IFSCC 2025 full paper (IFSCC2025-338)

Dynamics of Facial Shape: Unraveling the Non-Genetic Factors and Developing Face-Shaping Skincare Ingredients through Gravity-Responsive 3D Facial Imaging

Eisuke Takai[1,*], Munetaka Kawamoto[1], Nao Itai[1], Katsuyuki Maeno[1], Seiko Matsumoto[1], Joris Pauty[1], Enkhtuul Gantumur[1], Shinsuke Akita[2], Kentaro Kajiya[1], and Shunsuke Iriyama[1]

[1]MIRAI Technology Institute, Shiseido Co., Ltd., Yokohama, Japan; [2]Department of Plastic, Reconstructive, and Aesthetic Surgery, Chiba University, Chiba, Japan; *Presenting author

1. Introduction

Skin texture, pores, and wrinkles are now part of the range of skin concerns improved by skincare [1]. But why does current skincare efficacy not extend to enhancing facial shape? The procedures aimed at rejuvenating the facial morphology (e.g., facelift and tightening) are attracting more attention globally to achieve optimal well-being from economic, social, and cultural perspectives [2-4]. From 2005 to 2020 in the United States, the total expenditure on cosmetic medical procedures doubled to $20.1 billion [5]. The global market of esthetic medicine has been predicted to grow 12% on average from 2021 to 2026 [6]. Despite the large and growing market opportunities, so far, face-shaping skincare has remained stagnant at the conceptual level. Compared to invasive medical procedures performed sporadically or as a one-time event, the advantage of cosmetic skincare is the frequency with which skincare products can be applied daily, twice a day, or more for a long period of time. The key to develop face-shaping skincare is to identify a biological process that exacerbates facial shape conditions and can be alleviated by appropriate skincare. This type of translational science should unlock the potential of cosmetic skincare in this promising beauty category.

While differences in the shape of the mouth, nose, and forehead are due to genetic variants, differences in the shape of cheeks and faceline are determined by nongenetic factors [7, 8]. Consistently, antiaging surgical procedures target the lower lateral region of the face between the mouth/nose and ear/temple [9]. Face-shaping skincare should also focus on the cheeks and face line.

What nongenetic factors can be alleviated by adequate skincare? Which molecule should the skincare target? Aging is the best-known nongenetic factor affecting facial shape, and its impacts on perception [10] and anatomy [11] have been studied. As for the other nongenetic factors, referred to as lifestyle-related/environmental factors, smoking [12], body weight [13], and alcohol consumption [14] have been found to also impact the facial shape. However, the contributions of nongenetic factors to facial shape have only been evaluated qualitatively, and more importantly, little is known about the associated molecular mechanisms; that is to say, the lack of *in-vivo* methods to quantitatively measure the nongenetic factors hampers the development of face-shaping skincare.

To elaborate a quantitative measurement of nongenetic factors, we focused on the gravitational deformation of the face. The faces always appear deformed by gravity, as compared to their appearance in outer space (zero gravity) [15, 16]. The volume displacement on the face plays an important role in the morphogenesis of the midface aging [17] and appears as facial signs in the lower half of the face [18], which is considered facial sagging [19]. Similar to this phenomenon, interstitial fluid shifts into and out of the superficial tissues under microgravity [20] and causes facial edema on Earth [21]. Nonetheless, the exact relationship between gravitational deformation, facial sagging, and facial edema remains unclear. Considering the facts that facial sagging is a typical aging feature [22] and edema reflects physiological conditions [23], we hypothesized that clarifying the facial shape dynamics could lead to the discovery of molecular mechanisms related with nongenetic factors that can be improved by skincare, thereby taking face-shaping skincare into reality.

In the present study, we performed several cross-sectional and longitudinal human tests to clarify the nongenetic factors. We have identified the following two universally common factors: (i) an aging factor of facial sagging; and (ii) an age-independent physiological factor of facial edema. We then found that the key molecular mechanism behind facial edema is the epidermal inflammation with the cytokine vascular endothelial growth factor A (VEGFA). In a double-blinded, randomized, placebo-controlled trial (RCT), which is the most objective scientific research methodology [24], we demonstrated that an anti-inflammatory skincare ingredient specific to VEGFA could have an anti-edema and face-tightening effect, thus creating the first face-shaping skincare.

2. Materials and Methods

2.1. Study design, chemicals and skin specimens

With the aim to clarify the factors affecting facial shape and develop a specific ingredient for face-shaping skincare, we conducted this research in multi-steps. All the performed human studies summarized in Table 1 were approved by the research ethics committee of our institution and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from the participants before commencement of each study. Commercially available reagents were purchased and used. Skin samples of human participants were acquired from the patients undergoing cosmetic surgeries.

