doi:10.36849/JDD.9201

The Impact of an AGE-Inhibiting Moisturizer on Procedure Effectiveness

Zoe Diana Draelos MD,[a] Patricia Brieva PhD,[b] Hina Choudhary PharmD,[b] Stacy White PhD[b]

[a]Dermatology Consulting Services, PLLC, NC
[b]SkinCeuticals, New York, NY

ABSTRACT

The accumulation of endogenous advanced glycation end products (AGEs) has been shown to degrade the integrity of the extracellular matrix in the dermis, resulting in signs of aging. Resurfacing procedures are a first-line treatment option. Post-procedure skin care is integral in achieving optimal results with minimal downtime. This single-site, randomized, split-face, double-blind, controlled study investigated the efficacy and tolerance of an AGE inhibitory moisturizer on facial appearance on a diverse panel of 42 female subjects, including Fitzpatrick skin types I through VI, following either radiofrequency microneedling or a glycolic acid peel after twice daily application for 10 weeks. Investigator clinical efficacy was assessed using the modified Griffiths scale at baseline and weeks 1, 2, 4, and 8. Before and after images were captured with VISIA Imaging (Canfield Scientific) at the same timepoints as efficacy assessments. Objective and subjective tolerance assessments were conducted during the study. At pre-treatment, participants applied either the AGE inhibitory moisturizer or the bland moisturizer to one-half of the face in conjunction with cleanser and sunscreen for 14 days. At baseline, based on Fitzpatrick skin type, participants received either a single session of full-face ultrasound radiofrequency microneedling (RFMN) or a glycolic acid peel. For participants with Fitzpatrick skin type III-VI who were treated with a glycolic acid peel, the AGE inhibitory moisturizer-treated side of the face compared to the control-treated side of the face resulted in a greater statistically significant improvement at week 8 in 5 attributes: skin clarity, evenness of skin tone, fine lines, elasticity, and overall appearance (all $P<0.05$). Furthermore, the following 10 attributes were statistically significantly improved compared to baseline (overall facial appearance, wrinkles, fine lines, elasticity, laxity, firmness, evenness, radiance, clarity, and hyperpigmentation). For participants with Fitzpatrick skin type I-II who were treated with RFMN, the AGE inhibitory moisturizer-treated side of the face resulted in a greater statistically significant improvement in laxity, clarity, fine lines, elasticity, and overall facial appearance at week 8 versus the control moisturizer-treated side of the face (all $P<0.05$). The AGE inhibitory moisturizer is an effective and well-tolerated option for women of all skin tones to improve the signs of aging following resurfacing procedures.

J Drugs Dermatol. 2025;24(9): 904-909. doi:10.36849/JDD.9201

INTRODUCTION

Skin aging is a progressive process that impacts all physiological functions that are important for homeostasis and is the sum of intrinsic (chronological) and extrinsic (photo-aging) aging.[1,2]

Characteristic clinical features of intrinsically aged skin are the loss of elasticity and the appearance of fine wrinkles, crepiness, and sallowness. This is borne out microscopically by epidermal and dermal atrophy, which diminishes the biomechanical properties of the skin.[3]

Glycation plays a prominent role in intrinsic skin aging and has been implicated in the progression of various diseases, including chronic diseases such as diabetes, Alzheimer's disease, etc.[6] Because of its role in skin aging, glycation is a key anti-age strategy of great importance to cosmeceutical and pharmaceutical companies and is the subject of the present clinical study.

Glycation is a non-enzymatic reaction of a sugar, usually glucose, with lipids, proteins, or DNA. This process is known as the Maillard reaction.[7] The electrophilic carbonyl group of the reducing sugar reacts with free amino groups in the amino acids of proteins to form an unstable Schiff base. Further reactions result in the formation of more stable Amadori products.

