A novel micronutrient supplement in skin aging: a randomized placebo-controlled double-blind study

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Summary

Background Skin aging, a combination of intrinsic and environmentally induced processes, predominantly ultraviolet (UV) light from the sun, results in characteristic tissue alterations, such as the degradation of collagen and the formation of visible fine lines and wrinkles.

Objective To test the efficacy and safety of a novel micronutrient supplement (Estime®) in skin aging.

Methods A 4-month randomized double-blind controlled study including 40 subjects where the supplement was tested against placebo for 3 months followed by a 1-month supplement-free period for both groups to assess lasting effects. Efficacy measurements included skin surface evaluation, ultrasound measurement of sun-exposed and protected areas of the skin (back of the hand and ventral forearms, respectively), and photographic assessment.

Results All investigated parameters showed a continuous and significant improvement in the active group during the 3 months of supplementation as compared to placebo. Photographs showed visible improvement of the overall skin appearance and reduction of fine lines. Ultrasound measurements showed an increase in dermis density of up to 78% in the active group ($P < 0.0001$). The final assessment after 1 month without supplementation showed no further improvements, but a slight decrease was observed in most improved parameters. No treatment-related side effects were reported.

Conclusion The study demonstrated that the supplement appears to be effective and safe as an oral supplement to protect the skin and support its repair process. Recommendations are made for further evaluations.

Keywords: aging, Estime®, micronutrients, microscar, skin, UV

Introduction

Skin aging is a continuous and complex process with intrinsic and environmental components affecting the function and appearance of the skin.[1–3] The most important environmental factor that accelerates human skin aging is UV radiation from the sun.[4,5] It has been suggested, at least anecdotally, that as much as 80% of facial aging is attributable to sun exposure, although other factors such as cigarette smoking can also contribute to premature facial wrinkling.[6] This sun-induced chronic radiation injury is, like chronological aging, a cumulative process. The resulting microscars in the dermis accumulate over time with the degree of sun exposure to form macroscars leading to wrinkle formation.[7] In areas exposed to the sun, especially the face and the back of the hands,

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damage from accelerated aging is superimposed on tissue degradation from chronological aging. Individuals who have outdoor lifestyles, live in sunny climates, and are lightly pigmented will experience the highest degree of wrinkling and photoaging.[8]

Most of the yearly UV dose exposure is received under conditions when no sunscreen is applied. In the absence of topical protection, the skin only depends on endogenous defense. Skin wrinkling in a sun-exposed site may be influenced by types of food consumed.[9] Micronutrients can act as UV absorbers, antioxidants, and can interact in key pathways like modulation of enzyme activity (e.g., DNA repair enzymes, metalloproteinases) and/or anti-inflammatory pathways, upon UV exposure.[10–14]

A specially designed nutritional supplement containing specific bio-active phytonutrients, marine proteins, lipids, and antioxidants, has been suggested to be beneficial in the support and the protection of UV-exposed skin.[15] This novel micronutrient supplement differs from other products on the market by providing a unique multiple-level effect in protecting the skin from the main cause of aging signs. It provides nutrients and antioxidants and, in addition, has a unique synergistic action to strengthen the skin cells from the damaging effects of the UV light and support the skin's own regenerative properties toward optimal function and appearance. The aim of this study was to investigate the effects and safety of this novel supplement by using techniques for the evaluation of dermal structure parameters and skin surface microtopography.

Materials and methods

Design of the study

The trial was a 4-month randomized double-blind controlled study where the supplement was tested against placebo for 3 months, followed by a 1-month supplement-free period for both groups to assess lasting effects (Fig. 1). Participants were randomly assigned to receive either the supplement (Estime® Internal Beauty System, Swiss Pharmaceutical Industries SA, Neuchâtel, Switzerland), forming the active group, or a placebo of identical appearance and taste, forming the placebo group. One capsule of the supplement contained 220 mg marine protein, 308 mg marine lipids, of which 180 mg is polyunsaturated fatty acids of omega-3 type, 8 mg natural tocopherols, 18 mg plant flavonoids, and 6 mg natural carotenes. The daily dose was one capsule of the supplement or placebo. All study procedures were approved by the local ethics committee and all subjects signed an informed written consent before participating.