Table 1. Summary of seven human tests

Type of study*	CSS No.1	CSS No.2	LAS No.1 (0, 8W)	CSS No.3	LOS No.1 (0–3 M)	Ex vivo	LAS No.2 (0, 3, 6 W)
Note	Asian/Caucasian/African		Anti-sagging	Sunscreen users	Lymph-edema	Skin sample	Anti-edema in RCT
M/F	Female	Male	Female	Female	Male	Female	Female
Total	191	119	34	94	1	25	40
20s	53	60					
30s	53				1	2	9
40s	52	15		50		6	10
50s	22	44	10	44		11	10
60s	11		24			6	10
Fig no.	Fig. 1		Fig. 2	Fig. 3	Fig. 4	Fig. 5	Fig. 8

*CSS, cross-sectional study; LAS, longitudinal application study; LOS, longitudinal observation study

2.2. Acquiring 3D face shape and analysis: Gravity-responsive 3D (GR-3D) measurement
The overview of the flow of the measurement is shown in Fig. 1a. Three-dimensional images of the volunteers' faces in upright and supine positions, with the eyes closed, were acquired using a 3D imaging camera (VECTRA 3D, Canfield Technology, Fairfield, ND, USA). The shots were merged, and the differences in volume change between the upright and supine positions (VD1, VD2) were calculated using Mirror® (Canfield Technology, Fairfield, ND, USA). Using the rotation matrix formulation, two orthogonal factors of facial shape (F_d, F_i) were calculated from VD1 and VD2.

2.3. Photo assessment for sagging severity and face-tightening effect
For the sagging classification, we followed a published protocol [22]. The photographs of the left and right side of faces were graded by four trained evaluators and the sagging scores were calculated as the average grade of both sides. For the face-tightening assessment of the half-face application of active/placebo lotions, ten beauty experts and six trained evaluators evaluated whether half of the face appeared more tightened based on the photographs of the face that were taken in the RCT.

2.4. Stratum corneum proteomic analysis
In the sample preparation for mass spectrometry, including lysate preparation, protein digestion, and peptide enrichment [25], the EasyPep™ 96 MS Sample Prep Kit (Thermo Fisher Scientific) was used. For liquid chromatography with tandem mass spectrometry (LC–MS/MS) analysis [26], the UltiMate™ 3000 RSLCnano System and Orbitrap Fusion™ Lumos™ (both from Thermo Fisher Scientific) were utilized. For label-free quantification, both unique and razor peptides were selected.

2.5. Ex-vivo/in-vitro immunofluorescence staining
Immunostaining of the cryostat sections of *ex-vivo* skin samples was performed using primary antibodies against VEGFA (Abcam, ab52917) and ARPC5L (Abcam, ab169763), and secondary antibodies labeled with Alexa Fluor 568 (Invitrogen, Waltham, MA).

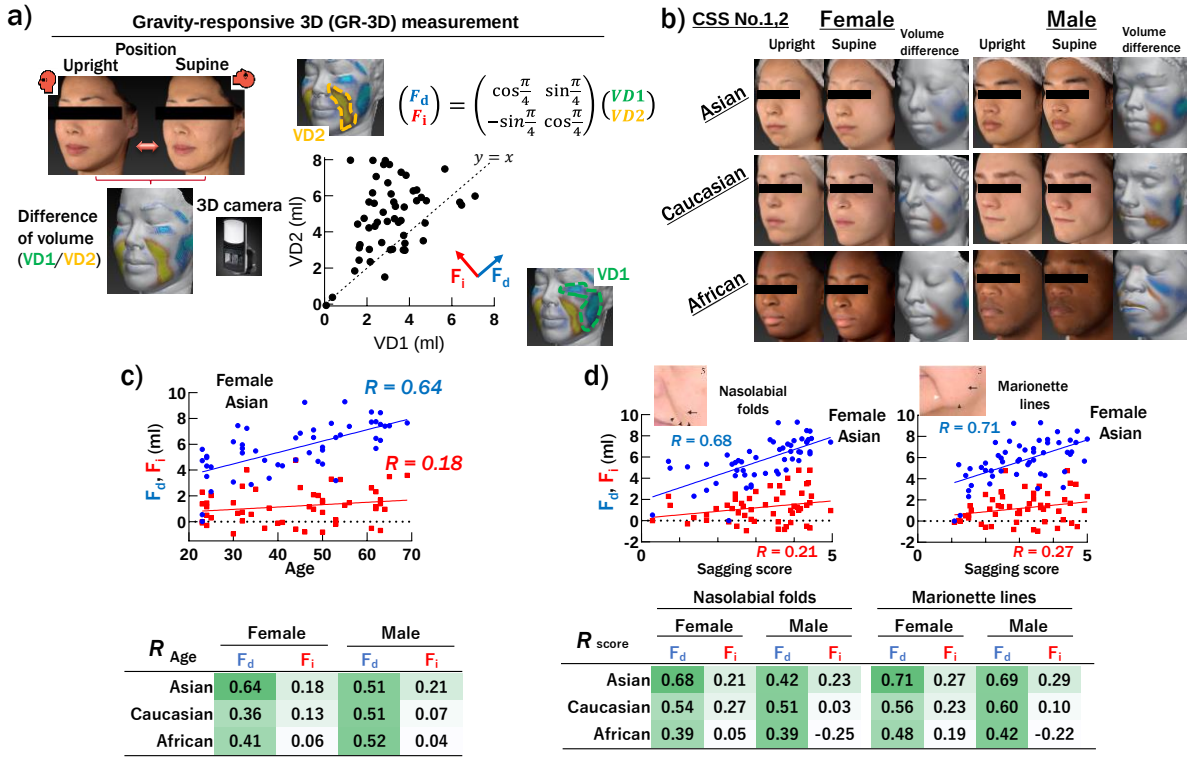
For the *in-vitro* assay, primary human dermal lymphatic endothelial cells (LECs) (Promocell, C-12216) were cultured and treated with 50 ng/mL recombinant human VEGFA (Peprotech, 100-20) or Interleukin-2 (Gibco, 200-02) for up to 6 days. After the fixation with 4% paraformaldehyde, HDLECs underwent the standard protocol of immunocytochemistry to detect VE-cadherin (Cell Signaling, #2500), actin (Thermo Fisher Scientific, A12380) and Prox1 (R&D Systems, AF2727). For each treatment condition, the fluorescence images of eight randomly chosen views were acquired, and the amount of VE-cadherin zippering was quantified for at least three cells per view, as described previously [27].

