Australasian Society of Cosmetic Dermatologists

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FACIAL AGEING 2

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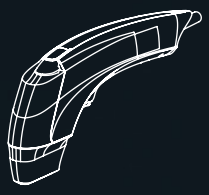

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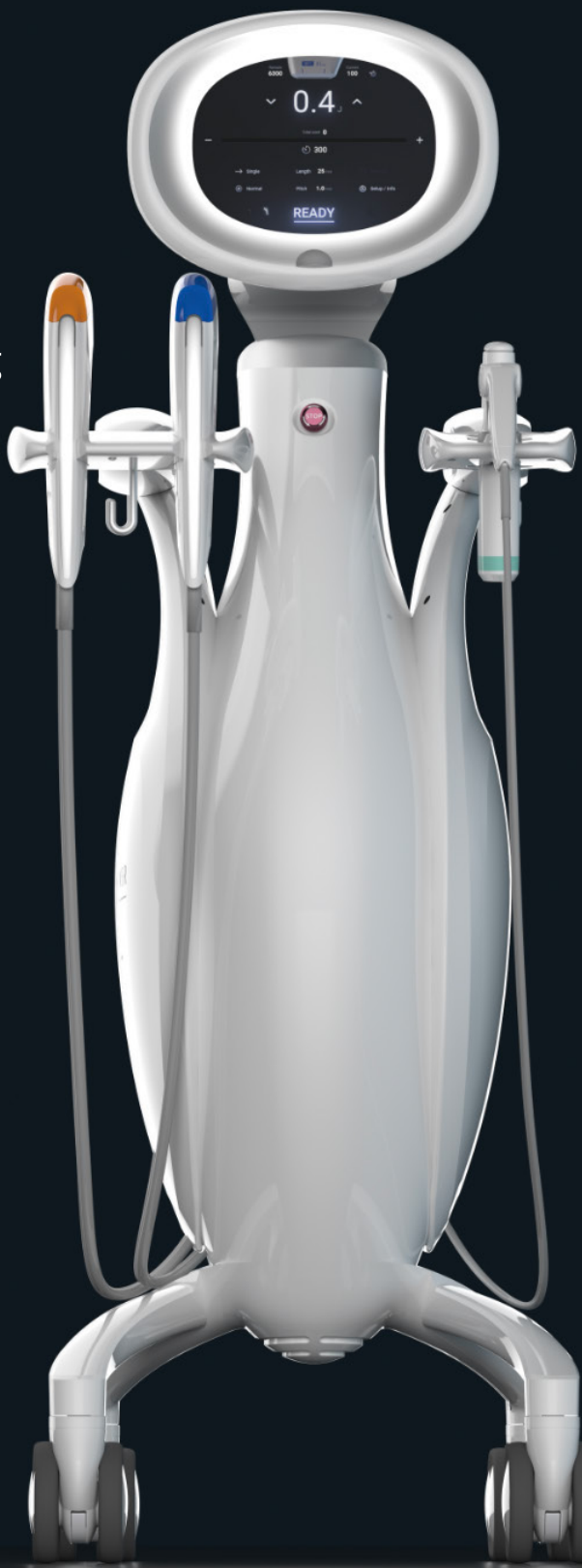

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OPINIONS AND PROGRESS IN
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FACIAL AGEING 2

Welcome to Facial Ageing 2: the second instalment of a two-part series on facial ageing. The Guest Editor for this issue is Dr Shreya Andric. She has put together an exciting edition, balancing cutting-edge science and practical clinical content to inform readers on the critical issues of facial ageing, from benchtop to bedside.

Following from the 2023 ASCD theme on "Challenges", we are thrilled to have two of the keynote speakers adapt their talks for this issue: Dr Izolda Heydenrych on the humbling perspective that as experts, we may have to accept that "we are just not that good", and Dr Phil Artemi on the controversial topic of botulinum toxin resistance – myth or reality?

"Emerging Trends" in cosmetic dermatology will close another exciting year for ASCD. In 2024, our Symposium theme will be "Next Generation", and we look forward to capturing all the compelling insights and ideas for the upcoming OPCD issues. Our well-received Coffee Chats with experts who spill secrets will also return in 2024.

The journal is now open to article submissions on all aspects of cosmetic dermatology. We welcome case studies, case series, original studies, review articles, procedural tips and tricks, opinion pieces, and correspondence letters. As always, we appreciate any feedback to help us improve on future editions and meet your education needs.

