A Novel Cosmetic Anti-inflammatory Peptide With Firming and Lifting Benefits: The Potential for Adjunctive Care for Skin Laxity Associated With Weight Loss

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BACKGROUND Glucagon-like peptide 1 receptor agonists (GLP-1 RAs) have demonstrated substantial therapeutic benefits for patients with Type 2 diabetes mellitus and/or obesity. Their use has recently expanded rapidly across diverse patient populations. However, GLP-1 RA–associated changes in body composition and skin quality, including premature skin aging and alterations in body contour, may create functional and aesthetic concerns for patients. Effective strategies to address these visible and unwanted effects are needed.

OBJECTIVE To summarize preclinical and clinical evidence supporting the potential role of AP31, a novel multifunctional micropeptide, in mitigating skin-laxity effects relevant to patients treated with GLP-1 RAs.

MATERIALS AND METHODS Preclinical studies have evaluated the biological activity of AP31 across multiple aging-related end points, including inflammatory pathways, extracellular matrix integrity, and age-associated gene expression. In addition, clinical studies have assessed AP31-containing regimens in middle-aged women, with outcomes focused on visible markers of skin aging such as firmness, elasticity, fine lines, wrinkles, facial contour, and structural support.

RESULTS Preclinical investigations demonstrated that AP31 reduced proinflammatory markers, increased key extracellular matrix components, and favorably modulated genes associated with intrinsic skin aging. In clinical studies, AP31-containing regimens produced rapid and visible improvements in multiple parameters of skin aging, including enhanced firmness and elasticity, reduction in fine lines and wrinkles, improvement in jawline definition, global facial lift, and reduced prominence of nasolabial folds.

CONCLUSION AP31 shows promising biological and clinical activity in improving visible signs of skin aging. While current findings are encouraging in the context of normal aging, randomized controlled trials are warranted to further establish the efficacy of AP31 for patients experiencing skin-related changes associated with GLP-1 RA use.

Since the approval of exenatide in 2005, the first glucagon-like peptide 1 (GLP-1) receptor agonist (GLP-1 RA) to be released to the market, GLP-1 RA drugs have revolutionized the treatment of Type 2 diabetes mellitus (T2DM). In addition to improving glycemic control, continued use also results in weight loss. Modern GLP-1 RAs such as semaglutide and tirzepatide have more recently been approved in the United Kingdom and the United States for the improvement of glycemic control in adults with T2DM, and for weight loss in obese individuals, or those who are overweight with at least 1 weight-related comorbidity. Their use has now become widespread among diverse populations of patients who achieve and sustain significant weight loss with continued GLP-1 RA use. A pooled cross-sectional study using electronic health records from the Epic Cosmos database (2010–2023) examined trends in GLP-1 RA use among 67.9 million patients with either T2DM-only, obesity-only, or patients with T2DM with obesity.[1] A gradual increase in the use of GLP-1 RA was apparent in all groups over 2010 to 2016, followed by a pronounced uptake from 2016.[1] The data show that in the obesity-only population, the rate of uptake among women was 1.47 times faster than that of men (annual rate of increase) and people with education beyond college had a 1.76 times faster uptake rate than their counterparts. Among those younger than 19 years with T2DM and obesity, use of GLP-1 RAs increased from 0% in 2017 to 35.3% in 2023.[1] Analysis of the French nationwide reimbursement health care database (Système National des Données de Santé) also shows that initiation of GLP-1 RA use rose sharply from 2017 (n = 5,117) to 2023 (n = 15,193).[2] Increased use was particularly evident among individuals without T2DM or obesity (representing ~2% of all GLP-1 RA users in 2020 and >5% of all users in 2022), a group (n = 10,376) consisting largely of women (68.7%) younger than 50 years of age (mean age = 48.9 years).[2] Notably, 4,683 of these individuals (2.2% of all GLP-1 RA users) did

