Treatment of Photodamaged Skin: Use of Meglumine and Arginine to Improve the Texture of Photodamaged Skin

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A double-blind, randomized, placebo-controlled study was used to assess a topical preparation containing the antiglycation ingredients meglumine and arginine for the ability to improve smoothness, texture, and overall appearance of photodamaged skin after a 4-week treatment period. Eighteen subjects with moderate photodamage and dryness on the lateral aspect of the upper arm were treated with applications of a base cream containing placebo on one arm and a base cream containing meglumine and arginine on the other arm twice daily for 4 weeks. An expert grader assessed the visual texture or crepiness, visual dryness, and tactile dryness or roughness of the treated areas at the beginning of the study and after the 4-week period. A greater improvement was seen in the 3 assessments of dryness and texture for the cream containing meglumine and arginine than that achieved with the placebo cream after 4 weeks of treatment. After 4 weeks of treatment, the cream containing meglumine and arginine reduced crepiness by 26%, visual dryness by 64%, and roughness by 48%.

Protein glycation is the result of reducing sugars that react nonenzymatically with amino groups on proteins. The initial reaction product, or Amadori product, between a sugar and an amine can be further modified by oxidation and chemical rearrangement to become an advanced glycation end product (AGE). These protein modifications accumulate in long-lived proteins, such as collagen and elastin, and increase with chronologic age in the skin.[1-5] Treatment of dermal fibroblasts with AGEs in vitro causes alterations in the expression of extracellular matrix components.[6,7] The presence of AGEs leads to increased oxidative stress, protein cross-linking, and inflammation, which are all detrimental factors for skin appearance. Taken together, there is an interest in cosmetic ingredients that can minimize the effects of glycation.

3-Deoxyglucosone (3DG) is an α-dicarbonyl sugar produced from the metabolism of glycated amino acids, such as fructoselysine, and is a precursor to certain AGEs.[8] Meglumine and arginine, the test products for this clinical study, are 2 ingredients that inhibit the formation and activity of 3DG. Meglumine inhibits the enzymatic formation of 3DG from fructoselysine by inhibiting the enzyme fructosamine 3-kinase, and arginine inactivates reactive dicarbonyls such as 3DG and methylglyoxal.[9] This report describes the results of controlled clinical testing of meglumine and arginine compared with a placebo in improving the appearance and texture of photodamaged skin.

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Dr. Kappler and Dr. Tobia are stockholders for Dynamis Therapeutics, Inc, and inventors of the patent for Supplamine.

MATERIALS AND METHODS

Investigational Agents

A placebo cream and a cream supplemented with arginine and meglumine in a liposomal delivery system were provided. The placebo cream contained liposomes, but did not have arginine and meglumine.

Study Design

This double-blind, randomized, placebo-controlled study was designed to enroll approximately 20 subjects. The purpose of this study was to determine if a 4-week treatment regimen with a novel skin care product could improve skin tone, smoothness, texture, and general overall skin appearance in the upper dorsal arm. The selected subjects were assigned a sequential number at their baseline visit to the clinic. All subjects signed a consent form after being informed of their obligations and the risks that they might encounter as participants in this study.

The formulations were supplied to each subject in individual jars that were labeled Product C and Product D. Each subject was assigned 2 products according to the randomization code. One product was active and contained the vehicle base cream plus the 2 test cosmetic ingredients meglumine and arginine. The other product was a placebo and contained only the vehicle base cream. Subjects were instructed to apply the product to the designated arm twice daily, once in the morning and again in the evening, being certain to always apply the product designated for the left arm to the left arm and vice versa for 4 weeks. Subjects were scheduled for weekly visits to the clinic.

Study Subjects

Subjects were recruited from a pool of healthy women. To enter the study, women had to be between 30 and 70 years of age with a Fitzpatrick skin type of I to III and show at least moderate photodamage and dryness on the lateral aspects of the upper arms. The subjects had to be free of medical problems and not using concomitant medications that might interfere with the study results. The subjects were screened to ensure that they had no known allergies to cosmetics or fragrances. Women who were either pregnant or breast-feeding were excluded from participating in this study. Women of childbearing age had to use an approved form of birth control.