The principal protein in the dermis is collagen; thus, it is a main target for glycation. The glycation products collectively are called advanced glycation end-products (AGE) and are not degradable. Thus, they accumulate with time and modify the structural properties of collagen. AGEs in the dermis play a role in intrinsically aged skin by disrupting the normal function of the dermis, which results in loss of elasticity and firmness and causes crepiness and sallowness.[8] The aforementioned signs of aging are most prevalent among Baby Boomers, currently those aged 61 to 79 years (born 1946-1964).[9-11]

Preventing the formation of AGEs is an interesting rationale in the prevention of the signs of intrinsic skin aging — loss of elasticity, firmness, clarity, and laxity — as evidenced by the exponentially growing number of peer-reviewed publications involving glycation. Flavonoid-rich fruit extracts have been demonstrated to effectively combat collagen glycation. In an in vitro study, 4% blueberry extract, 0.25% pomegranate fruit extract, or a combination of the two led to a significant reduction in AGE fluorescence after 4 weeks of incubation. Furthermore, a 5-day double-blind randomized clinical study conducted on 20 healthy female participants aged 50 to 67 years, using a fruit-flavonoid-rich cream, revealed a statistically significant (P<0.05) 34% reduction in AGE formation in skin exposed to 2x MED for 4 consecutive days, when compared to control.[12]

Aside from the normal aging process, AGEs are produced in excess in the skin of people with diabetes vs in the skin of those without diabetes.[13,14] This occurs because of the high levels of circulating blood glucose, which increases further collagen degradation, ultimately leading to higher levels of AGEs.[2]

Our earlier study on diabetic skin treated for 12 weeks with a topical product containing an AGE inhibitor and a glycosaminoglycan synthesis stimulator was insufficient to measure a change in skin AGEs, but longer application of the study product might produce different results. However, there were statistically significant improvements in skin caliper measurements on the face (P=0.004) and arm (P=0.014) and corneometry measurements (P<0.001) at week 12; additionally, clinical grading yielded statistically significant improvements in fine lines (P= 0.01), firmness (P=0.011), radiance (P<0.001), skin tone (P=0.014), skin smoothness (P<0.001), creping (P<0.004), and overall appearance (P<0.001).[15] Additionally, a newer AGE inhibitory cream that is high in fruit flavonoid extracts and proxylane significantly increased filaggrin expression by 92% (P=0.03) and reduced signs of aging (P<0.05) in a comprehensive, inclusive 12-week clinical study conducted with participants of all Fitzpatrick skin types.[16]

For many patients, facial rejuvenation procedures are a go-to treatment option to combat visible signs of aging. However, not every procedure is appropriate for each skin type. In a society with increasingly diverse skin tones, choosing the safest and most efficacious treatment is crucial and therefore warrants further attention in clinical studies. Importantly, optimal anti-aging results and reduction of post-procedure downtime can often be achieved with appropriate post-procedure care. Hence, we hypothesized that a topical skincare product that is designed to inhibit AGEs could reduce healing time after a procedure and further improve cosmetic outcomes.

To test this hypothesis, we designed an integrated approach featuring an inclusive cohort of participants of all Fitzpatrick skin types. We further designated participants to undergo a chemical peel or radiofrequency microneedling (RFMN) procedure based on suitability for each skin type and compared an AGE-inhibiting skin cream and a bland moisturizer over an 8-week period following the procedure to determine enhanced efficacy in a split-face use study.

Post-procedure skin care is important to achieving an optimal result with minimal downtime. This research examines post-procedure skin care in a variety of different Fitzpatrick skin types with patients undergoing facial rejuvenation procedures appropriate for their skin color to include facial peels and ultrasound RFMN, depending on Fitzpatrick skin type. It is theorized that a skincare product designed to inhibit AGEs will be useful in the post-procedure period by enhancing healing and improving the cosmetic outcome. The value of the AGE skin cream will be compared to a bland moisturizer over an 8-week post-procedure period to determine enhanced efficacy in a split-face use study. The inclusion criteria will include skin of color as well as sensitive skin panelists.

MATERIALS AND METHODS

Objective

The objective of this clinical study is to evaluate the efficacy and tolerance of an AGE inhibitory moisturizer on post-procedure facial skin after 8 weeks of twice daily use.[14]

Protocol

This single-site, randomized, split-faced, double-blind controlled study empaneled 42 female participants, aged 38 to 70 years. Participants had Fitzpatrick skin types I through VI with mild to moderate smoothness, hyperpigmentation, clarity, radiance, skin tone evenness, firmness, laxity, elasticity, global fine lines, global wrinkles, and overall healthy skin appearance. Efficacy assessments were performed by the dermatologist investigator using the modified Griffiths scale for the above parameters at the pre-procedure visit, baseline, and weeks 1, 2, 4, and 8.