Subjects

Forty healthy Caucasian female volunteers, ranging in age from 35 to 54 (mean age 44 ± 6 years), were enrolled in the study after written informed consent. Fitzpatrick sun sensitivity skin types were II or III. Exclusion criteria were known or suspected allergy to any cosmetic or food ingredient, severe illness, skin diseases, pregnancy or breast-feeding, smoking, subjects who within the last two months

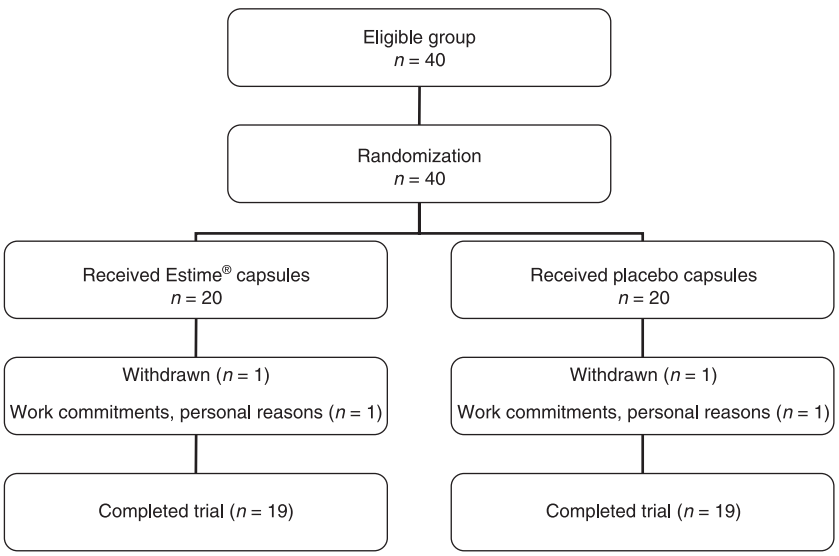

Figure 1 Flow chart describing the progress of the volunteers during the trial.

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prior to the study used any antiaging treatment (e.g., topical, oral, or resurfacing treatment), participation in any other clinical study during the 3 months preceding study entry, or need for daily medication except for oral contraceptives. Subjects were allowed to use their usual day and night care products during the whole study period.

Assessments

Assessments were carried out three times during the study: at baseline (D0), after 3 months of supplementation (D84), and 1 month after stopping supplementation (D112). Changes of skin ultrasonic echogenicity and thickness, as well as skin surface microtopography parameters, were recorded. Assessments were made at two sites with high and low environmental UV exposure: the back of the hand and the ventral forearm, respectively. Results were obtained during a period of low sun exposure (January–April). All measurements were carried out on subjects sitting in an air-conditioned room, with temperature set at 20–23 °C and relative humidity of 40–60%. Measurements started after a 15-min acclimatization period in the same atmospheric conditions. Subjects were not allowed to apply any cosmetic product on their hands and forearms 5 h before the measurement session.

Photography

Color photographs of subjects' faces were taken at baseline and after 3 months of supplementation. A digital camera (Nikon Coolpix 995, max. res. 3.5 mio pixels) was used and set on flash mode at a resolution of 1024×768 pixels. It was mounted on a fixed device at a distance of 1 m from the subject, in order to assure reproducible distance, height, and light conditions. Wrinkles and fine lines were assessed by comparing the 3-month photographs (D84) to baseline photographs (D0). Photograph assessments were performed by a panel of experienced professionals. Photographs at D0 and D84 were presented in blind and randomized sequence for each subject, using a simplified three-point scale: improved, no change, worse.[16] The following parameters were assessed: fine lines, wrinkles, skin color, oily skin appearance, and overall skin appearance.

Ultrasound measurements

Ultrasound measurements were performed using a 20 mHz resolution B scanner set on medium focus (Dermascan®C, Cortex Technology ApS, Hadsund, Denmark), producing cross-sectional images of the skin down to a depth of approximately 20 mm. A constant gain curve was applied, and skin thickness and density were determined as published elsewhere.[17–19] Measurements were made on the left ventral forearm at a distance of 10 cm from the elbow fold, and in the center of the left dorsal hand. The following parameters were measured: epidermis + dermis thickness and dermis density.

