

Biorevitalizing Solution Improves the Effects of CO₂ Fractional Laser: A Comparative Split-Face Pilot Study

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Abstract

Background: As skin ages, it loses hydration, which can reduce the effectiveness of laser treatments that rely on the water chromophore to target the deep dermis. Restoring hydration levels in the different layers of the skin before fractional CO₂ laser treatment could enhance treatment outcomes in this popular anti-aging treatment. **Methods:** We conducted a split-face pilot study to evaluate the combined effect of a biorevitalizing solution (NCTF®135HA) with an ablative fractional CO₂ laser to determine whether this combined approach could enhance both clinical outcomes and patient satisfaction in facial rejuvenation. Five participants were treated with an injectable biorevitalizing solution on Day 0, followed by laser and topical application of the same solution on Days 7, 30, and 50. Outcomes were assessed with subjective clinical scoring, satisfaction scores, and safety. **Results:** Combining these treatments achieved significantly greater improvements in hydration, pore size, and Global Aesthetic Improvement Scale satisfaction scores for both the investigator and participants. The combined treatment was well tolerated, and healing was comparable to the fractional CO₂ laser alone. **Conclusions:** Few studies report on the concomitant use of hyaluronic acid-based fillers and laser technology for facial rejuvenation, and this pilot study demonstrated that pre-conditioning skin with a biorevitalizing solution enhanced clinical outcomes and participant satisfaction compared to fractional CO₂ laser alone.

Keywords

Fractional CO₂ Laser, Biorevitalizing Solution, Skin Rejuvenation, Split-Face

1. Introduction

Skin aging is a complex process influenced by intrinsic (genetic and biological) and extrinsic (environmental) factors, leading to visible changes such as wrinkles, fine lines, pigmentation irregularities, and loss of elasticity [1] [2]. Intrinsic aging reflects natural changes in the skin and is characterized by epidermal thinning and weakened barrier function due to reduced cell turnover. This process is compounded by the fragmentation and decline of collagen and elastin, causing wrinkles and sagging, and reduced hyaluronic acid (HA), resulting in dehydration and a dull complexion [1] [2]. Extrinsic aging, due to environmental factors such as ultraviolet (UV) exposure, pollution, smoking, and lifestyle can accelerate collagen and elastin breakdown. This causes photoaging, characterized by hyperpigmentation (sunspots, age spots, and an uneven skin tone), deep wrinkles, and loss of elasticity [1] [2].

Fractional carbon dioxide (CO₂) laser treatment rejuvenates aging skin by resurfacing it and is widely considered a gold standard for skin rejuvenation, based on decades of research into laser-cutaneous interactions [3]. This technique delivers microscopic beams of light into the skin in a fractional, grid-like pattern, creating thousands of microthermal zones (MTZs), tiny, controlled injuries surrounded by healthy tissue. This results in controlled skin resurfacing and collagen regeneration, via three key mechanisms [4]-[6]. Firstly, the laser stimulates collagen production by creating microscopic, controlled injuries that trigger the skin's natural healing process, stimulating fibroblasts to produce new collagen. This results in improved skin structure, reduced fine lines and wrinkles over time, and restored elasticity and firmness. Secondly, it improves skin texture and tone by resurfacing the superficial layers of the skin and removing damaged cells, resulting in a smoother, more even skin texture and reducing pigmentation issues such as age spots and sun damage. Finally, it also minimizes pore size and improves the appearance of acne scars and other textural irregularities [4]-[6].