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Dermatol Surg 2026;52:S16–S22
http://dx.doi.org/10.1097/DSS.0000000000005181

not present with any overweight-related comorbidities.[2] The use of GLP-1 RAs among individuals without a diagnosis of T2DM or obesity (~5,000 individuals) equaled the annual treatment needs of approximately 1,700 patients with T2DM or obesity.[2] Analysis of health care databases in the United States shows similar results, with increasing GLP-1 RA prescribing rates from 2018 to 2023, particularly among individuals without T2DM or obesity.[3] The proportion of GLP-1 RA users without T2DM or obesity rose from 7,599 (4.5% of all users) in 2018 to 107,785 (17% of all users) in 2023.[3] These users, again, were largely female (80%) and younger than 50 years (median age = 48 years).[3] Hence, the data reveal a population of individuals who are not obese or diabetic who may be at risk of unwanted aesthetic side-effects of GLP-1 RA use, especially when such normal-weight patients are losing further weight.

GLP-1 RAs illicit cellular response by mimicking the action of GLP-1, a hormone secreted by gut enteroendocrine cells in response to food intake.[4–7] GLP-1 plays a key role in glucose metabolism and appetite suppression by stimulating glucose-dependent insulin secretion, inhibiting glucagon release, slowing gastric emptying, and modulating central nervous system pathways involved in appetite.[4–7] However, in addition to their effects on glycemic control and weight loss, GLP-1 RAs can have an unintended impact on the face and other regions of the body (e.g. neck, arms, stomach, thighs) that include decreased volume and premature aging.[4–7] For example, the term "Ozempic-face" (first associated with the use of the GLP-1 RA semaglutide) refers to a gaunt aged appearance characterized by sunken eyes, sagging jowls, wrinkles, and hollow cheeks.[4–7] Although believed to result from a rapid and nonselective loss of subcutaneous layers of supporting facial fat in tandem with naturally decreased elasticity of aging skin, other factors likely play a role in this accelerated aging process.[4–7]

Dermal white adipose tissue (DWAT) is a source of adipose-derived stem cells (ADSCs) that protects skin health through secretion of a variety of hormones and growth factors involved in skin rejuvenation.[6] As subcutaneous DWAT gradually depletes with normal aging, dermal fibroblasts lose structural integrity and collapse due to decreased collagen synthesis; this results from reduced mechanical tension on the fibroblasts and presents as thin and wrinkled skin.[6] Conditioned media from ADSCs has been shown to support wound healing by promoting the migration and secretion of collagen by dermal fibroblasts.[6] GLP-1 RAs target GLP-1 receptors in DWAT, inhibiting the proliferation and adipogenic differentiation of ADSCs.[6] As a result of reduced DWAT and ADSC function, GLP-1 RAs also indirectly reduce production of estrogen and other growth factors in the skin such as transforming growth factor-beta,[6] which reduces stimulation of fibroblasts to produce collagen.[8] Estrogen plays a key role in maintaining integrity, elasticity, and hydration of the skin, with substantial loss of collagen and altered fibroblast activity correlating with reduced estrogen production during menopause.[6] DWAT becomes the primary supplier of estrogen as levels of sex hormones produced by the gonads naturally decrease with age.[6] This localized production of estrogen is believed to protect the skin from the effects of aging.[6] The totality of evidence, therefore, suggests that the detrimental effects of GLP-1 on skin health and aging are not simply due to the structural loss of supporting fat layers (i.e., rapid weight loss does not allow skin time to adjust loss of supporting fat cells) but also due to alterations in adipose tissue (i.e., DWAT and ADSC) function that supports skin health and rejuvenation.[6]

In addition to premature aging of the skin, other dermatologic adverse events potentially associated with GLP-1 include injection site reactions (e.g., pain, swelling, or itching due to immunogenic or inflammatory responses), altered skin sensation (e.g., dysesthesia, paresthesia, or hyperesthesia due to unknown effects of GLP-1 on sensory nerves directly or indirectly through changes in fat distribution), and alopecia (i.e., hair loss).[4,7] Alopecia and telogen effluvium (a form of hair loss caused by metabolic stress) may be associated with the use of GLP-1 RAs, possibly due to bodily stress that results from rapid weight loss and nutritional deficiency,[4,7] and a recent study also reported an increased risk of androgenic alopecia associated with GLP-1 RA exposure,[9] but further research is required to confirm this association. It is also noteworthy that DWAT is located close to sebaceous glands and hair follicles and has been shown to affect hair follicle growth cycles through paracrine signaling, suggesting a potential mechanism whereby hair loss is due to GLP-1 RA effects on DWAT.[6]