In addition, the subjects were required to stop all use of moisturizing products on their arms for a 3-day pretrial conditioning period, and during the study they were not allowed to swim more than once a week, receive a significant tan, or apply any other products on their arms; however, they could continue their normal cleansing routines on their arms.

EVALUATIONS

Evaluations were performed on the lateral aspect of the upper arms at baseline and at the final visit, including expert grader assessments of crepiness, visual dryness, and roughness, as well as macrophotography of the lateral aspect of the upper arms. Tolerance and compliance were assessed at all visits after the baseline visit.

Expert Grader Assessment

To maintain the expert grader's blindness to the products, visual assessments were conducted in a separate area. The expert grader assessed the appearance of the lateral aspect of the left and right upper arms for crepiness, visual dryness, and roughness. Each feature was graded on a scale of 0 to 8, with 0 indicating skin that is smooth, firm, resilient, and moisturized, and 8 indicating skin that is rough, inflexible, and wrinkled. Intermediate grades were allowed.

Images by Macrophotography

Digital photographs were taken with a 90-mm macro lens incorporating a pair of light strobes at fixed positions and inclinations. The focal distance was fixed using a standoff device to which the camera and strobes were mounted. The approximate full image field was 5×7.5 cm.

Statistical Analysis

Statistical analysis of the findings was done using a statistics software package. To allow the use of parametric statistics, the expert grader's ratings were considered as interval measurements.[10] Net change from baseline to end point for each of the 2 test products was analyzed by a paired *t* test. A Wilcoxon matched pairs test was employed to compare the expert grader's ratings. Because the Wilcoxon matched pairs test ignores tied values, real differences from baseline may be overestimated. The analysis followed general recommendations of a monograph published in 1987 by the International Federation of Societies of Cosmetic Chemists.[11]

RESULTS

Clinical Trial

Since AGEs in skin increase with chronological age, we tested the cosmetic effects of a topical cream containing ingredients that target the formation of 3DG, a precursor to an AGE. A total of 20 subjects were recruited for this study, 18 of whom completed the entire study. One subject withdrew for personal reasons unrelated to the study, and another subject was disqualified for noncompliance. The 18 subjects who participated in the study were all female with a mean age of 51.1 years (median, 54 years; range, 39–62 years).

To measure the effect of the active ingredients on skin

Expert Grader's Assessments

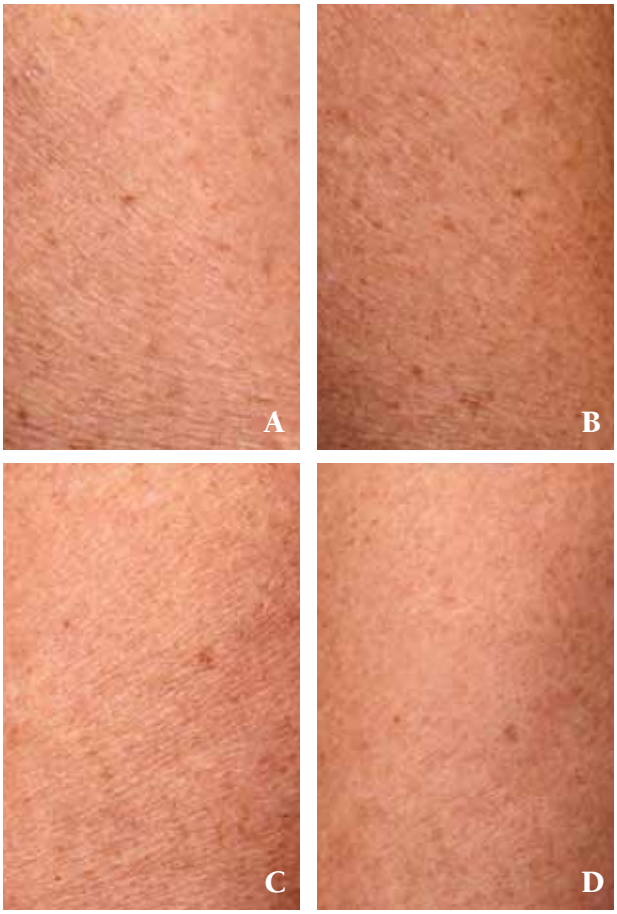
Assessment	Week 0		Week 4		Grade Change		*P* Value
	Placebo	Active	Placebo	Active	Placebo	Active	
Crepiness, mean (SD)	5.0 (1.0)	5.0 (1.0)	4.1 (1.4)	3.7 (1.3)	-0.9	-1.3	.064
Visual dryness, mean (SD)	2.9 (1.3)	2.8 (1.3)	1.8 (1.3)	1.0 (1.0)	-1.1	-1.8	.012
Roughness, (SD)	3.9 (1.2)	4.0 (1.2)	2.6 (1.5)	2.1 (1.3)	-1.3	-1.9	.102