Skin surface evaluation

Skin surface evaluation was performed using a Visioscan®VC 98 system and a b/w CCD camera, illuminating the skin with integrated UVA and halogenated light sources. A surface evaluation of living skin (SELS) image of the skin surface was obtained by the camera, digitalized, and further processed by a computer to yield several surface parameters.[20,21] Because the microtopography of the skin significantly varies within a few millimeters, exact location of the test area was obtained by carefully comparing microdetails (e.g., furrows or melanin spots) on the skin with the baseline image, and moving the camera sideways accordingly, in order to obtain an exactly matching picture. Four parameters were investigated in this study: surface, entropy, contrast, and circular roughness.

Surface
Parameter surface is an indicator of the smoothness of the skin. The surface value grows proportionally to the increase of microfurrows and furrows. The closer it is to 1, the smoother the skin.[21]

Entropy
Entropy parameter represents the "disorder" of an image. A highly hydrated skin has a higher entropy value.[21]

Contrast
Parameter contrast describes the amplitude of the difference between grey levels of two neighboring pixels. A good skin condition will show low contrast values.[21]

Circular roughness (Rz)
Circular roughness (Rz) is a key parameter for studying changes on the skin surface. It is the arithmetic average of five measurements of the distance between the highest and the lowest value, referred to a reference length 1, on a selected line. Lines can be arranged horizontally, vertically, or circularly. The advantage of circularly arranged lines is that any influence from the direction of the wrinkles is compensated. Therefore, circular roughness (Rz) was chosen to represent roughness evolution.[21]

Statistical analysis

Data were analyzed using the nonparametric Page test for multiple-ordered samples for groups smaller than 30 subjects, as each group (active group, 19 subjects and placebo group, 19 subjects) was analyzed individually. Software was STATXACT version 4.0.1.[22] Statistical significance was set for $P \leq 0.05$.

Results

Out of the 40 volunteers enrolled in the study, 38 completed the entire 4-month trial. Two subjects, one in each group, withdrew for nonrelated reasons. After 3 months of study, significant improvements could be seen in all parameters of the active group.

Photography

The 38 pairs of photographs were assessed by experienced professionals. Visible significant improvements could be documented in all parameters studied ($P < 0.05$), as shown in Table 1. Photographs at baseline and 3 months were presented in blind and randomized sequence for each subject, using a simplified three-point scale: improved, no change, worse.[16] Each of the visual parameters assessed showed a positive development.

Table 1 Photo evaluation of 38 subjects after 3 months treatment.

Estime® group	Improved	No change	Worse
Fine lines	63%	37%	0%
Overall skin appearance	68%	32%	0%
Shiny look	63%	37%	0%
Skin color	47%	53%	0%
Placebo group			
Fine lines	21%	63%	16%
Overall skin appearance	16%	84%	0%
Shiny look	26%	74%	0%
Skin color	5%	95%	0%

Ultrasound

Epidermis + dermis thickness

The active group's results showed a 3-month continuous increase of this parameter, on both the forearm (+20%, $P < 0.0001$) and the hand (+15%, $P < 0.0001$) (Fig. 2, Table 2). Epidermis + dermis thickness decreased when the supplementation stopped. However, residual values at the end of the fourth month still represented 115% ($P < 0.0001$) of the forearm's baseline value and 108% ($P < 0.05$) of the hand's baseline value, respectively. In the placebo group, after 3 months, no statistically significant change could be observed.