Although GLP-1 RAs are very effective in achieving rapid weight loss, as mentioned above, patients can experience unwanted cosmetic side effects which may be unexpected and undesirable for them. This can be especially visible when there is loss of volume in parts of the face associated with looking youthful, such as the jawline, temples and cheeks, and, along with decreased levels of collagen and elastin, this leads to a more aged appearance with drooping and wrinkles.[10,11] These consequences have led to some patients seeking interventions to help mitigate the impact of such visible side effects of GLP-1 RA use. A Google Trends search of trend data in the United States from June 2022 to June 2025 for searches for terms related to Ozempic face and various relevant corrective procedures (e.g., "face filler," "face fat grafting," "cheek filler") reported a significant increase in search terms related to Ozempic face during this period.[10] The increased interest in facial weight loss-related terms was significantly associated with "filler" terms, although no relationship with surgical terms was found.[10]

In a retrospective analysis of data from the deidentified insurance claims PearlDiver database, prescription data for GLP-1 RAs (semaglutide and liraglutide) across 30 US states from 2011 to 2022 were investigated for any correlation with body contouring procedures, comparing GLP-1 RA users (mainly women in their mid-forties) and nonusers.[12] The findings showed significant correlations between GLP-1 RA use and an increase in body contouring procedures,

and the time to surgery from drug initiation varied depending on the GLP-1 RA in question, with users of the more potent semaglutide having a mean time to surgery of ~100 days, compared with ~1,200 days for users of liraglutide.[12] Higher surgery counts were observed for all users of GLP-1 RAs in the analysis (compared with nonusers), with users of semaglutide showing differences in surgery counts dependent on dose, indicating a dose-related link between GLP-1 RA use and increased body contouring surgeries.[12]

The cellular changes (e.g., reduced collagen from loss of DWAT) and facial aging experienced by users of GLP-1 RAs are more pronounced in those with naturally lower levels of collagen (e.g., patients older than 40 years),[11] further accentuating the visible signs of collagen depletion. Hence, there is great value in introducing technologies that can improve collagen depletion and symptoms of aging, especially in the middle-aged population.

While increased use of GLP-1 RAs has improved treatment of T2DM and obesity, it has given rise to a new set of challenges regarding the management of aesthetic and function issues related to skin laxity, redistribution of fat deposits and altered body contour, and hair loss. Thus, there is an unmet need to more thoroughly understand the long-term aesthetic impact of GLP-1 RA use to better prevent and address these concerns more effectively.[5] Although awareness of these issues is increasing and dermal fillers or skin-tightening procedures may offer some benefit, there is a lack of empirical data to support such procedures,[5] which come at a high cost. As such, further research in the form of large-scale clinical trials and prospective studies assessing the efficacy of these treatments is required.[5]

The objectives of this review were to summarize: (1) the biological and physiological changes observed due to rapid weight loss secondary to GLP-1 RA use; (2) the scientific development, mechanism of action, and clinical value of acetyl dipeptide 31 (AP31) technology as a promising preventive maintenance strategy to address skin-related consequences resulting from GLP-1 RA–mediated weight loss.

AP31 Technology

There are a variety of antiaging agents that target a single process such as low-level chronic inflammation or dermal biosynthesis.[13] These agents, however, may not address the most important processes involved in aging of the skin.[13] Procedures such as dermal filling and surgical lifting are also commonly used to increase facial volume and restore contour with aging, but there is a need for less invasive options.[13] Peptides are a nonirritating and safe class of antiaging agents that act in 1 of 4 ways: as a carrier for biologically important molecules, as signal peptides that regulate extracellular matrix (ECM) components (i.e., collagen and elastin), as an enzyme inhibitor, or as inhibitors of neurotransmitters with a neurotoxin-like mechanism of action.[13] The ability of peptides to penetrate skin depends greatly on their size and net charge at physiological pH.[13] Because they are naturally hydrophilic, the lipid-rich stratum corneum limits their bioavailability unless chemically modified.[13]