Investigator-assessed tolerability was evaluated at baseline and weeks 1, 2, 4, and 8 for erythema, scaling, and dryness using a 4-point ordinal scale (0=none, 1=mild, 2=moderate, 3=severe) for each side of the face.

Participant-assessed tolerability was obtained for burning, stinging, and itching. All assessments were made on a 4-point ordinal scale (0=none, 1=mild, 2=moderate, 3=severe) at baseline, week 1, week 2, week 4, and week 8 for each side of the face.

Color photographs were taken with standard lighting of the central, right, and left face with a VISIA-CR4.3 (Canfield Scientific, Inc.). Photographs were taken at the following time points: baseline, weeks 1, 2, 4, and 8.

After completing an informed consent form, the participants were evaluated for inclusion/exclusion criteria. At the pre-procedure visit, the recruited participants were given a cleanser and a sunscreen to replace their existing cleanser and sunscreen and instructed to use them on the entire face for the duration of the 10-week study. The participants also received the AGE inhibitory moisturizer for application to one randomized side of the face and a control moisturizer to apply to the other side of the face. Participants were screened for suitability to either a (VIVACE, Aesthetics Biomedical) procedure or a 20% glycolic acid face peel (MicroPeel 20, SkinCeuticals) by the dermatologist investigator and were instructed to return to the research center after 2 weeks of moisturizer application at baseline for the procedure.

At baseline, the participants were prepared for and received either a full-face RFMN or glycolic acid peel procedure, based on dermatologist evaluation and Fitzpatrick skin type. Immediately following treatment, participants who received RFMN applied an anhydrous bland ointment for 1 week; afterwards, the participants resumed the application of the AGE inhibitory moisturizer and the control moisturizer to the pre-assigned randomized sides of the face for the remainder of the study. Participants who underwent a peel applied the AGE cream and bland moisturizer to the pre-assigned sides of the face immediately after the procedure for the remainder of the study.

RESULTS

Efficacy

42 participants were enrolled and 41 completed the study. The diverse panel included Fitzpatrick skin types I through VI. The breakdown was as follows: type I, n =8; type II, n = 10; type III, n = 6; type IV, n= 6; type V, n = 6; type VI, n = 6. In total, 18 participants received RFMN (type I, n = 8; type II, n =10 [9 completed]), and 24 participants received the glycolic acid peel, equally distributed among Fitzpatrick skin types II, IV, V, and VI (Table 1).

TABLE 1.

Study Participant Demographic Breakdown: Glycolic Peel and RFMN			
Procedure	**Completed Subjects**	**Mean Age**	**Age Range**
Glycolic 20 Peel	24	50.4	38-68
Radiofrequency Microneedling (RFMN)	17	58.2	38-66

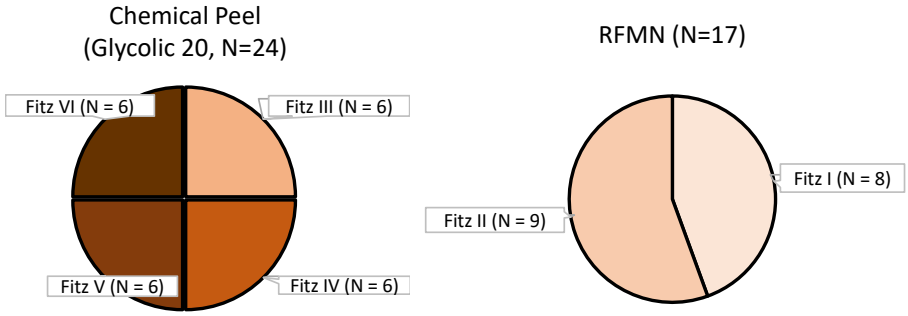


FIGURE 1. Skin Evenness. AGE inhibitory moisturizer vs control at baseline and week 8. Participant is a 58-year-old female with Fitzpatrick skin type VI.