Dermis density

The evolution of dermis density is related to epidermis + dermis thickness. In the active group, dermis density significantly increased during the 3 months of supplementation, both on the forearm (+48%, $P < 0.0001$) and on the hand (+78%, $P < 0.0001$) (Fig. 2, Table 2). Dermis density slowly decreased after the supplementation was

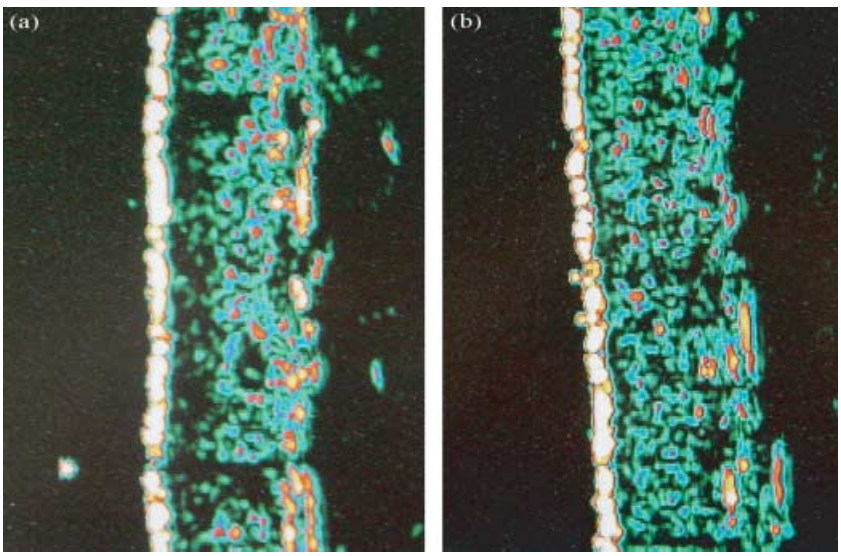

Figure 2 Cross-sectional ultrasound images, back of hand. A 43-year-old subject, active group. At study entry (a), and 3 months (b). A progressive replenishment of low echogenic, dark areas is seen over time.

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Table 2 Results from instrumental assessments at 3 and 4 months (Estime® and placebo group), including statistical significance.

Group measured area	Estime®		Placebo	
	Forearm	Hand	Forearm	Hand
Dermis density				
D0†	1432.5	1487.5	1617.5	1493.5
D90†	745.0	327.5	2004.0	1022.0
D90‡	48%***	78%***	–24%*	32%***
D120†	1266.0	767.0	1903.0	1015.0
D120‡	12%*	48%***	–18%^{ns}	32%***
Epidermis + dermis thickness				
D0§	1.007	1.080	1.106	0.882
D90§	1.211	1.238	1.113	1.145
D90‡	20%***	15%***	1%^{ns}	30%^{ns}
D120§	1.159	1.165	1.119	1.132
D120‡	15%***	8%*	1%^{ns}	28%^{ns}
Surface				
D0¶	3.19	3.07	2.95	2.97
D90¶	2.74	2.72	2.74	2.78
D90‡	–14%*	–11%***	–7%*	–6%***
D120¶	2.84	2.64	2.80	2.74
D120‡	–11%*	–14%***	–5%^{ns}	–8%***
Contrast				
D0††	0.52	0.47	0.46	0.47
D90††	0.42	0.40	0.42	0.42
D90‡	–19%**	–16%**	–9%^{ns}	11%**
D120††	0.43	0.38	0.42	0.41
D120‡	–17%*	–19%***	–9%^{ns}	–13%^{ns}
Circular roughness Rz				
D0‡‡	30.0	32.0	29.0	31.0
D90‡‡	27.0	29.0	26.0	27.0
D90‡	–10%*	–9%*	–10%^{ns}	–13%*
D120‡‡	27.0	29.0	26.0	27.0
D120‡	–13%**	–14%**	–7%^{ns}	–7%**

All results of test group are equal to median values out of 19 single results.
All results of placebo group equal median values out of 19 single results.
If $P = 0.05$ the result is considered insignificant.
*If $0.01 < P \leq 0.05$ the result is considered significant.
**If $0.001 < P \leq 0.01$ the result is considered very significant.
***If $P \leq 0.001$ the result is considered extremely significant.
†Values are expressed in pixels, measured on Dermascan C images.
‡Values are expressed in percentages relative to baseline. Values have been rounded up to the next integer percentage value.
§Values are expressed in millimeters, measured on Dermascan C images.
¶Values are expressed in surface units, calculated by VisioScan vc 98 software.
††Values are expressed in contrast units, calculated by VisioScan vc 98 software.
‡‡Values are expressed in roughness units, calculated by VisioScan vc 98 software.