AP31 is a novel multifunctional antiaging micropeptide, developed as part of a dermatologist-directed research program.[13] Its size (229.3 Da) is well below the 500 Da threshold whereby skin penetration and absorption declines greatly.[13] During development, the structure of AP31 was optimized to further increase penetration of the stratum corneum through acetylation of its N-terminus and amide conversion.[13] It has been shown to readily penetrate skin and remain bioactive in a variety of formulations including creams, lotions, and water-in-silicone base.[13] Addition of a proprietary noisome carrier (i.e., a nonionic surfactant bilayer vesicle) to the AP31 formulation increased skin penetration by 4-fold compared with the base formulation.[13] Bioavailability is also affected (increased or decreased) by the presence of specific types (and percentages) of alpha-hydroxy acids, with 4% glycolic acid, for example, increasing bioavailability by more than 4.6-fold.[13]

Preclinical Studies With AP31: Effects on Proinflammatory Markers

Administration of AP31 (0.1, 1, 10, and 100 μM) to human endothelial cells exposed to nickel for 24 hours significantly reduced the release of the proinflammatory markers IL-6 (by 100%) and IL-8 (by 73%–92%) compared with vehicle control ($p < .05$ for all doses).[13] Similarly, the same doses of AP31 significantly reduced the release of IL-4 (by 100%) and IL-7 (by 71%–85%) compared with vehicle control in T-cell receptor-activated peripheral blood mononuclear cells ($p < .05$ for all doses).[13] Reduced release of IL-8 (by 0%–20%; $p < .05$ for 100 μM dose only) and TNFα (by 8%–42%; $p < .05$ for all doses) compared with vehicle control has also been demonstrated for AP31 in epidermal keratinocytes exposed to 12-O-tetradecanoylphorbol-13-acetate.[13] In all 3 models, the highest dose of AP31 (100 μM) was nearly as effective as dexamethasone (a corticosteroid) and tacrolimus (a nonsteroidal anti-inflammatory agent) without any signs of toxicity (in contrast to tacrolimus 100 μM).[13]

Preclinical Studies With AP31: Effects on Extracellular Matrix Components

Administration of AP31 0.01% to adult dermal fibroblasts for 72 hours statistically increased the levels of ECM components including elastin, decorin, fibronectin, procollagen, and hyaluronic acid compared with vehicle control (Figure 1; all $p < .05$).[13] Notably, there were no adverse effects observed regarding cell viability or metabolism.[13] Collagen and elastin levels were also increased in human skin explants administered AP31 0.01% in formulation for 8 days compared with untreated controls (Figure 2; all $p < .05$).[13]

Preclinical Studies With AP31: Effects on Gene Expression

AP31 (0.1% and 0.5% in cream base) has been shown to enhance skin and epidermis development, epidermal cell