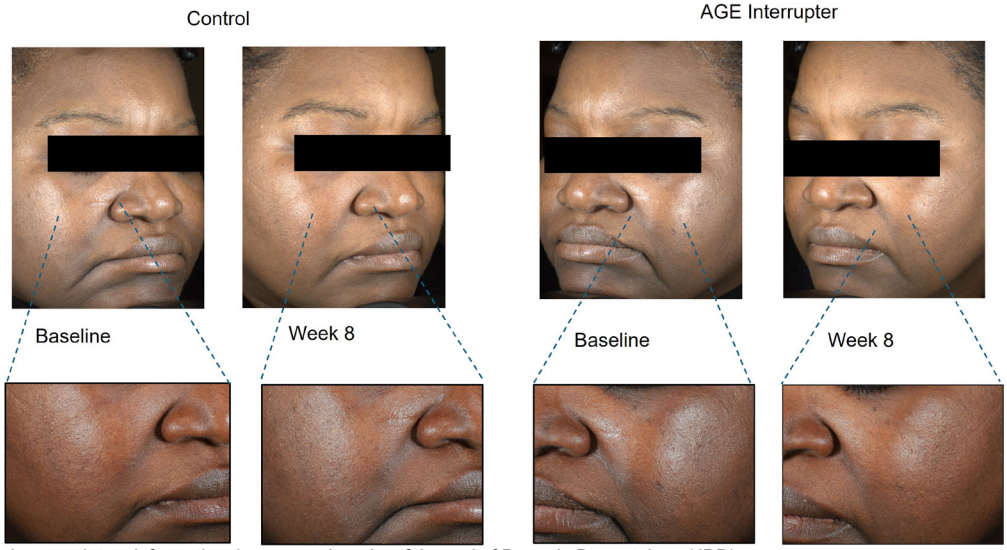
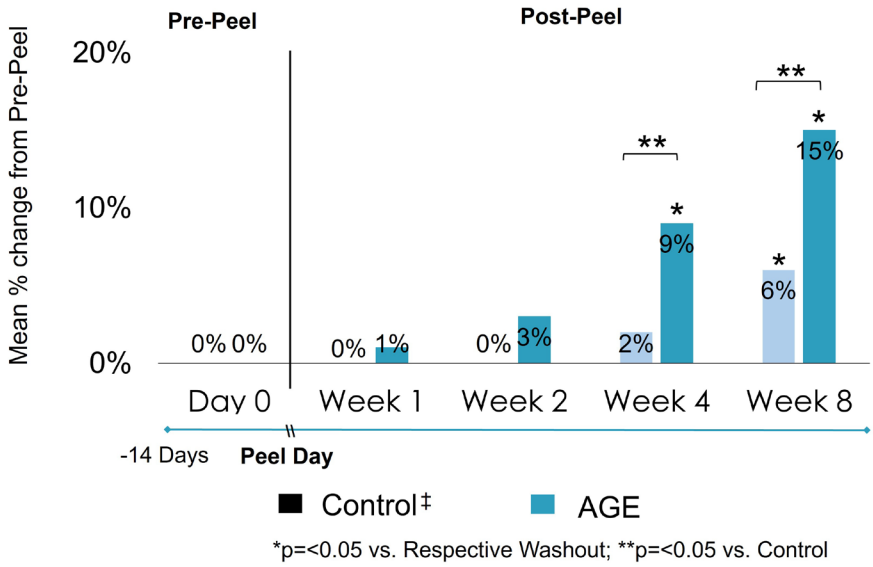


FIGURE 2. Skin tone evenness. % Mean change from pre-procedure (peel)