2.6. ELISA-like interaction assay for screening of efficacious ingredients
For immobilization, 96-well plates of the urokinase-type plasminogen activator receptor (uPAR) ELISA kit (R&D Systems, DUP00) were incubated overnight at 4°C, with 100 µL of 2 µg/mL uPAR used in PBS. After washing, the indicated compounds were added and incubated for 1 h. Then, horseradish peroxidase-labeled urokinase-type plasminogen activator (uPA) (Molecular Innovations) in PBS was then added and incubated for 1 h. After washing, the same procedure was repeated with 100-µl of the TMB substrate (3,3´,5,5´-tetramentylbenzidine, Thermo Fisher) for an additional 20 min. The signal at 450 nm was detected using a microplate reader.

3. Results

3.1. Universally common factors of facial shape revealed using GR-3D measurement

To clarify the facial shape dynamics focusing on its gravitational deformation, we developed GR-3D measurement through cross-sectional studies (Fig. 1a,b). we calculated two parameters of gravitational volume displacements between the upright and supine positions: VD1 (blue region indicating the volume shifted from the cheeks to the front of the ear) and VD2 (orange region reflecting the volume reduction resulting from the position change). Gravitational volume displacements showed one-sided dispersion of each point in the VD1–VD2 plot over a straight line (y = x), indicating two orthogonal factors (Fig. 1a). Using the rotation matrix formulation, F_d and F_i were calculated from VD1 and VD2. F_d was found to be correlated with age, but F_i was not (Fig. 1c). These unexpected characteristics were universally common (Fig. 1c). Using this method, we continued to elucidate the factors affecting facial shape.



R Age	Female		Male	
	F_d	F_i	F_d	F_i
Asian	0.64	0.18	0.51	0.21
Caucasian	0.36	0.13	0.51	0.07
African	0.41	0.06	0.52	0.04

R score	Nasolabial folds				Marionette lines			
	Female		Male		Female		Male	
	F_d	F_i	F_d	F_i	F_d	F_i	F_d	F_i
Asian	0.68	0.21	0.42	0.23	0.71	0.27	0.69	0.29
Caucasian	0.54	0.27	0.51	0.03	0.56	0.23	0.60	0.10
African	0.39	0.05	0.39	-0.25	0.48	0.19	0.42	-0.22

Figure 1. Two nongenetic factors of facial shape dynamics (a) Schematic diagram of gravity-responsive 3D (GR-3D) measurement. For the details of the experimental steps, see Section 2.2 of the Methods. **(b)** GR-3D of male and female Asian, Caucasian, and African volunteers (CSS No.1, 2). **(c, d)** Correlation of F_d and F_i with age and sagging scores. The graphs are of female Asian volunteers. All correlation coefficients are summarized in tables with darker green parts indicating higher coefficient.

3.2. F_d represents the aging factor of sagging

Next, we examined the age-dependent factors of F_d. Sagging plays an important role in the shape of the lower half of the face [19]. Consistently, F_d was universally correlated with the sagging scores in the nasolabial folds and marionette lines of the patients (Fig. 1d), indicating that it represents sagging.

We then investigated whether F_d could be improved by skincare. As an antiaging product, we used 5% niacinamide cream and conducted an 8-week skincare study (Fig. 2a). As expected, the F_d decreased after the 8-week application (Fig. 2b). Taken together, F_d

represents an aging factor of sagging and can be used to show the clinical outcomes of the use of anti-sagging skincare products.

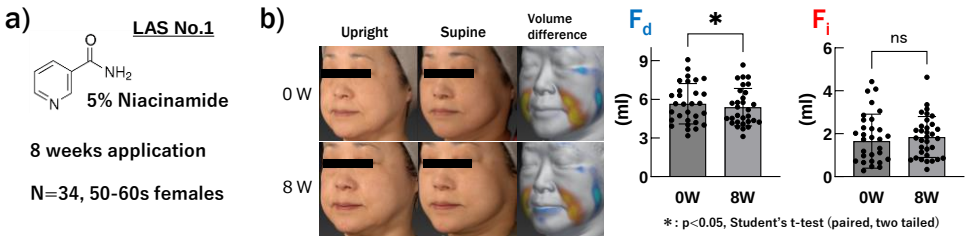


Figure 2. Anti-sagging by use of antiaging skincare (a) The antiaging skincare study (LAS No.1) involving the application of a skincare cream containing 5% niacinamide. **(b)** GR-3D measurement showed that F_d, but not F_i, significantly decreased after the application.