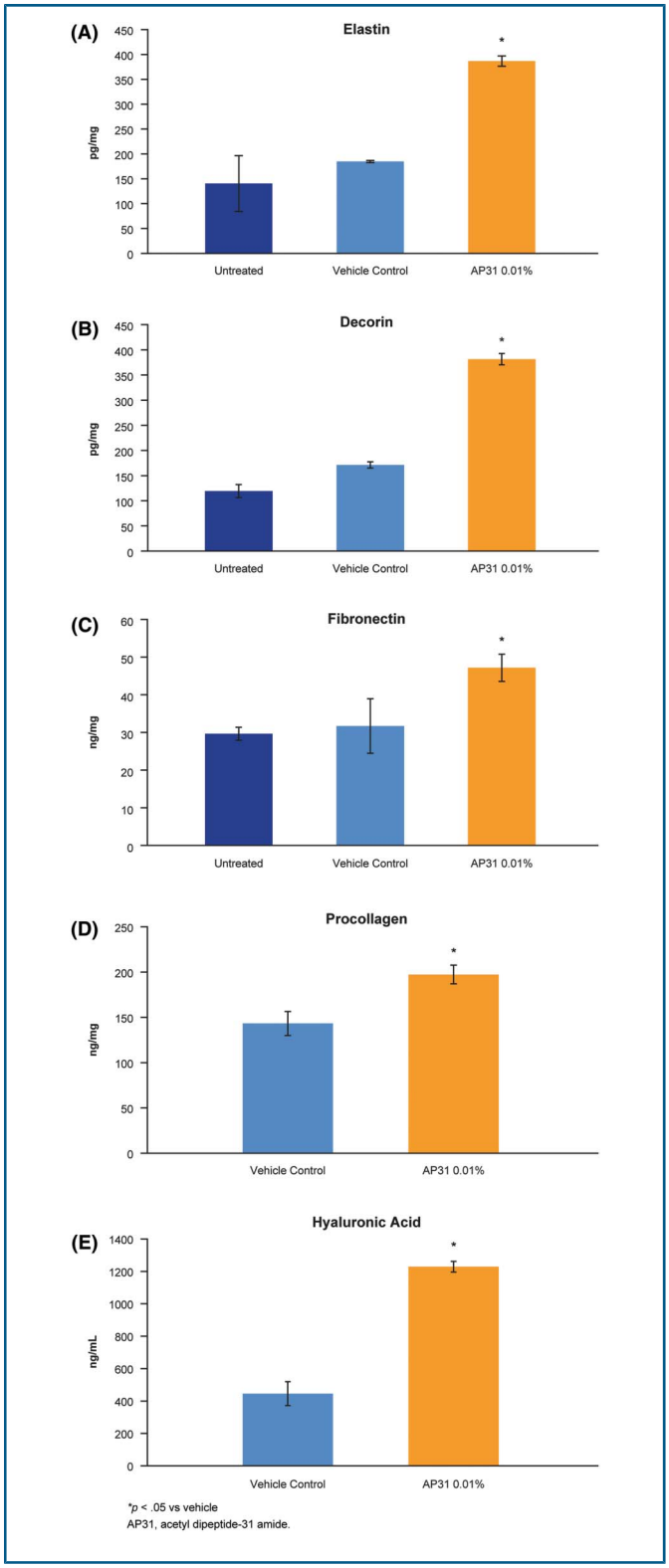

Figure 1. Levels of extracellular matrix biomarkers in normal adult human fibroblasts treated with AP31 0.01% or vehicle for 72 hours. *$p < .05$ versus vehicle. AP31, acetyl dipeptide-31 amide. Reproduced with permission from Edison BL, Parsa R, Dufort M, Tierney NK, Green BA, Farris PK. Acetyl dipeptide-31 amide: a novel cosmetic anti-inflammatory peptide that demonstrates antiaging, firming, and lifting benefits. J Drugs Dermatol 2025;24(1):23–33. 10.36849/JDD.8786.

and keratinocyte differentiation, keratinization, and peptide-cross linking in full-thickness human skin equivalents.[13] Of note, the AP31 0.01% cream upregulated 7 top pathways that are downregulated during normal aging of the skin and downregulated 4 pathways that are upregulated during skin aging.[13] Individual gene analysis showed a positive effect on expression of several genes involved in ECM barrier function (*PADI1*, *TGM1*, and *IVL*), skin hydration (*AQP5* and *HAS3*), epidermal metabolism (*GLUD1*), the dermal–epidermal junction (*ITGB7*), lipid metabolism (*LIPN*), and inhibition of senescence (*CDKN2A*).[13]