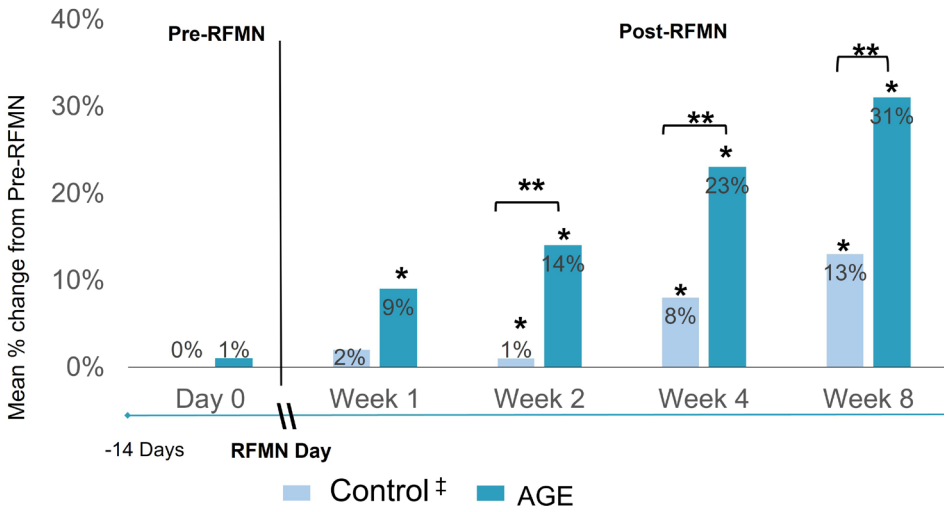


*P<0.05 vs respective baseline; **P<0.05 vs control.

In participants with Fitzpatrick skin types III-VI (treated with a chemical peel), the side treated with the AGE Inhibitory moisturizer showed a statistically significant (P<0.05) improvement in skin tone evenness by week 4 post-procedure compared to the control moisturizer, which continued to increase through the remainder of the study (Figure 2). Additionally, by week 8, the side treated with the AGE Inhibitory moisturizer showed a statistically significant (P<0.05) improvement in skin clarity (see Figure 1), fine lines, elasticity, and overall appearance in skin of color.

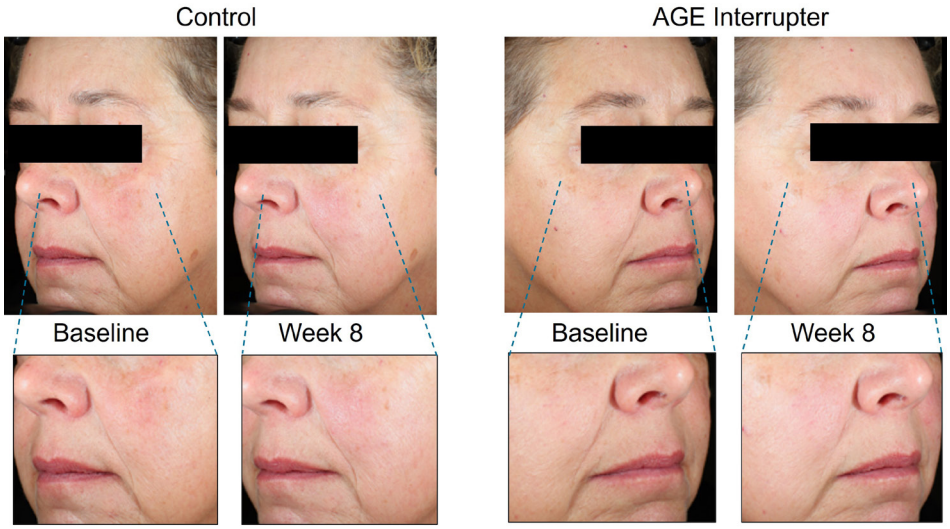
In participants with Fitzpatrick skin types I-II (treated with RFMN), the side of the face treated with the AGE Inhibitory moisturizer showed a statistically significant (P<0.05) improvement in skin clarity vs control starting at week 2 post-procedure which continued to improve at each subsequent timepoint through the remainder of the study (Figure 3). These same participants also showed a statistically significant (P<0.05) improvement on the side of the face treated with the AGE Inhibitory moisturizer in skin laxity vs control starting at week 4 post-procedure, which continued through the remainder of the study (Figures 4 and 5). Additionally, there were statistically significant improvements

FIGURE 3. Clarity. % Mean change from pre-procedure (RFMN).



*P<0.05 vs respective baseline; **P<0.05 vs control.

FIGURE 4. Skin laxity. AGE inhibitory moisturizer vs control at baseline and week 8. Participant is a 61-year-old female with Fitzpatrick skin type I.



on the side of the face treated with the AGE Inhibitory moisturizer in fine lines, elasticity, and overall facial appearance vs control at week 8.