On a sad note, Professor Saxon Smith will retire as OPCD Co-Editor-in-Chief in the face of significant health challenges. Professor Smith has been a Foundation Editor of great distinction and has artfully contributed to and guided the journal from conception to maturity. ASCD is indebted to Professor Smith's outstanding contribution to the journal, and we wish him the very best for the journey ahead.

Co-Editors in Chief
Dr Adrian Lim
Clinical Professor Saxon D Smith

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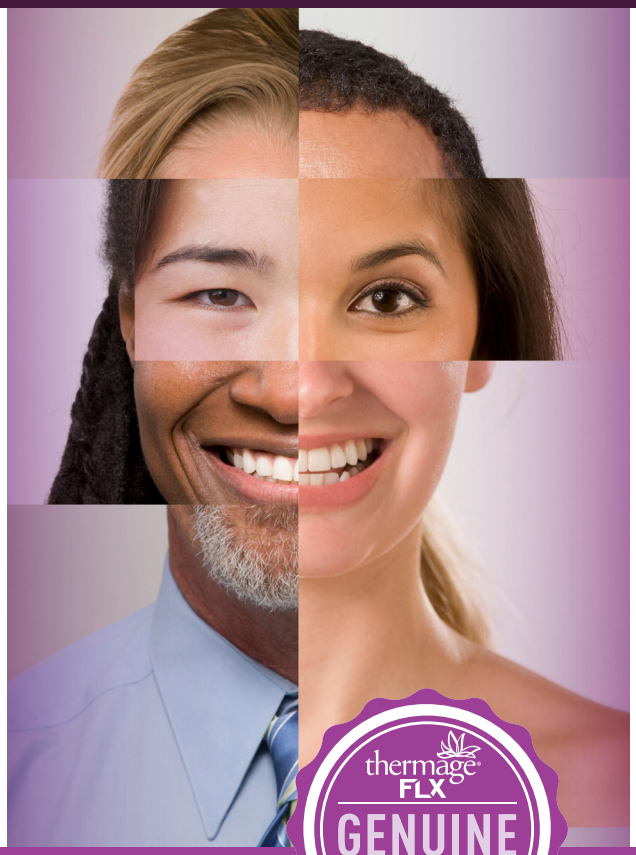

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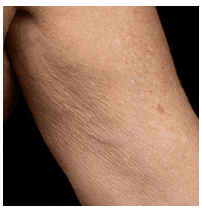
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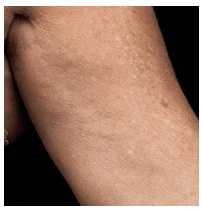
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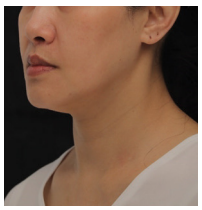
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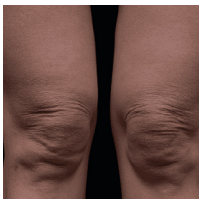
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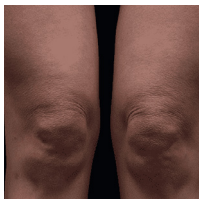
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Guest Editorial – Facial Ageing Part Two

Shreya Andric

Correspondence: Shreya Andric shreyaandric@gmail.com

Andric S. Guest Editorial – Facial Ageing Part Two. Opin Prog Cosmet Dermatol 2023;3(2):1.

Welcome to Facial Ageing Part Two. In the first edition, structural changes contributing to the appearance of ageing were described, as well as social determinants of ageing and approaches to patient consultation. The concept of transcutaneous electrical muscle stimulation was also introduced.

In this edition, Dr. Ishana Dixit provides an overview of the role of cellular senescence in skin ageing, including an introduction to senolytics and senomorphics. This is an exciting area that will likely change our practice in the future.

Botulinum toxin is something we all use daily to reduce signs of ageing. There are always thoughts for and against botulinum neurotoxin type A resistance – Dr. Philip Artemi breaks down the science and lays out the facts.

The population, in general, is moving away from overfilled faces and more towards a natural approach to ageing. Biostimulatory injectables are a highly efficient means of addressing facial ageing, but which one should you choose? Dr. Davin Lim provides a summary and discusses how we can use these alongside our energy-based devices.

Regarding energy-based devices, Dr. Shobhan Manoharan and his team discuss various energy-based techniques used in facial skin rejuvenation, including plasma skin resurfacing.

Whilst the theme is "Facial Ageing", we cannot ignore that the skin ages all over the body. Dr. Adrian Lim provides an excellent overview of the five primary energy devices used for non-invasive body contouring.