Fractional CO₂ laser treatment is relatively quick and simple. It requires minimal skin preparation, topical anesthesia, and selection of the appropriate parameters such as energy, density, and pattern based on the device and desired depth and treatment requirements, followed by simple aftercare [3]. Recovery varies with treatment intensity, and a break of a few days to a few weeks is required between treatments. Multiple sessions are potentially needed for optimal results. Results develop over weeks as collagen production increases, with continued improvements in skin texture, elasticity, and appearance that can last for months. Overall, fractional CO₂ laser treatments offer an effective, minimally invasive solution to counteract the signs of aging, producing a more youthful and refreshed appearance through controlled skin resurfacing and collagen regeneration [4]-[6]. However, aging reduces skin hydration, which can affect laser efficacy as it uses

the water content of the skin cells to penetrate the target tissue (the deep dermis) [7]. Restoring hydration levels in the different layers of the skin before treatment could enhance treatment outcomes.

Biorevitalizing solutions are injectable formulations that can improve the skin hydration level and are designed to compensate for the negative effects of skin aging and oxidative stress. A biorevitalizing solution called NCTF®135HA, developed by Laboratoires FILLMED (France), is a viscoelastic injectable solution containing 5 mg/mL of non-crosslinked HA of non-animal origin in a formulation with 59 components, including 12 vitamins, 24 amino acids, 6 minerals, 5 nucleosides, and 6 coenzymes and antioxidants [8]-[12].

While these different approaches are effective as standalone treatments, there is a shift towards combination therapy, incorporating technologies such as fractional ablative lasers with minimally invasive formulations to achieve synergistic aesthetic outcomes [13]. A recent survey found that approximately 24.7% of practitioners already combine biorevitalizing solution with fractional ablative lasers despite the limited number of associated published studies [13] [14]. This split-face pilot study was conducted to determine if using a biorevitalizing solution with fractional CO₂ laser treatment could enhance clinical outcomes and patient satisfaction in facial rejuvenation.

2. Materials and Methods

2.1. Study Design

This investigator-initiated, split-face, comparative, monocentric, randomized pilot study included five healthy participants aged 30 - 55 years. Participants received a biorevitalizing solution (NCTF®135HA) pre-treatment on one side of the face, before undergoing fractional CO₂ laser on the full face. All participants received the same biorevitalizing solution treatment on the other side of the face after the end of the study. Side allocation was determined using a simple computer-generated randomization list, which was concealed in sequentially numbered, sealed opaque envelopes. The sequence was generated and kept by an independent clinic assistant not involved in outcome evaluations.

2.2. Ethical Considerations

The study was initiated and conducted at the Hair and Skin Center, Dubai, United Arab Emirates, within the treating investigator's private clinical practice between September and November 2023. As an exploratory pilot evaluation evaluating standard protocols within private practice, formal prospective Institutional Review Board or Ethics Committee review was not obtained, and the study was not prospectively registered in a public clinical trial registry. Nevertheless, all procedures strictly adhered to the principles outlined in the Declaration of Helsinki and Good Clinical Practice: ethical standards were strictly upheld, and all participants provided comprehensive written informed consent before enrollment, including explicit authorization for the publication of their clinical images.

2.3. Treatment Protocol

During their first visit, all participants received an intradermal injection of biorevitalizing solution on the randomized side of the face and normal saline on the other side, after a topical anesthetic had been applied. The injections were administered in a grid pattern across the treatment area to ensure an even distribution. A total of 3 mL of biorevitalizing solution was injected intradermally at around 50 - 60 points, ~0.05 mL per point by 32 G × 4 mm. After seven days, an ablative 10,600 nm fractional CO₂ laser treatment (FIRE-XEL, Bison Medical, Korea) was performed uniformly across both sides of the face, 60 minutes after topical anesthesia. Laser parameters were standardized based on the patient's skin type and condition, with energy levels ranging from 15 to 25 mJ/microbeam, and pulse durations of 200 to 400 μs. All parameter settings were maintained identically across both facial sides for each participant throughout the study duration. The laser could be applied in multiple passes to ensure comprehensive coverage and to target deeper layers of the skin, as needed. This was followed by split-face topical application of either biorevitalizing solution or normal saline using a sterile gauze, with biorevitalizing solution applied on the same side that had received the injection on Day 0. It was then covered by a plastic sheet for 30 minutes. Fractional CO₂ laser and topical application of the biorevitalizing solution or saline were repeated on Days 30 and 50.

