PLE) is the most common photodermatosis. Little is known about the efficacy of systemic photoprotection provided by nutritional supplements in PLE patients.

Purpose
The purpose of this study was to assess efficacy of nutritional supplement containing lycopene, β-carotene, and Lactobacillus johnsonii to diminish skin lesions induced by ‘photoprovocation’ testing in PLE patients.

Methods
In this randomized, placebo-controlled, double-blinded study, 60 PLE patients were supplemented with the nutritional supplement or placebo. For inducing skin lesions, patient skin was exposed to single daily doses of 100 J/cm² ultraviolet A1 (UVA1) for two consecutive days. Skin lesions were evaluated using a PLE score. Skin biopsies were taken before and after supplementation from unexposed and exposed skin, and intercellular adhesion molecule 1 (ICAM-1) mRNA expression was assessed by real-time polymerase chain reaction.

Results
Prior to supplementation, skin lesions were induced in all patients with comparable PLE scores. After 12 weeks, intake of the supplement significantly reduced the PLE score after one exposure as compared with patients taking placebo (P < 0.001). After two exposures, these differences were no longer significant. At a molecular level, the development of skin lesions was associated with an increased expression of ICAM-1 mRNA, which was significantly reduced after supplementation (P = 0.022), but not with placebo.

Conclusion
The nutritional supplement provides protection against the development of UVA-induced PLE lesions at clinical and molecular levels.
Polymorphic light eruption (PLE) is the most frequent acquired photodermatosis typically arising in the spring period (1). The pathophysiology of PLE is not fully understood yet but seems to involve immunological mechanisms, which are associated with an increased expression of intercellular adhesion molecule-1 (ICAM-1) on keratinocytes and the concomitant development of an inflammatory infiltrate (reviewed in Vandergriff & Bergstresser (1)). There is also evidence that ultraviolet (UV)-induced production of reactive oxygen species may contribute to the development of skin lesions in PLE patients. Accordingly, a link between polymorphisms in the glutathione-S-transferase gene and susceptibility to PLE has recently been reported (2) Also, topical application of an antioxidant-containing skin care product appears to provide protection against the UV-induced development of skin lesions in PLE patients (3).

In most cases, PLE may be avoided by limiting sun exposure, wearing protective clothing, and, most importantly, regularly using broad-spectrum sunscreens. In this regard, it is important to note that only sunscreens providing both ultraviolet A (UVA) and ultraviolet B (UVB) protection appear to be effective, emphasizing the role of UVA rays in the pathophysiology of PLE. Accordingly, ‘photoprovocation’ testing has clearly established that the majority of PLE patients are hypersensitive to UVA rather than UVB exposure (4).

More recently, there is a growing interest toward systemic photoprotection achieved with orally administered nutritional supplements. Although less effective in preventing sunburn, systemic photoprotection has specific advantages because it provides homogenous photoprotection of human skin by avoiding irregular topical application. Also, measures of oral photoprotection are thought to have a superior compliance because it is easier to swallow a capsule once a day than to repeatedly and evenly apply a sunscreen product. It is important to note that endogenous photoprotection is complementary to topical photoprotection, and that these two forms of prevention clearly should not be considered mutually exclusive. Despite the constantly growing interest into oral photoprotection of human skin (reviewed in Krutmann & Humbert (5)), little is currently known about the efficacy of nutritional supplements in the prevention of photodermatoses in general and PLE in particular.

In the present randomized, placebo-controlled, double-blinded study, we have therefore assessed whether oral supplementation with a nutritional supplement containing the antioxidants lycopene and β-carotene as well as the specific probiotic Lactobacillus johnsonii (La1) may prevent or diminish the development of UVA-induced skin lesions in PLE patients at clinical and molecular levels.

PATIENTS AND METHODS

Patients and trial protocol

The study was approved by the local Ethics Committee of the Heinrich-Heine University, Düsseldorf. A total of 60 subjects (17 males and 43 females) (demographic data are summarized in Table 1) with a comparable history of PLE according to the PLE severity index (PLESI), a questionnaire concerning clinical characteristics of PLE symptoms over the last 12 months (6), were enrolled and randomly assigned to one group to be supplemented with a nutritional supplement (n = 30) or another group to be supplemented with a placebo (n = 30) according to their arrival at the study center following the randomization list provided by the external provider. Inclusion criteria were a typical history consistent with PLE, skin phototypes I–III according to Fitzpatrick scale, a normal body mass index (19 ≤ 30 kg/cm²), a low intake of fermented food (<125 g/day), and willingness to avoid excessive exposure to natural or artificial UV radiation during the duration of the study. Exclusion criteria were:

- Pregnant or lactating women, women wishing to get pregnant in the next 6 months or having delivered in the last 6 months, postmenopausal women, smokers, intake of chronic medications except oral contraceptives;
- Intake of photosensitizing medications and/or medical treatment for skin diseases, use of topical or systemic treatments that may interfere with the results of the study according to investigator’s judgment, vitamin and/or mineral and/or antioxidant supplementation over the 3 months preceding the initiation or during the study;
- A skin cancer or a history of or disposition to skin cancer, a history of photodermatosis other than PLE, scars, cuts, wounds, acne lesions, freckles, body piercings, tattoos or body paintings in the test areas, a history of wound healing disorders, allergy to lidocaine-adrenalin, a history of coagulation disorders or treatment with anticoagulants, immunosuppression or treatment with immunosuppressants in the 2 months preceding the study start;
- A particular diet or presenting a history of food behavioral problem, a known allergy to one of the ingredients of the nutritional supplement or related products, a diagnosed food allergy, daily exposure to sun more than 1 week during the 2 months preceding the initiation of the study;
- Subjects exposed to natural or artificial UV during the month before the study start, adult subjects protected by
law, subjects currently participating or having participated in another clinical trial during the last 4 weeks prior to study start, subjects who were hospitalized for any other reason than biomedical research, and subjects who had forfeited their freedom by administrative or legal award.

The study was performed from October 2011 until June 2012.

The study design was randomized, placebo-controlled, double-blinded and is depicted in detail in Fig. 1. In all patients, the typical PLE skin lesions were induced prior to supplementation. Specifically, for ‘photoprovocation’, patient’s skin was exposed to single daily dose of 100 J/cm² UVA using a Sellamed 2000 UV device (Sellamed, Gevelsberg, Germany) for two consecutive days. To assess PLE severity, a modified PLE test score according to Gruber-Wackernagel et al. (7) was used. This score was calculated as SI + 0.4 P (range 0–7), where SI denotes the skin infiltration score (range from 0–3) and P pruritus score (range 0–10) after each exposure, that is, after one and two exposures. Patients in group 1 were then supplemented with one capsule per day of a commercially available nutritional supplement (verum) containing 2.5 mg lycopene, 4.7 mg of β-carotene, and 5.10^8 cfu of the probiotic L. johnsonii (Inneov Sun Sensitivity, Laboratoires Innéov, Asnières sur Seine, France); patients in group 2 were supplemented with one capsule per day of placebo containing microcrystalline cellulose of identical size and color (provided by Inneov R&D, Anières sur Seine, France).

After 12-week supplementation with verum or placebo, all patients were subjected again to ‘photoprovocation’.

Table 1. Demographic characteristics of the population at baseline

<table>
<thead>
<tr>
<th>Population (n = 60)</th>
<th>Placebo (n = 30)</th>
<th>ISS (n = 30)</th>
<th>Placebo vs. ISS (P value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Mean ± SD</td>
<td>41.03 ± 9.22</td>
<td>38.43 ± 9.79</td>
</tr>
<tr>
<td></td>
<td>Max/min</td>
<td>18/50</td>
<td>18/50</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>Mean ± SD</td>
<td>72.63 ± 14.27</td>
<td>73.20 ± 12.49</td>
</tr>
<tr>
<td></td>
<td>Max/min</td>
<td>48/110</td>
<td>53/110</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>Mean ± SD</td>
<td>170.70 ± 9.96</td>
<td>170.03 ± 9.35</td>
</tr>
<tr>
<td></td>
<td>Max/min</td>
<td>155/196</td>
<td>157/196</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>Mean ± SD</td>
<td>24.76 ± 3.30</td>
<td>25.20 ± 2.81</td>
</tr>
<tr>
<td></td>
<td>Max/min</td>
<td>19.72/30.11</td>
<td>20.70/29.98</td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>22</td>
<td>21</td>
</tr>
<tr>
<td>Skin type</td>
<td>I</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>II</td>
<td>30</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td>III</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PLESI score</td>
<td>Mean ± SD</td>
<td>77.37 ± 2.64</td>
<td>76.60 ± 4.63</td>
</tr>
<tr>
<td></td>
<td>Max/min</td>
<td>69.0/81.0</td>
<td>58.5/82.5</td>
</tr>
</tbody>
</table>

BMI, body mass index; ISS, Inneov Sun Sensitivity; NS, not statistically significant; PLESI, polymorphic light eruption severity index; SD, standard deviation.

Fig. 1. Study design. The study consisted of a screening visit to assess eligibility (D22), a 3-week wash-out period, two consecutive days of exposure to single daily doses of 100 J/cm² ultraviolet A (UVA) (D2, D1), a baseline visit (D0), 3-month supplementation followed by two consecutive days (D86, D87) of exposure to single daily dose of 100 J/cm² UVA, and a final visit (D88). During the 3 week wash-out period, the subjects were not allowed to use any treatment for polymorphic light eruption (PLE) and any other nutritional supplement or other treatments that may affect the outcome of the trial. A 4 mm punch biopsies were taken before and after supplementation (D0 and D88) from unexposed and exposed skin areas. PLE symptoms were assessed at D1 and D0 before supplementation, and D87 and D88 after supplementation. ICAM-1, intercellular adhesion molecule-1.
testing as described, and UVA-induced skin lesions were again evaluated using PLE score.