Dr. Izolda Heydenrych offers us a moment of self-reflection – do we need to accept that we are just not that good?

We hope this thought-provoking and practical issue provides insights into various treatment options you can incorporate into your practice. We are very grateful to the contributors and wish you all a happy holiday period.

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The Challenge of Accepting That We Are Just Not That Good – An Opinion Piece

Izolda Heydenrych[1,2]

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Disclosures: *None*

KEYWORDS: aesthetic consultation, injection safety, beauty perception

Heydenrych I. The Challenge of Accepting We Are Just Not That Good – An Opinion Piece. Opin Prog Cosmet Dermatol 2023;3(2):3–4.

In the words of Lisa Feldman Barrett:

> *"Sometimes we are responsible for things not because they are our fault But because we are the only ones that can do something about them."*[1]

As a human species, we are uniquely defined by our ability to create our own social reality. As aesthetic practitioners, we wield a similar power regarding our aesthetic reality. Yet, while patient reality is measurable and documented through patient-reported outcomes, our aesthetic reality is far less well-defined. The Dunning -Kruger curve demonstrates that the confidence that we project may be unfounded.

To gauge the opinion of the Australian aesthetic fraternity, we recently surveyed the perception of "How good we think we are" on behalf of the worldwide fraternity. Three vital topics were polled:

1. Aesthetic consultation skills
2. Safety
3. The perception of beauty and naturalness

Tellingly, the result for each section was 4–6/10, in essence defining a significant deficit in the perceived excellence of what our fraternity represents.

This merits some thought:

Aesthetic Consultation demands high levels of interpersonal skills and emotional management.

Sufficient time should thus be allocated for attentive listening and building trust. However, pre-procedural consultation is often neglected, and the average time before the physician interrupts a patient is documented as <11 seconds.[2]

The health care professional's (HCP) emotional intelligence (EQ) is a quality indicator for patient satisfaction, being vital for managing complex aesthetic expectations, patient emotions, and interpersonal relationships. Importantly, it also predicts the HCP's empathy, flexibility, and stress tolerance. Yet, this invaluable and teachable attribute which erodes, together with trust, is not routinely taught during medical training.

Tellingly, two years ago the World Economic Forum published the six uniquely human skills that are irreplaceable by artificial intelligence.

These were:

1. Attentive listening
2. The ability to communicate warm feelings beyond words
3. The ability to show deep empathy
4. Undertaking growth management and mind management
5. Sharing knowledge and wisdom
6. Creativity

These vital aspects, previously regarded as "soft skills", represent opportunities supremely applicable to the aesthetic consultation space.

However, despite the fact that aesthetic consultation has become a specialised and increasingly documented academic discipline, routine practical training is sadly neglected in lieu of technical aspects.[3]

Injection safety, especially pertaining to vascular occlusion and late onset adverse events, remains a vital and hotly debated topic. Despite growing procedural numbers, more extensive treatment paradigms and increasing documentation of serious complications, supervised training and follow-through regarding patient selection criteria, facial anatomy and hand skills are inconsistent and often suboptimal.

Although experiential learning through fresh cadaver anatomy instils insight and respect for injectables, which is incomparable to that induced by purely cognitive or e-learning, only a small minority of injectors have access to this privilege.

Injection skills represent a virtuoso activity requiring intricate hand skills, physical control, and mental agility. Unlike virtuoso sportsmen, who routinely prepare for the game through dedicated technical exercises, few injectors develop intrinsic hand skills other than on the patient. The latter should be actively encouraged to improve factors such as volume control and angulation. Further, since subtle variations may be inadvertent, impacting both depth and placement, supervised training may help to ingrain the conscious difference between safety and catastrophe.

Although aseptic non-touch technique is universally accepted as the gold standard for the prevention of infection and late-onset nodules, it is seldom taught through long-term, structured peer review and audit.

Since marketing may supersede science, problems arising from the huge disparity in practitioner qualifications, which should ideally be standardised through non-commercial and academic forums. As a fraternity, we should be taking responsibility for the wellbeing of our field.

The perception of beauty, naturalness and especially how we choose to manifest it through our work, is a point of growing discussion. Beauty, as projected by a patient, may be defined as a three-dimensional cube with vectors comprising physical beauty, confidence, and naturalness. However, perception by an external observer comprises a discrete fourth dimension.[4]

Between 1997–2015 the growth of aesthetic procedures amounted to 679%. This number crashed to 6.7% in 2017, with the biggest single reason identified by the American Society for Aesthetic Plastic Surgery as fear of an unnatural look. Naturalness, per definition, is highest at birth and can only diminish. Since the human brain inherently prefers subtlety, transecting this graph beneath a certain point can lead to a negative perception of beauty.