2.4. Outcomes Measures

Both sides of the participants' faces were evaluated at baseline and on Days 7, 30, 50, and 10 days after the last treatment (Day 60). Clinical parameters were independently assessed at every visit by two blinded assessors, one dermatologist and one aesthetic clinician, using standardized visual grading scales for lower-face sagging (Bazin Skin Aging Atlas; 0 - 5), skin radiance (0 - 4), hydration, firmness, and homogeneity (0 - 9), and pore size (0 - 9). Grading of skin wrinkles was performed using the Bazin scale for crow's feet, forehead, and nasolabial wrinkles [15]. Higher scores indicated improvement for all parameters except sagging, pore size, and wrinkles for which lower scores indicated improvement. The assessors were calibrated using reference photographs before the study and evaluated each side under standardized lighting while blinded to treatment allocation. Investigator and patients' satisfaction rates were measured by the Global Aesthetic Improvement Scale (GAIS), and standard photography was taken before and after treatment. Tolerability of the treatment was evaluated separately on both sides of the face using a local reaction evaluation score, which included assessments of erythema, ecchymosis, hematoma, oedema, dyschromia, papules, and pruritus. Each reaction was scored from 0 (no reaction) to 3 (severe reaction).

2.5. Statistical Analysis

Final assessor scores were calculated as the means of both assessors' ratings. Each participant served as their own control. Intra-individual comparisons between

treatment sides were analyzed using the paired Student's *t*-test; a *p*-value < 0.05 was considered indicative of clinically significant improvement.

3. Results

Five healthy adults aged 30 - 55 years old participated in this study.

3.1. Clinical Scoring Outcomes

The combination of the biorevitalizing solution with fractional CO₂ laser led to greater improvements in all outcome measures compared to using the fractional CO₂ laser with normal saline (**Figure 1** and Supplementary **Table A1**). Clinical significance was achieved for hydration (Days 30, 50, and 60, *p* = 0.008, *p* = 0.005, and *p* = 0.008, respectively) and pore size (Day 7, *p* = 0.04). When compared to baseline, clinically significant improvements were observed with the biorevitalizing solution for skin hydration (Day 30, *p* = 0.01; Day 50, *p* = 0.007 and Day 60, *p* = 0.002), skin firmness (Day 60, *p* = 0.04), radiance (Day 50, *p* = 0.01 and Day 60, *p* = 0.008), homogeneity (Day 30, *p* = 0.05; Day 50, *p* = 0.02 and Day 60, *p* = 0.002), and pore size (Day 7, *p* = 0.04; Day 50, *p* = 0.04 and Day 60, *p* = 0.009) (**Figure 1(a)-(e)**). Based on the Bazin scores, there were also notable improvements in forehead and crow's feet wrinkles for both sides of the face at Days 50 and 60 (**Figure 1(f)**, **Figure 1(g)**), although the difference was not statistically significant.

3.2. Satisfaction Outcomes

Investigators and participants reported significantly greater overall aesthetic improvements, as measured by the GAIS, with the combination of the biorevitalizing solution and fractional CO₂ laser treatment compared to laser alone (Day 30: investigator *p* = 0.004, participant [*p* = 0.04]; Day 60: investigator [*p* = 0.0004], participant [*p* = 0.0003]) (**Figure 2**). Investigator GAIS scores were significantly improved for the side that received the combination of fractional CO₂ laser and the solution compared to baseline at Days 7, 30, and 60 (*p* < 0.001). Following treatment, both investigators and participants assessed the appearance as 'much improved' relative to baseline with the formulated solution combined with CO₂ laser treatment, relative to only 'improved' with the CO₂ laser alone, at Days 30, 50, and 60. The visual improvements can be seen in the before and after photos in **Figure 3**.