smoothness, texture, and appearance, we tested both the placebo and the topical test formulation containing meglumine and arginine on the lateral aspect of the upper arms of the subjects. Use of this skin area is likely to have several advantages over a split-face study where one product is applied to half of the face and compared with another preparation applied to the other half of the face. We anticipated a higher level of adherence to the 4-week study protocol that was performed on the arms than to a split-face study with regard to the subjects' avoidance of sun exposure, discontinuation of use of other topical products on the study area (eg, moisturizers or cosmetics), and consistent use of each product on the same side of the body.

Efficacy

Test areas were evaluated by expert grader assessments of crepiness, visual dryness, and roughness. All evaluations were performed using a numerical scale of 0 to 8, with 0 indicating skin that is smooth, firm, and resilient, and 8 indicating skin that is rough, inflexible, and wrinkled. Intermediate grades were allowed. The evaluations were done at the beginning of the study and after 4 weeks of treatment.

Subjects' left and right arms showed nearly identical values for crepiness, visual dryness, and roughness at the beginning of the study (Table). After 4 weeks of treatment, improvement was seen in the 3 assessments of dryness and texture. The table presents the means and standard deviations of the scores of the expert grader. All parameters for the active cream containing meglumine and arginine showed a greater improvement over baseline (week 0) than did those for placebo at week 4. These differences approached statistical significance for crepiness ($P=.064$) and roughness ($P=.102$), and reached statistical significance for visual dryness ($P=.012$). The cream containing the active ingredients meglumine and arginine reduced crepiness by 26%, visual dryness by 64%, and roughness by 48%. To illustrate the visual effects of the skin treatments, photographs were taken at the start of the study and at week 4 (Figure). The figure illustrates a typical case and shows the dramatic improvement in the appearance and smoothness of the skin on the upper arm after treatment with the active formula-



Lateral aspect of the right upper arm before treatment (A) and after 4 weeks of treatment with a placebo cream (B), and the lateral aspect of the left upper arm before treatment (C) and after 4 weeks of treatment using a cream containing meglumine and arginine (D).

tion containing meglumine and arginine as compared to the placebo formulation alone. The skin treated with the placebo formulation did not show such an improvement.

Safety

There were no adverse events reported, including skin redness, itching, or scaling as noted by either the expert grader or subjects using either the cream containing meglumine and arginine or the cream containing placebo in this study.

DISCUSSION AND CONCLUSIONS

As collagen and elastin turn over relatively slowly compared to other proteins, modifications such as those due to glycation accumulate over time. Ingredients that inhibit the formation of AGEs due to 3DG were tested for their ability to improve the appearance of photodamaged skin. After 4 weeks, the appearance and texture of dry, photodamaged skin improved with both the active cream containing meglumine and arginine and the placebo cream; however, the cream containing meglumine and arginine was statistically significantly superior to the placebo cream at improving visual dryness. The improvement for crepiness approached statistical significance. These quantitative measures were also reflected in improved appearance of photographed skin after 4 weeks. The expert grader results clearly demonstrate that the active formulation with meglumine and arginine is superior to the placebo formulation for improving the appearance and texture of photodamaged skin.

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