3.3. F_i represents a lifestyle-related/environmental factor

Next, we examined the other factors of F_i. As shown in the antiaging skincare study, F_i did not change after the 8-week application of 5% niacinamide (Fig. 2b), which was consistent with the finding showing that F_i was age-independent (Fig. 1c). To test whether F_i is a lifestyle-related/environmental factor, we performed GR-3D measurement in a cross-sectional study involving sunscreen- and non-sunscreen users (Fig. 3a). Interestingly, we observed no significant difference in age, L*, b*, and F_d, but the a* and F_i values in the non-sunscreen users were significantly higher than in the sunscreen users (Fig. 3a,b). These results suggest that F_i is a lifestyle-related/environmental factor and is activated by sun exposure, which is associated with skin inflammation.

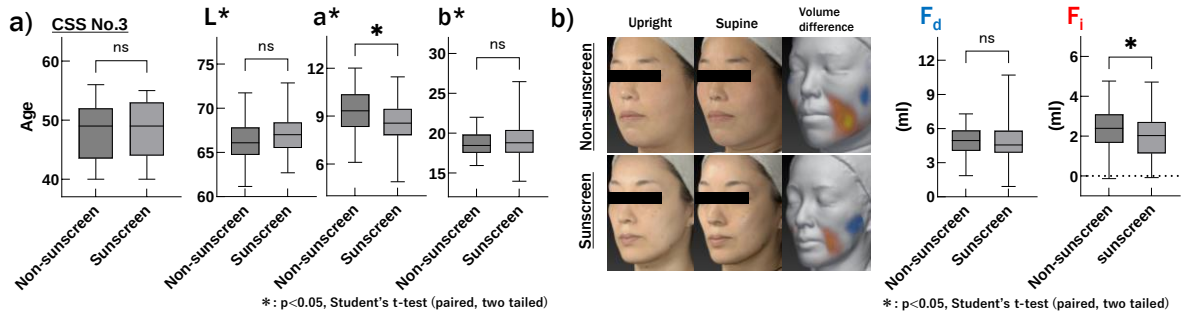


Figure 3. Age-independent factor related to sunscreen use. (a) A volunteer study (CSS No. 3) involving sunscreen- and non-sunscreen users without significant difference in age. Skin color measurement of the cheek showed significant difference in a*. **(b)** GR-3D measurement showed a significant difference in F_i, but not in F_d.

3.4. Direct evidence showing that F_i represents edema and its association with VEGFA

To clarify the type of lifestyle-related/environmental factor F_i, we conducted GR-3D measurement in a clinical case with hemifacial lymphedema. A patient underwent a neck dissection surgery to remove a benign cyst under the right chin. Although all the medical treatments were successfully completed, lymphedema occurred only on the right side of the face after the surgery (Fig. 4a). In the recovery process, the GR-3D measurement and sampling of the stratum corneum (SC) were carried out. Compared to the control side, F_i, but not F_d, of the lymphedema side decreased with its recovery (Fig. 4b). The non-biased proteomic analysis using the SC samples identified the upregulation of the inflammatory cytokine VEGFA (Fig. 4c), which was consistent with the finding showing that F_i was associated with skin inflammation (Fig. 3). Collectively, the pathological case of hemifacial lymphedema outlined F_i as edema and its association with VEGFA as its key molecule.

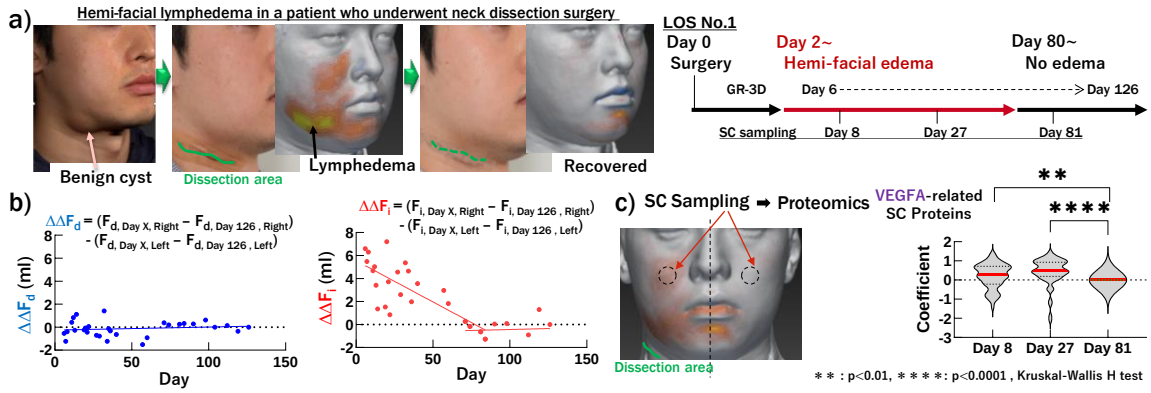


Figure 4. Decrease of age-independent factor in recovery process of hemifacial lymphedema **(a)** Experimental progress along with the recovery from lymphedema. **(b)** GR-3D measurement showed that F_i, but not F_d, diminished with the recovery. **(c)** SC proteomics identified the upregulation of the inflammatory cytokine VEGFA in lymphedema. The expression coefficients of the VEGFA signaling pathway (61 proteins) decreased with the recovery.