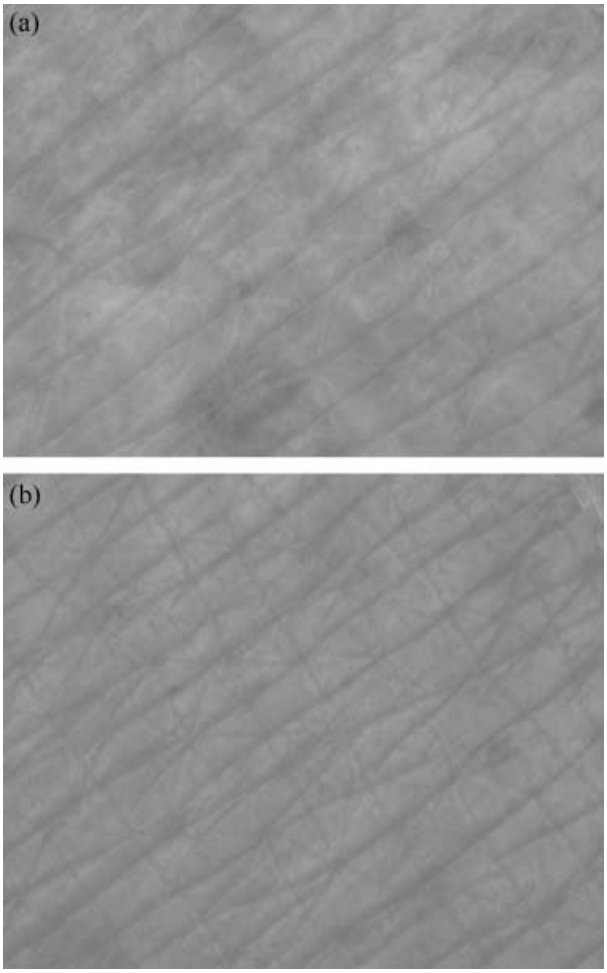

Figure 3 Skin surface images 30× magnification, using a Visioscan® UV camera. Back of hand, 43-year-old subject, active group. At study entry (above), and at 3 months (below). An improvement of the surface structure, a smoothing effect and a reduction of UV damage can be observed.

stopped; at the 4-month measurement, it still represented 112% ($P < 0.05$) of the forearm's baseline value and 148% ($P < 0.0001$) of the hand's baseline value. In the placebo group, after 3 months, an increase in dermis density was observed on the hand by 32% ($P < 0.001$). However, the active group's values were 40% higher than those of the placebo group.

Skin surface evaluation

Surface

In the active group, parameter surface constantly decreased toward the value of 1 during the first 3 months, both on the forearm (–14%, $P < 0.05$) and on the hand (–11%, $P < 0.001$) (Fig. 3, Table 2). After stopping supplementation,

the surface value slightly increased during the fourth month on the forearm and slightly decreased on the hand. Final data were 89% ($P < 0.05\%$) of the forearm's baseline value and 86% ($P < 0.0001$) of the hand's baseline value, respectively. Placebo results showed a skin surface evolution pattern analogous to that of the active groups, but amplitudes were about half of it. After 3 months, skin surface was reduced by 7% ($P < 0.05$) on the forearm and by 6% ($P < 0.001$) on the hand. Four-month placebo results showed a residual surface of 95% (ns) of the baseline value for the forearm, and 92% ($P < 0.01$) for the hand.

Entropy

Entropy increased on the forearm by 2.2% ($P < 0.05$) and on the hand by 0.8% ($P < 0.01$). At 4 months, the forearm value was about the same at 2.1% (ns), and the hand value increased to 1.9% (ns), as compared to the baseline value. Placebo results also showed a small change, being about half of active group's, and most of the changes were not significant.

Contrast

Parameter contrast constantly decreased in the active group during the first three months on the forearm (–19%, $P < 0.01$) and on the hand (–16%, $P < 0.01$). Measurement at the fourth month (i.e., 1 month after having stopped supplementation) showed that contrast slightly increased on the arm and slightly decreased on the hand. Final data were 83% ($P < 0.05$) of the forearm's baseline value and 81% ($P < 0.001$) of the arm's baseline value, respectively. Placebo results showed much lower values without significance.