In addition, 4 mm punch biopsies were taken before and after supplementation from unexposed and exposed skin areas (four biopsies/patient), and ICAM-1 mRNA expression was assessed by real-time polymerase chain reaction (RT-PCR) as previously described (8, 9).

Statistical analysis
A statistical analysis plan was written prior breaking the blind code. The nonparametric Student’s t-test was used for analysis of the PLE score, and P values < 0.05 were considered statistically significant. Messenger RNA expression of ICAM-1 was measured from exposed as well as unexposed skin biopsies before and after supplementation. Significance was determined by the Kruskal–Wallis test with P ≤ 0.05.

RESULTS
At baseline, prior to supplementation, UVA exposure induced typical skin lesions in all 60 patients. Assessment of PLESI scores did not show a significant difference between patients in group 1 (to be supplemented with the nutritional supplement) vs. group 2 (to be supplemented with placebo).

After 12-week supplementation, ‘photoprovocation’ testing was repeated in all subjects. As shown in Fig. 2, intake of the nutritional supplement significantly reduced PLE scores, which were induced after one UVA exposure (P < 0.001), whereas PLE scores remained unchanged in the placebo group (P = 0.145). As compared with placebo, PLE scores were significantly less important after intake of the nutritional supplement (P < 0.001). Moreover, the percentage of subjects who presented PLE symptoms after one UVA exposure decreased from 87% (before supplementation) to 53% after supplementation with the nutritional supplement as shown in Fig. 3.

No significant difference was observed between the two groups when PLE scores were assessed after two UVA exposures (data not shown).

Assessment of ICAM-1 mRNA expression was performed in 59/60 patients. One subject was exposed three times to UVA dose (100 J) instead of two like the other subjects. Accordingly, we decided not to include this subject in the analyzed population for ICAM-1 expression. In the remaining 59 patients, RT-PCR analysis revealed that, as previously reported, development of skin lesions was associated with a significant increase in ICAM-1 mRNA steady state levels (P < 0.001), and that this increase was significantly weaker in patients supplemented with the nutritional supplement, but not with placebo (P = 0.022) as shown in Fig. 4.

DISCUSSION
This study provides compelling evidence at clinical and molecular levels that patients with UVA-sensitive PLE may benefit from supplementation with a nutritional supplement containing lycopene, β-carotene, and L. johnsonii. Accordingly, the induction of typical PLE lesions by artificial UVA exposure was significantly
reduced by oral intake of the nutritional supplement, but not by placebo. Similarly, UVA-induced development of skin lesions was associated with an increased expression of ICAM-1 mRNA in patients’ skin, and this increase was again reduced by the oral uptake of the nutritional supplement, whereas intake of placebo did not bring such effect. It should be noted, however, that protection provided by the nutritional supplement was not complete because the significant reduction in PLE scores of patients treated with the nutritional supplement, although significant as compared with patients receiving placebo after one UVA exposure, was no longer detectable after a second UVA exposure. We therefore conclude that the regular intake of a nutritional supplement containing lycopene, β-carotene, and *L. johnsonii* may provide partial photoprotection in PLE patients. To the best of our knowledge, this is the first randomized, placebo-controlled double-blind study suggesting that nutritional supplements are beneficial for patients with PLE. Hence, our results support and extend the conclusion from a recently published, uncontrolled trial that oral treatment might be beneficial for the prevention of PLE (10).

The nutritional supplement used in this trial contains a combination of lycopene, β-carotene, and *L. johnsonii* as active ingredients. The study design does not allow any conclusions to what extent the observed beneficial effects may be attributed to either of these active ingredients. In fact, this combination was chosen because it is likely that each of the three may be relevant. In particular, there is ample evidence that oral intake of carotenoids including β-carotene as well as lycopene provides significant photoprotection to human skin [reviewed in Köpcke & Krutmann and Stahl (11, 12)]. There is also evidence...
that oral supplementation with the specific probiotic *L. johnsonii* may have photoprotective effects. Indeed, the oral supplementation for 10 days with *L. johnsonii* was reported to protect against UV-induced suppression of contact hypersensitivity, decrease in Langerhans cell (LC) density, and increase in IL-10 serum levels in a preclinical model (13). In addition, *L. johnsonii* has been shown to accelerate the recovery of LC functionality after UV radiation exposure in humans (14). The photoprotective effect of the combination of *L. johnsonii* with carotenoids was also demonstrated in three clinical studies conducted on human healthy subjects using different UV sources (15).

These three clinical trials demonstrate the efficacy of the combination in reducing early UV-induced skin damage as well as in modulating early skin biomarkers of UV effects (15).

In aggregate, the present study adds to the constantly growing evidence that oral supplementation with selected nutritional supplements may be used to achieve significant photoprotection of the human skin. As shown here, this concept is not restricted to healthy human individuals but may be extended to subjects suffering from photodermatosis such as PLE.

REFERENCES


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