3.3. Safety

An improved treatment tolerance was observed on Day 50 with the combination treatment compared to CO₂ laser alone. The most reported reactions following the procedure were erythema, which was observed at a slightly higher intensity in the control (laser only) side, and edema, which had equivalent intensity on both sides of the face.

4. Discussion

This pilot study demonstrated that the combination of a biorevitalizing solution

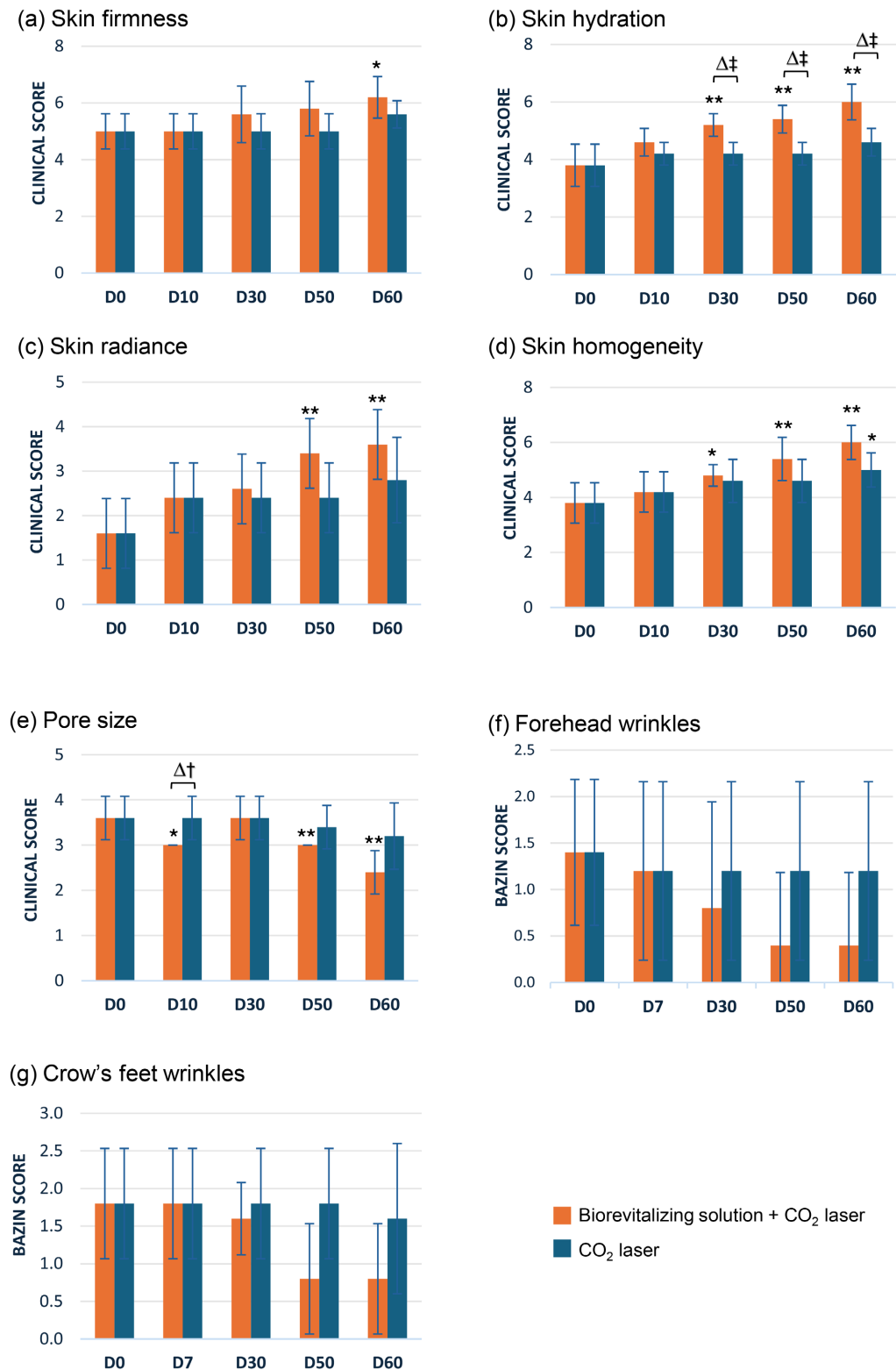


Figure 1. Clinical scoring outcomes over 60 days with the biorevitalizing solution combined with fractional CO₂ laser compared to fractional CO₂ laser alone. Panels show skin firmness (a), skin hydration (b), skin radiance (c), skin homogeneity (d), pore size (e), forehead wrinkles (f), and crow's feet wrinkles (g). Error bars are 95% CI. *p < 0.05, **p < 0.01 versus baseline. †p < 0.05, ‡p < 0.01 versus the control group (fractional CO₂ laser alone).

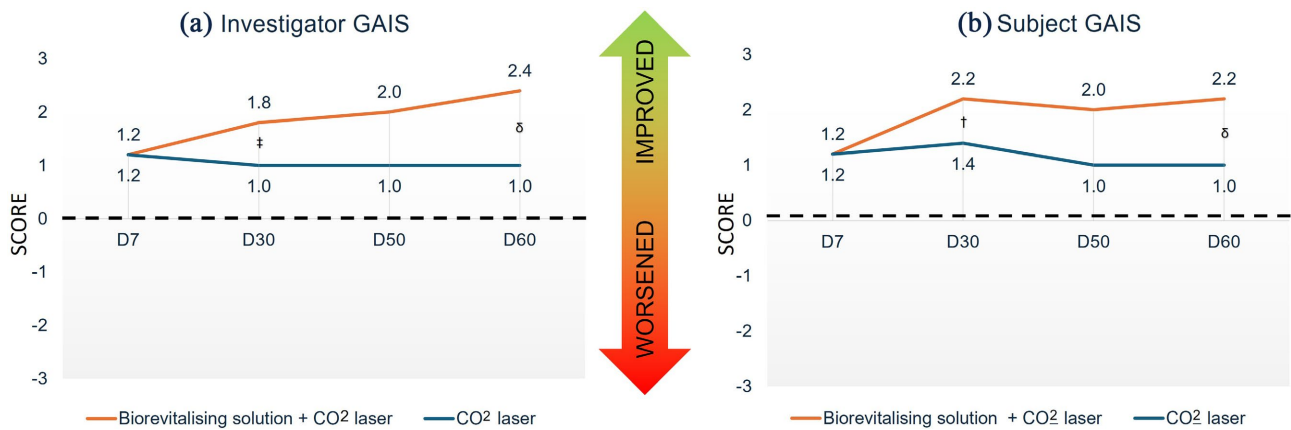


Figure 2. GAIS outcomes for investigators (panel A) and participants (panel B) over 60 days with the biorevitalizing solution combined with fractional CO₂ laser compared to fractional CO₂ laser. [†] $p < 0.05$, [‡] $p < 0.01$, ^δ $p \leq 0.001$ versus the control group (fractional CO₂ laser alone). GAIS scores are rated on a seven-point scoring system from -3 to +3 (-3 very much worse, -2 much worse, -1 worse, 0 no change, 1 improved, 2 much improved, 3 very much improved).



Figure 3. A 44-year-old woman, before (left panel) and 60 days after (right panel) treatment with biorevitalizing solution combined with fractional CO₂ laser. The study participant has given consent to participate and to publish these images.

and ablative fractional CO₂ laser could provide a considerable improvement in clinical outcomes for skin rejuvenation across a number of measures compared to baseline, and meaningful improvements compared to fractional CO₂ laser alone, with significant improvements in hydration, pore size, and GAIS.