3.5. The molecular mechanism of edema and VEGFA inflammation

VEGFA inflammation was identified as a key molecule mechanism for facial edema (Fig. 4). We then examined the generality of the mechanism using ex-vivo skin samples of secondary lymphedema. Immunostaining showed that the VEGFA expression was significantly increased at the early stage (Fig. 5a). ARPC5L, which is among the VEGFA signaling proteins detected in the SC proteomic analysis shown in Fig. 4c, also showed significantly increased expression at the early stage (Fig. 5a). These results indicated that VEGFA inflammation was commonly associated with lymphedema.

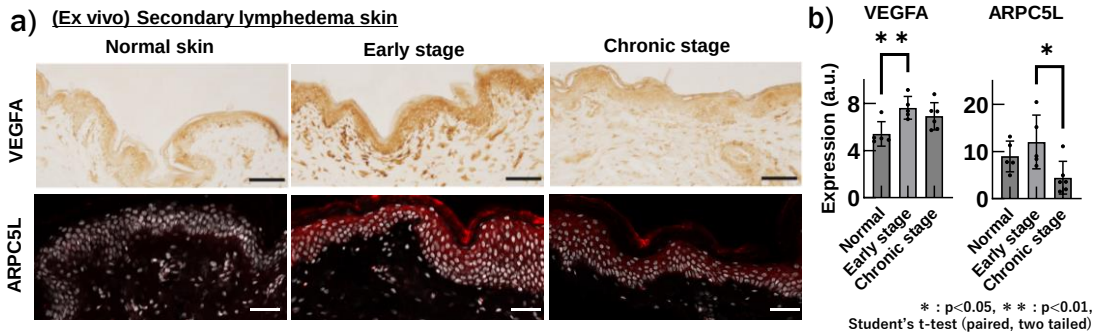


Figure 5. VEGFA inflammation associated with lymphedema (a) Immunostaining of the skin with secondary lymphedema. The skin samples were classified as follows: normal skin (limb skin from the patients without secondary lymphedema), early stage (reversible lymphedema), and chronic stage (advanced lymphedema) [28]. Scale bars = 50 μm. **(b)** Upregulation of VEGFA and ARPC5L was observed in the early stage.

We then evaluated how VEGFA inflammation exacerbates edema. As a positive control, we used the inflammatory cytokine interleukin-2 (IL-2), which is known to tighten lymphatic cell–cell junctions impeding lymphatic drainage [27]. The in-vitro experiment using human dermal LECs showed that the exposure to VEGFA changed the lymphatic cell–cell junctions from button-like to zipper-like, a shape associated with a reduced drainage function (Fig. 5a,b). Interestingly, the zippering effect was more consistent with VEGFA than with the positive control IL-2 (Fig. 5b). Taken together, along with the results shown in Fig. 3–6, edema and VEGFA inflammation mutually cause each other, creating a vicious cycle (Fig. 7a).

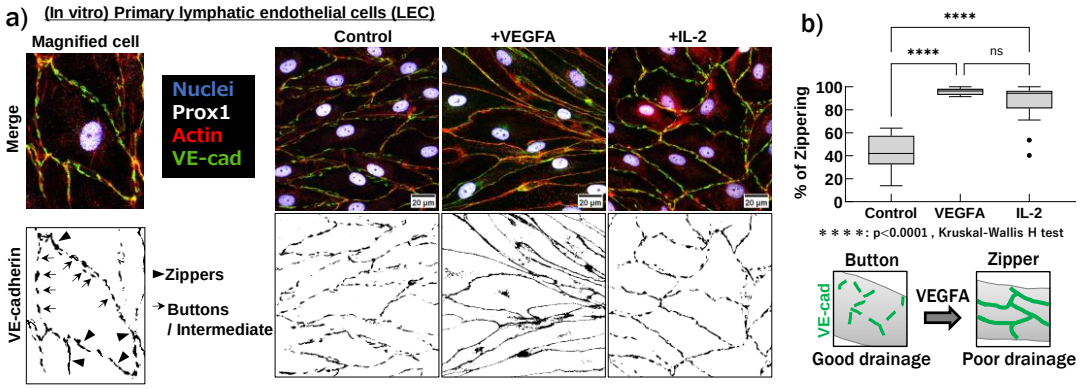


Figure 6. **Effect of VEGFA on lymphatic cell–cell junctions (a)** Immunostaining of lymphatic endothelial cells (LECs) showing the adherens junction marker VE-cadherin. **(b)** The percentage of zipper junctions increased after VEGFA exposure.

3.6. Target-based chemical screening for efficacious ingredients

Then, we attempted to develop an ingredient that interrupts this vicious cycle of VEGFA inflammation and edema (Fig. 7a). VEGFA functions by binding to the heparan sulfate chain of the epidermal base-membrane (Fig. 7b) [29]. We targeted the binding interaction between uPA and uPAR, which is the first switch in the VEGFA-activation cascade. An ELISA-like chemical screening identified the skincare ingredient 1-(hydroxyethyl)ethyleneurea (HEU) inhibiting uPA–uPAR binding (Fig. 7b). HEU is also known to inhibit the enzymatic activity of MMP-9 and heparinase [30]. Collectively, these results suggest that HEU specifically and robustly suppresses epidermal VEGFA inflammation.