Circular roughness (Rz)

The lowest roughness values were found after 4 months: –13% (arm, $P < 0.01$) and –14% (hand, $P < 0.01$). Placebo values showed about half of these reductions: –7% (arm, ns) and –7% (hand, $P < 0.01$).

Discussion

The results obtained in this study indicate that oral supplementation with specific micronutrients may positively influence the signs of skin aging. We found it interesting to observe that changes in internal skin parameters, like ultrasound assessments, could be correlated with external skin surface parameters. Photo evaluation showed a significant improvement in overall skin appearance, reduction of fine lines, and oily skin appearance as compared to placebo (Table 1). The effects observed in the photo assessment were supported by objective measurements.

Both ultrasonic DermaScan® C and skin surface VisioScan® vc 98 results showed in this study that the supplement had a positive influence on skin connective tissue and surface. Previous studies have shown that both epidermis + dermis thickness and dermis density are important parameters for assessing skin regeneration.[23–27] Ultrasound results moreover revealed that sun-induced microscars (solar elastosis), represented by low echogenicity in the papillar dermis, are reversible using the supplement.

The ultrasound parameter epidermis + dermis thickness continuously increased in the active group during the supplementation period. One month after supplementation was stopped, 75% of the 3 months' increase in epidermis + dermis thickness was still present in the forearm, and about 50% in the hand. Studies have revealed that this parameter decreases with age.[24–26] An additional analysis of ultrasound results divided the active and placebo groups into two subgroups, younger and older (for each group: younger, mean age 40, 9 subjects; older, mean age 50, 10 subjects). Results showed a statistically significant increase of epidermis + dermis thickness in the older group. After 1 month of supplementation, the older group's value equaled that of the 10-year younger subjects.[28]

Dermis density significantly increased up to three times during the supplementation period (+78%), and this interesting finding was confirmed on both sites with different levels of cumulative UV exposure on the back of the hands and on ventral forearms. This result is in line with the findings of Gniadecka *et al.*[26] Results showed marked, significant, and continuous increases of overall dermis density for all the active subjects, on both the ventral forearm and the back of the hand during the supplementation period. After the supplementation stopped, a positive residual effect could be demonstrated of approximately one-fourth of the result of the forearm and about two-thirds of the hand value. Both results were highly significant. In the placebo group, we also observed an increase of 32% in dermis density on the back of the hand, after 3 months. This value remained unchanged after supplementation was stopped and results were significant, maybe as a result of the skin's basic regenerative process. However, the subjects in the active group improved their dermis density to a much larger extent, by 46% after 3 months and 16% after 4 months, respectively.

Ultrasound results were supported by the statistically significant improvements in the skin surface parameters, namely surface, entropy, contrast, and circular roughness (Rz) on the forearm and the back of the hand in the active group as compared to placebo.

A positive surface reduction could be observed after 3 months, showing a similar development to Rz. Because

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the reduction in the depth of microwrinkles is related to a reduction of roughness, changes in these values should be correlated. Placebo results represented about half of the active group's results.

As previously mentioned, an increase of the parameter entropy is related to higher skin moisture.[21] Entropy showed a slight but statistically significant improvement (2%) in the active group. This result shows a trend to a better moisturization of the skin. This tendency correlates with the perception of a better moisturized skin as expressed by most participants in the active group.

The parameter contrast also showed a positive development as compared to placebo.

In several studies about skin improvement, circular roughness (Rz) has been found to be an important parameter.[29] An increase in skin smoothness could be demonstrated as circular roughness (Rz) was reduced in the active group as compared to placebo subjects.

Conclusions

The study supports previous reports that this supplement can improve the skin condition of aging skin. Key parameters such as dermis density – reflecting the state of the collagen and elastin network – and epidermis + dermis thickness were significantly improved during the supplementation period as compared to placebo. Skin surface parameters and face photographs confirmed these results.

Oral administration of the supplement is considered safe and no side effects were reported by the subjects. Further studies would be of interest to study the effects in different skin types, the effects in reducing pigmentation of age spots (solar lentiges), and other skin conditions.

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