In this study, a biorevitalizing solution was injected seven days before the first fractional CO₂ laser session to increase tissue hydration through its non-cross-linked HA content. This approach is supported by evidence showing that HA-based fillers remain stable following fractional CO₂ laser treatment at 10,600 nm [16]. This stability is consistent with the sustained efficacy observed in the present study. Additionally, the numerous MTZs interspersed with untreated tissue created by fractional CO₂ lasers have been shown to improve the absorption of subsequent topically applied substances through a laser-assisted drug delivery mechanism [17] [18]. While the improved hydration observed after combination ther-

apy aligns with these reported mechanisms, direct biological synergy and tissue penetration were not measured in this pilot study.

Significantly better tolerance was also recorded with the combination treatment, indicating that this combination could decrease the intensity of skin inflammatory reactions, such as erythema and edema, and improve the healing process post-laser treatment, as the skin is more hydrated.

A strength of this pilot study was the blinded split-face design, allowing for a direct intra-individual comparison of a biorevitalizing solution combined with fractional CO₂ laser versus fractional CO₂ laser and normal saline in the same participant. Key limitations of this study were the small number of participants which limited the statistical design, as well as the lack of objective measures, such as Corneometer® for hydration level, Cutometer® for elasticity, and digital images for pore size and density. Based on the results of this study, it would be worthwhile investigating the combination of biorevitalizing solutions with fractional CO₂ laser in a larger number of participants and establishing longer-term outcomes.

5. Conclusion

Treatment with either biorevitalizing solutions or fractional CO₂ laser is a well-established, minimally invasive skin rejuvenation technique. Combining these treatments resulted in significant improvements in hydration, pore size, and satisfaction scores, while maintaining good tolerance and healing compared to fractional CO₂ laser alone. The injections are given superficially, causing minimal discomfort and allowing quick recovery, making them an effective preparatory approach to prime the skin before fractional laser treatment. This type of skin preparation could enhance the passage of waves/radiations in the tissue with any CO₂ laser energy-based device (light-, electricity- or sound-based), improving their penetration and effectiveness. Combining these modalities may help clinicians achieve personalized aesthetic goals, including minimizing aging signs, addressing dehydration and uneven texture, as well as potentially reducing excessive inflammatory responses, which can lead to complications like post-inflammatory hyperpigmentation, particularly in patients with higher Fitzpatrick phototypes.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Supplementary

Table A1. Clinical scoring outcomes over 60 days with the biorevitalizing solution combined with fractional CO₂ laser compared to fractional CO₂ laser alone.