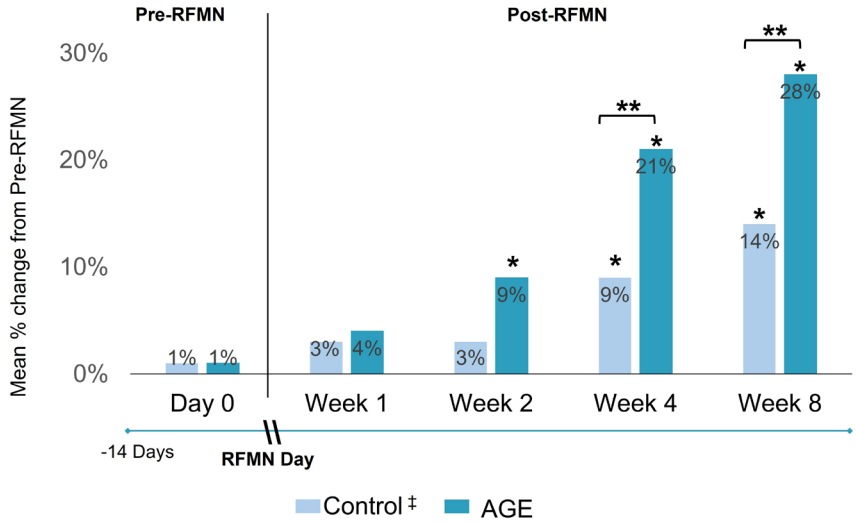
Tolerance

Based on investigator evaluation, there were no statistically significant differences between the AGE cream-treated side of the face vs the bland cream-treated side of the face in erythema, scaling, and dryness (all $P>0.05$) for both the glycolic acid peel group and the RFMN group.

Based on self-assessment evaluation by participants, there were no statistically significant differences in burning, stinging, and itching (all $P>0.05$) between the AGE cream-treated side of the face vs the bland moisturizer-treated side of the face for both the glycolic acid peel group and the RFMN group. No tolerability issues were reported for either product.

In the RFMN group, 1 participant experienced an adverse event post-procedure. Specifically, irritant contact dermatitis, probably related to the test product. The participant subsequently

FIGURE 5. Skin laxity. % Mean change from pre-procedure (RFMN).



*$P<0.05$ vs respective baseline; **$P<0.05$ vs control.

withdrew from the study. This adverse event resolved without further treatment. No additional participants experienced product-related adverse events during the course of the study.

DISCUSSION

Multiple biological targets exist for anti-aging strategies.[18,19] They include both non-invasive and minimally invasive interventions (peels, microneedling, etc.). Combining different modalities aimed at different targets offers the possibility of enhanced efficacy. Careful selection of each modality by the dermatologist is required based on each patient's unique skin characteristics. Some minimally invasive modalities may not be suitable for patients with skin of color. In this study, a diverse panel of participants was recruited with Fitzpatrick skin types I through VI. Participants with Fitzpatrick skin types I and II were treated with RFMN on Day 0, while those with Fitzpatrick skin types III-VI were treated with a glycolic acid peel. With a growing aging population, particular attention was given to individuals over 55, including a significant portion of baby boomers, who are increasingly seeking solutions for age-related skin concerns. Overall, when integrated with RFMN, the AGE inhibitory moisturizer was shown to be safe and effective in participants with Fitzpatrick skin types I and II in improving laxity, clarity, fine lines, elasticity, and overall facial appearance vs the control moisturizer. For participants with skin of color (Fitzpatrick III-VI), the AGE inhibitory moisturizer was demonstrated to be a safe and effective adjunct to chemical peels in improving skin clarity, evenness of skin tone, fine lines, elasticity, and overall appearance.

It should be noted that a single adverse reaction was observed (an irritant contact dermatitis); no other product-related adverse events were observed during the study. The safety endpoint was met.

For future work, it could be advantageous to integrate the AGE inhibitory moisturizer with other minimally invasive procedures to better understand treatment outcomes in diverse patient populations.

The results of this study clearly demonstrate the efficacy of an AGE inhibitory moisturizer in improving skin health attributes and visible signs of aging compared to a bland control following a skin type-appropriate, minimally invasive procedure. These results could inform future work integrating an AGE inhibitory cream with other mechanical or energy-based procedures to further improve patient outcomes.

DISCLOSURES

ZDD received a research grant to conduct the research presented in this manuscript. PB, HC, and SW are employees of L'Oreal.

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AUTHOR CORRESPONDENCE

Stacy White PhD
E-mail:..... Stacy2.white@loreal.com