Clinical Studies With AP31

A prospective, single-arm, single-center 16-week study of 38 women aged 40 to 65 years (mean age of 54.5) mainly with Fitzpatrick skin Type II ($n = 13$, 43.2%) or III ($n = 20$, 52.6%) with mild-moderate jawline sagging and wrinkles, and moderate fine lines, evaluated an AP31 0.4% cream product applied every morning and evening to the neck, face, and jawline.[13] Application of AP31 was part of a regimen as follows: AM: nonmedicated cleanser + AP31 0.4% cream + SPF 35 sunscreen; PM: nonmedicated cleanser + AP31 0.4% cream.[13] This cohort of women were at an age where pre-existing collagen decline is expected and participants were possibly more likely to use GLP-1 RAs (although these data were not collected). At Weeks 12 and 16, all clinically graded parameters significantly improved ($p < .01$), notably improvements in the lower face including jawline sagging, global lift, and the appearance of nasolabial folds (Table 1).[13] Fine lines and wrinkles, smoothness, skin tone, and hyperpigmentation were all also improved compared with baseline.[13] Subject self-assessment of efficacy was consistent with the clinical grading, with participants noting firmer, more elastic skin as early as Week 2.[13] At Week 16, 92% of participants reported an improvement in their jawline and facial contouring.[13] No statistically significant changes from baseline in tolerability assessments of edema, erythema, dryness, burning, stinging, itching, or tightness were reported by participants.[13]

A 12-week single-center, single-arm clinical trial involving younger women aged 25 to 55 years ($n = 46$) with mild to moderate photoaged skin assessed a twice daily (AM/PM) regimen of AP31, sunscreen and bakuchiol: AM: AP31+SPF (Neutrogena Collagen Bank SPF Moisturizer); PM: AP31+bakuchiol (Neutrogena Collagen Bank Moisturizer).[14] In this trial, adherence to the AP31-containing regimen resulted in significant improvements in early visible signs of collagen decline (Figure 3, $p < .05$). The clinical gradings for lack of clarity, global fine lines, roughness, lack of radiance/brightness, and elasticity were improved as early as Week 1 ($p < .05$) and maintained at Weeks 4, 8, and 12.[14] A significant reduction in photo-damage was observed at Weeks 8 and 12 ($p < .05$) and a significant reduction in skin glycation index at Week 12 ($p < .05$).[14] Participants also self-reported significant improvements in the look and feel of their skin, as early as Week 1 and, after