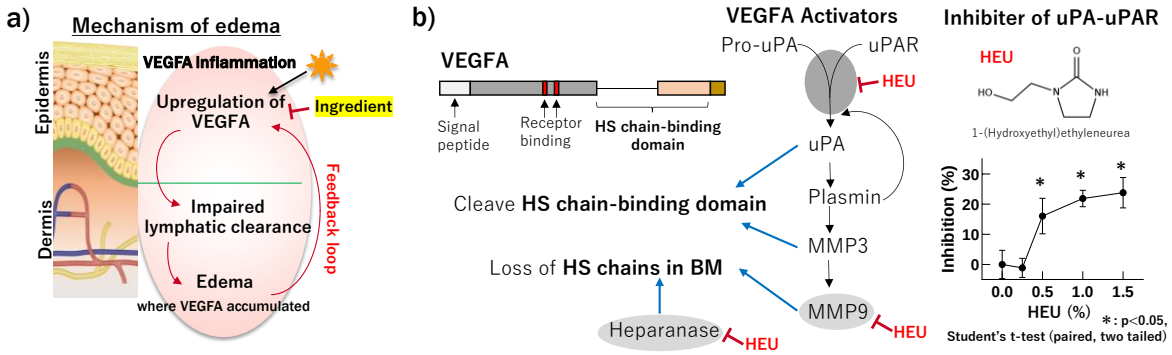


Figure 7. Anti-inflammatory ingredient to improve edema (a) Feedback loop model of VEGFA and edema. (i) As a trigger, sun exposure upregulated VEGFA, as shown in Fig. 3. (ii) The increased VEGFA expression impaired the lymphatic clearance (Fig. 6). (iii) The poor drainage accelerated edema shown in Fig. 4. (iv) Further VEGFA accumulation accompanied edema as shown in Fig. 5, indicating a feedback loop to step ii. **(b)** VEGFA sequence and activators. Screening for ingredients that lower the uPA–uPAR interaction identified HEU.

3.7. Face-tightening skincare using the anti-inflammatory ingredient

At the end of this research, to assess the potential of the anti-VEGFA ingredient as a face-shaping skincare solution, we conducted the half-face study using active/placebo lotions, as shown in Fig. 8a. As expected, SC proteomic analysis detected the anti-inflammatory effects of HEU at 6 weeks (Fig. 8a). The GR-3D measurement showed that F_i in the active side significantly improved after the 6-week application of 1.5% HEU (Fig. 8b). These results showed the high efficacy of the anti-inflammatory ingredient for facial edema, demonstrating that simply applying of a skincare ingredient for several weeks can enhance the facial shape.

In addition, to test whether the anti-edema effect is visually recognizable, we conducted double-blinded photo evaluations, selecting the side of face that appeared the more tightened. At 0 weeks, both the active and placebo sides were equally selected, indicating no difference between them. According to the beauty experts, the improvement of edema was significantly recognizable as a face-tightening effect (Fig. 8c). Interestingly, the non-specialist evaluators also significantly recognized the face-tightening effect of HEU (Fig. 8c). This result indicates that the efficacy of face-shaping skincare is recognizable for the general population of our skincare market.

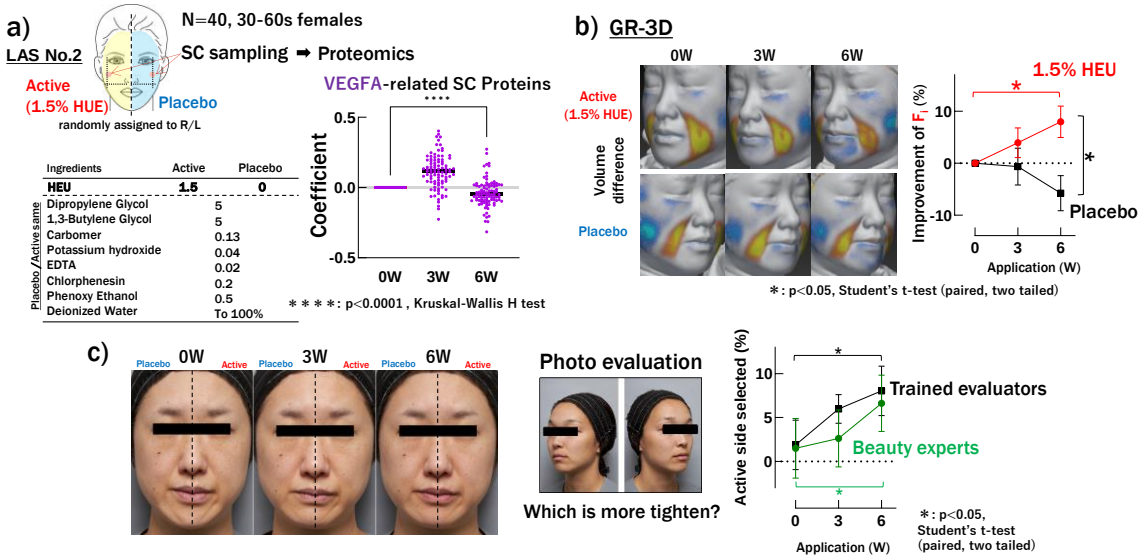


Figure 8. Face-tightening effect of the anti-inflammatory ingredient (a) Experimental design of the half-face study (LAS No. 2) with the 6-week application of 1.5% HEU or a placebo formula. The active and placebo treatments were randomly allocated to the right and left sides of the face. Proteomic analysis of SC from the active and placebo sides. The expression of the VEGFA signaling pathway (95 proteins) decreased in 6-week. **(b)** GR-3D measurement showed that F_d did not change significantly (data not shown), but F_i in the active side improved with the treatment application. **(c)** Double-blinded photo evaluations by the following evaluators: (i) beauty experts (makeup artists with 10 years and more of experience) and (ii) trained evaluators (regular people who were instructed for this test). They assessed half of the face that appeared more tightened according to the photographs taken in the RCT.