	D0		D10		D30		D50		D60	
	Biorevitalizing solution + CO ₂ laser	CO ₂ laser alone	Biorevitalizing solution + CO ₂ laser	CO ₂ laser alone	Biorevitalizing solution + CO ₂ laser	CO ₂ laser alone	Biorevitalizing solution + CO ₂ laser	CO ₂ laser alone	Biorevitalizing solution + CO ₂ laser	CO ₂ laser alone
Firmness (scored 0 - 9)										
N	5	5	5	5	5	5	5	5	5	5
Mean	5	5	5	5	5.6	5	5.8	5	6.2	5.6
SD	0.71	0.71	0.71	0.71	1.14	0.71	1.10	0.71	0.84	0.55
Range	4 - 6	4 - 6	4 - 6	4 - 6	4 - 7	4 - 6	4 - 7	4 - 6	5 - 7	5 - 6
CI (95%)	0.62	0.62	0.62	0.62	1.00	0.62	0.96	0.62	0.73	0.48
Skin hydration (scored 0 - 9)										
N	5	5	5	5	5	5	5	5	5	5
Mean	3.8	3.8	4.6	4.2	5.2	4.2	5.4	4.2	6	4.6
SD	0.84	0.84	0.55	0.45	0.45	0.45	0.55	0.45	0.71	0.55
Range	3 - 5	3 - 5	4 - 5	4 - 5	5 - 6	4 - 5	5 - 6	4 - 5	5 - 7	4 - 5
CI (95%)	0.73	0.73	0.48	0.39	0.39	0.39	0.48	0.39	0.62	0.48
Skin radiance (scored 0 - 4)										
N	5	5	5	5	5	5	5	5	5	5
Mean	1.6	1.6	2.4	2.4	2.6	2.4	3.4	2.4	3.6	2.8
SD	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	0.89	1.10
Range	0 - 2	0 - 2	1 - 3	1 - 3	1 - 3	1 - 3	2 - 4	1 - 3	2 - 4	1 - 3
CI (95%)	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.96
Skin homogeneity (scored 0 - 9)										
N	5	5	5	5	5	5	5	5	5	5
Mean	3.8	3.8	4.2	4.2	4.8	4.6	5.4	4.6	6	5
SD	0.84	0.84	0.84	0.84	0.45	0.89	0.89	0.89	0.71	0.71
Range	3 - 5	3 - 5	3 - 5	3 - 5	4 - 5	3 - 5	4 - 6	3 - 5	5 - 7	4 - 6
CI (95%)	0.73	0.73	0.73	0.73	0.39	0.78	0.78	0.78	0.62	0.62
Pore size (scored 0 - 4)										
N	5	5	5	5	5	5	5	5	5	5
Mean	3.6	3.6	3	3.6	3.6	3.6	3	3.4	2.4	3.2
SD	0.55	0.55	0.00	0.55	0.55	0.55	0.00	0.55	0.55	0.84
Range	3 - 4	3 - 4	3 - 3	3 - 4	3 - 4	3 - 4	3 - 3	3 - 4	2 - 3	2 - 4
CI (95%)	0.48	0.48	0.00	0.48	0.48	0.48	0.00	0.48	0.48	0.73

Continued

Forehead wrinkles (Bazin scored 0 - 4)										
N	5	5	5	5	5	5	5	5	5	5
Mean	1.4	1.4	1.2	1.2	0.8	1.2	0.4	1.2	0.4	1.2
SD	0.89	0.89	1.10	1.10	1.30	1.10	0.89	1.10	0.89	1.10
Range	1 - 3	1 - 3	0 - 3	0 - 3	0 - 3	0 - 3	0 - 2	0 - 3	0 - 2	0 - 3
CI (95%)	0.78	0.78	0.96	0.96	1.14	0.96	0.78	0.96	0.78	0.96
Crow's feet wrinkles (Bazin scored 0 - 4)										
N	5	5	5	5	5	5	5	5	5	5
Mean	1.8	1.8	1.8	1.8	1.6	1.8	0.8	1.8	0.8	1.6
SD	0.84	0.84	0.84	0.84	0.55	0.84	0.84	0.84	0.84	1.14
Range	1 - 3	1 - 3	1 - 3	1 - 3	1 - 2	1 - 3	0 - 2	1 - 3	0 - 2	0 - 3
CI (95%)	0.73	0.73	0.73	0.73	0.48	0.73	0.73	0.73	0.73	1.00
Nasolabial folds (Bazin scored 0 - 4)										
N	5	5	5	5	5	5	5	5	5	5
Mean	2	2	2	2	2	2	2	2	1.4	2
SD	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.52	1.00
Range	1 - 3	1 - 3	1 - 3	1 - 3	1 - 3	1 - 3	1 - 3	1 - 3	0 - 3	1 - 3
CI (95%)	0.88	0.88	0.88	0.88	0.88	0.88	0.88	0.88	1.33	0.88
Lower face sagging (Bazin scored 0 - 4)										
N	5	5	5	5	5	5	5	5	5	5
Mean	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.6	1.8
SD	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.10	1.34	1.10
Range	1 - 3	1 - 3	1 - 3	1 - 3	1 - 3	1 - 3	1 - 3	1 - 3	0 - 3	1 - 3
IC (95%)	0.96	0.96	0.96	0.96	0.96	0.96	0.96	0.96	1.18	0.96