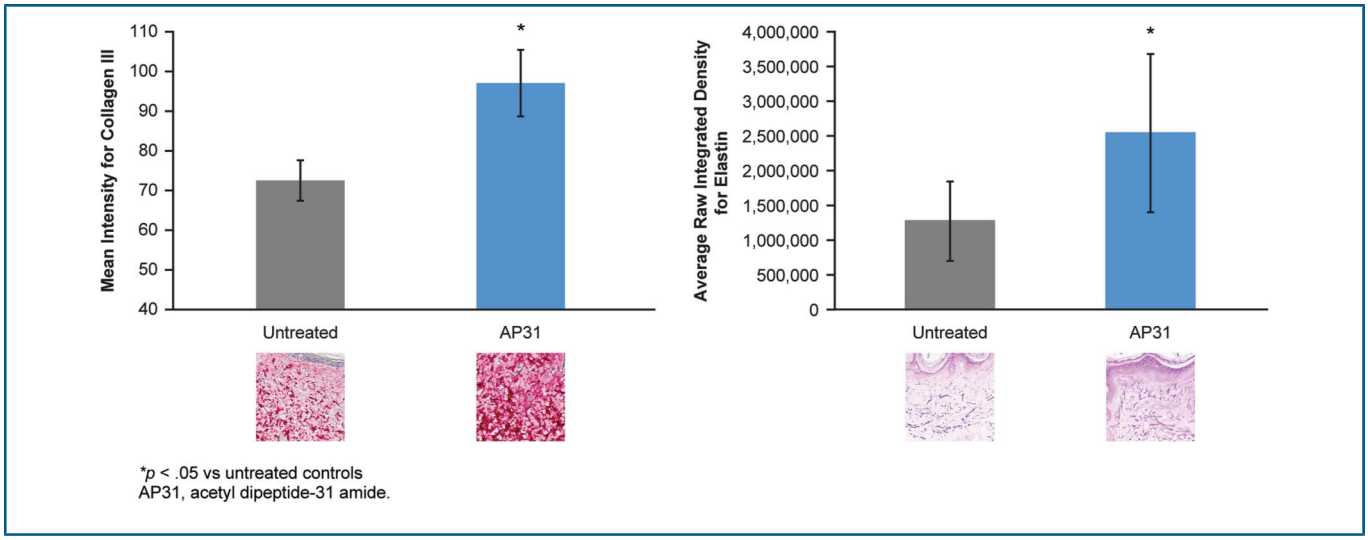

Figure 2. Collagen and elastin levels in human skin explants treated or not with AP31 0.01% in formulation every 2 days for 8 days. *$p < .05$ versus untreated controls. AP31, acetyl dipeptide-31 amide. Reproduced with permission from Edison BL, Parsa R, Dufort M, Tierney NK, Green BA, Farris PK. Acetyl dipeptide-31 amide: a novel cosmetic anti-inflammatory peptide that demonstrates antiaging, firming, and lifting benefits. J Drugs Dermatol 2025;24(1):23–33. 10.36849/JDD.8786.

12 weeks, 87% reported improvement in feel of skin firmness and elasticity.[14] These data are encouraging, although it is recognized that the already known effects of SPF and bakuchiol can contribute to the effectiveness of this regimen.

The AP31-containing regimens in both of these clinical trials were well-tolerated with no serious adverse events reported.[13,14] When considering both the preclinical and clinical data, AP31 is a novel, multifunctional, nonirritating, cosmeceutical signaling micropeptide that has been shown to improve the clinical signs of aging, and lift and contour facial skin.[13,14] In addition, a reduction in inflammation markers, increased levels of ECM components, and the expression of genes involved in ECM barrier function, skin hydration, epidermal metabolism, the dermal–epidermal junction, lipid metabolism, and inhibition of senescence were observed in preclinical studies.[13,14]

Discussion

While use of GLP-RAs can provide significant health benefits to patients who are obese, overweight, and/or diagnosed with T2DM, their increased uptake both on- and off-label has led to a rise in patients seeking cosmetic or surgical procedures[10,12] to counter unwanted observable side-effects such as premature aging, wrinkling, and reduced skin elasticity. Reductions in DWAT in normal aging leads to loss of structural integrity of fibroblasts due to a decrease in collagen synthesis, and data show that GLP-1 RAs target GLP-1 receptors in DWAT, indirectly reducing the production of estrogen and other growth factors such as TGF-b in the skin.[6] There is also a substantial loss of collagen and altered fibroblast activity associated with lower levels of estrogen during menopause[6]; hence, collagen depletion during normal aging is further exacerbated through GLP-RA use. However, there are reports of antioxidant and cytoprotective effects of semaglutide in human dermal fibroblasts in vitro,[15] and further research is warranted to help elaborate on the interplay between aging and skin condition in the context of GLP-1 RA use.

Clinical studies have shown positive data on the benefits of AP31 in reducing visible signs of aging (clinically similar to the accelerated aging phenotype seen among GLP-1 RA users due to rapid weight loss). The studies captured relevant demographics wherein the recruited participants

TABLE 1. Clinical Improvement From Baseline in Parameters of Lower Face Aging With Use of AP31 0.4% Cream Twice Daily

	Mean Percent Improvement		
	Week 6	Week 12	Week 16
Appearance of nasolabial folds	3*	7*	11*
Jawline sagging	0	7*	9*
Global lift	3*	8*	10*

* $p < .01$.
AP31, acetyl dipeptide-31 amide.