4. Discussion

4.1. Facial shape dynamics: nongenetic factors of sagging and edema

Here, we demonstrated that gravitationally deformed faces were caused by the following two universally common factors: age-dependent sagging and age-independent edema (Fig. 2). Facial sagging is a typical feature of aging [22], whereas edema represents physiological conditions [23]. These nongenetic factors of facial shape were found to be alleviated by cosmetic skincare. Specifically, by clarifying the association of edema with epidermal VEGFA inflammation, we identified that the specific inhibitor HEU robustly suppresses VEGFA and alleviates facial edema (Figs. 7 and 8). The anti-edema skincare showed that simply applying a skincare ingredient to the face daily for weeks is sufficient for enhancing the facial shape.

Facial edema was found to be the key factor unveiling the dynamics of facial shape. A gravity-responsive interstitial fluid is present in the dermis [31]. Its contribution to facial signs was predicted in 2015 by Flament et al. [18], but it remains to be investigated because of the lack of *in-vivo* methods for quantitatively measuring the exact contribution of the gravity-responsive interstitial fluid to the facial shape. In the present research, the combination

of hemifacial lymphedema with GR-3D measurement gave direct evidence of the contribution of the gravity-responsive interstitial fluid to facial shape (Fig. 4b). Interestingly, the factor was considered age-independent (Fig. 1c), lifestyle-related/environmental (Fig. 3b), and physiological (Fig. 4b). These properties show that facial edema are clearly different from sagging, which is the best-known nongenetic factor of facial shape. To understand the dynamics of facial shape, it is thus important to distinguish between facial edema and sagging.

Facial deterioration has been researched in different anatomical structures, focusing on dermal structure [32], subcutaneous fat infiltration into the dermal layer [33, 34], and skin appendages [35]. Development of a face-shaping skincare was expected based on these findings, but the challenge lied in how to approach this deep structure, as the skin has an innate barrier function. Our face-tightening solution targets epidermal inflammation. The mechanism of action of our face-tightening solution is groundbreaking and reasonable, focusing on the causal relationship between epidermal inflammation and facial edema via dermal lymphatic function (Fig. 7a). As a result, the face looked tightened after the application of the product (Fig. 8c). This comprehensive research indicates the importance of taking a scientific approach to unlock the potential of skincare ingredients in new beauty categories.

4.2. Reconciling face-shaping effect with no downtime: Advantages and Limitations

The effects of face-shaping skincare were demonstrated in volunteer tests without any adverse events. The demand for facelift and tightening medical procedures is not fully satisfied because of their side effects, including downtime. The drastic changes in facial appearance were easily recognized in the photographs before and after the surgical rejuvenation of the aging faces [36]. In this research, we showed the considerable face-shaping effects of the evaluated skincare (Figs. 2b and 8c), but these effects were not as strong as those of the esthetic medical techniques. The clinical outcomes indicate a limitation of face-shaping skincare. The effects of the product's long-term use and the reversibility after discontinuing these products remain to be investigated for their practical use.

The subtle effects of face-shaping skincare products have comparative advantages over esthetic medicine: (i) no downtime, (ii) no need for a doctor's prescription, and (iii) adjustability based on the desired outcome, as they are cosmetic skincare products. Non-surgical medical treatment has gained increased interest since the COVID-19 pandemic [37], because of its lesser downtime as compared to surgical rejuvenation, but they sometimes have side effects. Thus, face-shaping skincare serves as another alternative to facial rejuvenation treatments.

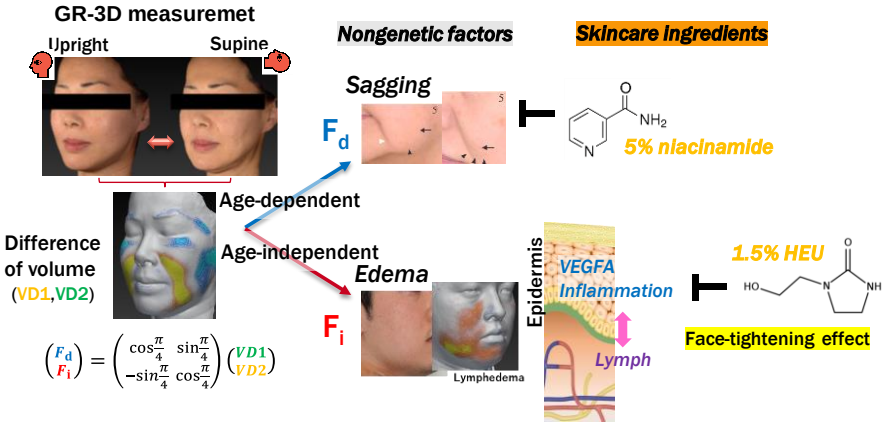


Figure 9. Schematic representation of the main findings of the present study.