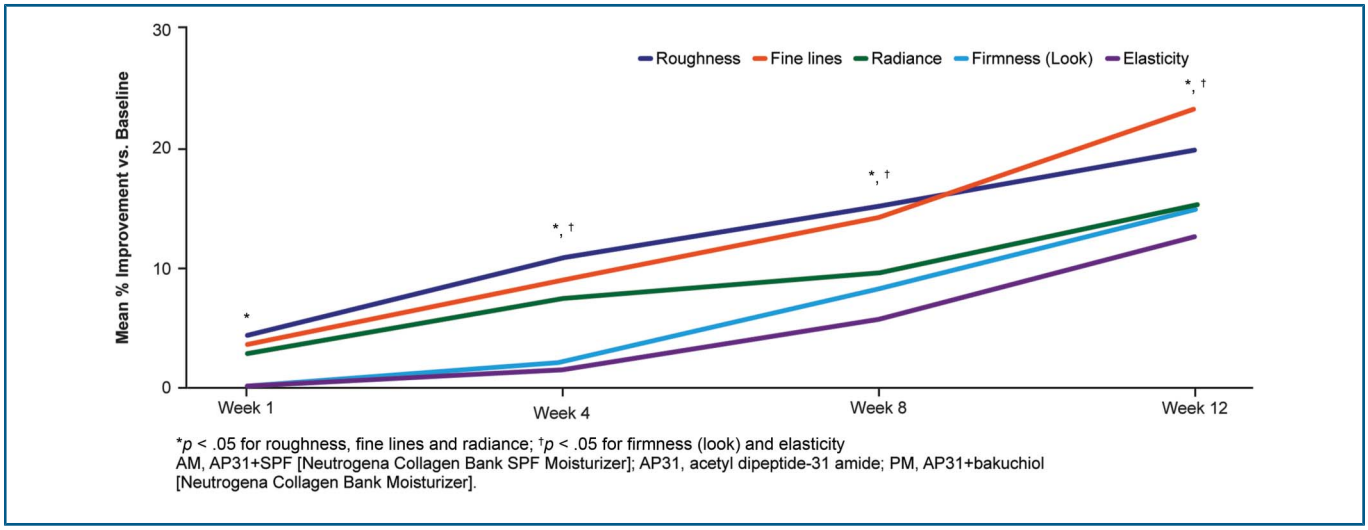

Figure 3. Clinically graded improvement in parameters representing collagen decline beginning at Week 1 or 4 and continuing through Week 12 after twice-daily use of AM/PM AP31 preaging formulations. *$p < .05$ for roughness, fine lines and radiance; †$p < .05$ for firmness (look) and elasticity AM, AP31+SPF [Neutrogena collagen Bank SPF Moisturizer]; AP31, acetyl dipeptide-31 amide; PM, AP31+bakuchiol [Neutrogena collagen Bank Moisturizer]. Reproduced with permission from Farris P, Frey C, Parsa R, Miller D, Shyr T, Li WH. INDIVIDUAL ARTICLE: A scientific approach to defining, evaluating, and treating preaging with a cosmetic regimen containing a novel cosmetic peptide, acetyl dipeptide-31 amide (AP31). J Drugs Dermatol 2025;24(5):51181s4-51181s14. 10.36849/JDD.51181.

included those 40 years and older, who would be more likely to receive a GLP-1 prescription in real-world practice, and a 'younger' cohort with photo-damage and signs of aging. Participants following a twice daily application of AP31 had rapid and significant improvements in the appearance of their skin, including reduced photo-damage.[13,14] Preclinical data revealed a reduction in markers of inflammation, increased levels of ECM components (including collagen and elastin), increased expression of genes involved in ECM barrier function, and genes involved in skin hydration, epidermal metabolism, the dermal–epidermal junction, lipid metabolism, and inhibition of senescence.[13,14]

The AP31 technology is a foundational topical strategy in dermatologic regimens to address and prevent aging, preaging, and unwanted accelerated aging from the use of GLP-1 RAs. It also provides a valuable adjunct complementing in-office procedures used to treat skin laxity and sequelae secondary to weight loss associated with GLP-1 RA use. However, there are a number of limitations to the clinical studies reported here, including small sample sizes, the nonrandomized nature, and the lack of control groups. In addition, the evaluation of AP31 was in the context of combination regimens.

Conclusion

Use of GLP-1 RAs, while a critical component of T2DM and obesity, can cause a variety of skin-related issues including premature aging and alterations in body contour that result in both functional and aesthetic burdens for patients. While there is a need for further research to better understand the processes underlying skin aging, particularly in the context of GLP-1RA use, AP31 technology represents a promising therapeutic option to address and prevent aging, preaging, and unwanted accelerated aging of the skin. The potential benefits for AP-31 in users of GLP-1 RAs remains speculative, and further research in the form of randomized controlled trials is needed to strengthen the evidence for its use in such patients.

Acknowledgments

Editorial support was provided by David Sunter, PhD and Matthew Soulsby, PhD of Envision Pharma Group.

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