5. Conclusion

Using a proprietary method of gravity-responsive 3D (GR-3D) measurement, we identified the universally common factors of facial shape (Fig. 9). The aging factor of sagging improved with the use of anti-sagging skincare products with 5% niacinamide. In a rare case of hemifacial lymphedema, the previously unknown age-independent factor was found to be facial edema. Clarifying the dynamics of facial edema and its molecular mechanism of epidermal inflammation with the cytokine vascular endothelial growth factor A (VEGFA) led us to the development of a novel face-tightening skincare ingredient 1-(hydroxyethyl)ethyleneurea (HEU). Based on the global trend in the field of esthetic medicine, this translational science heralds a new era, in which cosmetic skincare is recognized as a new alternative for enhancing and rejuvenating an individual's facial morphology without any side effects.

1. Skiba, R., ***After Midnight Publishing***, 2025.
2. Dimitrov, D. and G. Kroumpouzos, ***Clin Dermatol***, 2023. 41(1): p. 33-40.
3. Ramirez, S., et al., ***Plast Reconstr Surg Glob Open***, 2024. 12(6): p. e5935.
4. Liew, S., et al., ***Aesthetic Plast Surg***, 2016. 40(2): p. 193-201.
5. Moon, J., J. Ha, and D. Kang, ***Plast Reconstr Surg Glob Open***, 2023. 11(5): p. e4981.
6. Olivier Leclerc, N.P., A. Scaglione, and J. Waring, ***McKinsey & Company***, 2021.
7. Zhang, M., et al., ***Nat Genet***, 2022. 54(4): p. 403-411.
8. Claes, P., et al., ***Nat Genet***, 2018. 50(3): p. 414-423.
9. Trussler, A.P. and H.S. Byrd, ***Semin Plast Surg***, 2009. 23(4): p. 274-282.
10. Elliott, M.L., et al., ***Nat Aging***, 2021. 1(3): p. 295-308.
11. Okuda, I., et al., ***Aesthet Surg J***, 2023. 43(4): p. 408-419.
12. Okada, H.C., et al., ***Plast Reconstr Surg***, 2013. 132(5): p. 1085-1092.
13. Imaizumi, K., et al., ***Int J Legal Med***, 2015. 129(2): p. 385-393.
14. Goodman, G.D., et al., ***J Clin Aesthet Dermatol,*** 2019. 12(8): p. 28-39.
15. Karlin, J.N., et al., ***Ophthalmic Plast Reconstr Surg***, 2021. 37(6): p. 592-594.
16. Garrett-Bakelman, F.E., et al., ***Science***, 2019. 364(6436): p. eaau8650.
17. Mally, P., C.N. Czyz, and A.E. Wulc, ***Aesthet Surg J***, 2014. 34(6): p. 809-822.
18. Flament, F., R. Bazin, and B. Piot, ***Int J Cosmet Sci***, 2015. 37(3): p. 291-297.
19. Ezure, T. and S. Amano, ***Skin Res Technol***, 2012. 18(3): p. 259-264.
20. Kirsch, K.A., et al., ***Clin Investig***, 1993. 71(9): p. 687-689.
21. Parazynski, S.E., et al., ***J Appl Physiol***, 1991. 71(6): p. 2469-2475.
22. Ezure, T., et al., ***Skin Res Technol***, 2009. 15(3): p. 299-305.
23. Wiig, H. and M.A. Swartz, ***Physiol Rev***, 2012. 92(3): p. 1005-1060.
24. Kaptchuk, T.J., ***J Clin Epidemiol***, 2001. 54(6): p. 541-549.
25. Inoue, D., et al., ***Int J Cosmet Sci***, 2023. 45(6): p. 775-790.
26. Suttinont, C., et al., ***Cell Physiol Biochem***, 2024. 58(4): p. 292-310.
27. Lee, E., et al., ***Proc Natl Acad Sci U S A***, 2023. 120(41): p. e2308941120.
28. Itai, N., et al., ***J Invest Dermatol***, 2024. 144(3): p. 659-668 e7.
29. Iriyama, S., et al., ***Arch Dermatol Res***, 2011. 303(4): p. 253-261.
30. Iriyama, S., et al., ***Exp Dermatol***, 2019. 28(3): p. 247-253.
31. Diridollou, S., et al., ***Skin Res Technol***, 2000. 6(3): p. 118-127.
32. Ezure, T., et al., ***Skin Res Technol***, 2016. 22(2): p. 152-157.
33. Ezure, T., et al., ***Skin Res Technol***, 2022. 28(6): p. 872-876.
34. Ezure, T., et al., ***Skin Res Technol***, 2022. 28(2): p. 311-316.
35. Ezure, T., et al., ***Skin Res Technol***, 2021. 27(4): p. 569-575.
36. Alpert, B.S., et al., ***Plast Reconstr Surg***, 2009. 123(3): p. 1025-1033.
37. Melinda Lem, B., et al., ***Am J Cosmet Surg***, 2024. 41(3): p. 189-195.