Importantly, the definition of beauty varies according to gender, ethnicity, race, and familiarity. Generation is also an influencing factor, with selfie-culture, "likes" and dopamine hits dictating choices. This variance is further complicated when parameters become disturbed due to a phenomenon termed visual facial adaptation, which may profoundly affect the practitioners' ability to achieve natural and beautiful outcomes. The observer's perception of attractiveness may be shifted by an average of 20% after even short exposures to overtreated areas such as lips. This ensuing subconscious shift may lead to extreme provider bias, with certain patient sub-groups being over-treated.

Observation of the widely publicised aesthetic failures impacting the credibility of our field, speaks to the dire need for instilling inter-collegial checks and balances.

Social reality is a superpower emerging from an ensemble of human brains. It gives us the possibility to chart our own destiny[1]. Like social reality, our aesthetic reality is a superpower enabling us to chart our aesthetic destiny.

The 40–60% deficit identified in all three polled sections at the recent Australasian Society of Cosmetic Dermatologists symposium identifies a need that needs to be addressed collectively by our fraternity. We are currently being pincered between marketing, consumerist pressure, and public perception. We should have agency over our field.

All superpowers work best when we know we have them. Let's use ours to make a difference, because if we don't change direction we might just end up where we are heading.

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Botulinum Neurotoxin Type A Resistance: Why, Who and How?

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Disclosures: No funding or assistance was provided for this article. Dr Artemi is a KOL for Merz Australia.

OUTLINE: The following statements are factual: (i) There is accepted scientific evidence that repeated injection of botulinum neurotoxin type A (BoNT-A) may stimulate innate immunity, leading to the formation of neutralising antibodies (NAb) and subsequent reduction of treatment efficacy; (ii) regarding therapeutic protein products, both the European Medicines Agency and the US Food and Drug Administration advocate that where efficacy and safety are comparable a formulation that is potentially less likely to cause immunogenicity should be considered as a first-line therapy; (iii) Aesthetic BoNT-A indications are rising, and aesthetic doses in many individuals are now comparable to neurological BoNT-A; (iv) There are now hundreds of clinical indications for BoNT-A such that the use of BoNT-A is no longer exclusively within neurology and cosmetic dermatology; (v) The fundamental principle of health care that prevention is better than cure applies equally to aesthetic treatment. The challenge of BoNT-A resistance is to continue raising awareness of this potential immunological side effect and to develop guidelines to reduce the risk of NAb development and manage individuals who develop NAb.

KEYWORDS: immunogenicity, neutralising-antibody, secondary non-responsiveness, resistance, dendritic cell, naïve T-cell, guidelines.

ESSENTIAL TERMINOLOGY

Biologic substance: One made from a living organism or its products. Biologic drugs are abundant in medicine and include antibodies, vaccines, and BoNT-A.

Immunogenicity: The ability of a protein product (BoNT-A) to function as an antigen to elicit antibody formation.

Dendritic cell: An antigen-presenting cell with the highest concentration in the skin and gut, the first line of defence against a foreign protein.

Naive T-cell: A lymphocyte that circulates continuously through the bloodstream and lymph nodes, contacting antigen-presenting cells in the lymphoid tissues throughout the day.

Neutralising antibody: An anti-drug antibody produced by the immune system that reduces or renders the pharmaceutical agent that triggered its production ineffective.

Secondary non-responsiveness: After initially responding well, the individual becomes less responsive to the treatment over time.

Artemi P. Botulinum Neurotoxin Type A Resistance: Why, Who and How? Opin Prog Cosmet Dermatol 2023;3(2):6–12.

How does the immune system respond to biological proteins?

All therapeutic proteins may trigger an immune response and antibody formation depending on their degree of immunogenicity. The immune response can be (i) beneficial when used in vaccination to prevent infectious disease or to treat various cancers, (ii) of no consequence when the antibodies are non-neutralising, or (iii) detrimental when neutralising antibodies (anti-drug antibodies) develop, leading to secondary non-responsiveness rendering treatments less effective or ineffective. This loss of efficacy is reported in the medical literature.[1–3]

How are neutralising antibodies made?

The pathway to NAb formation involves a complex network of cells, microbial and protein surface structures, adhesion molecules, receptors, and cytokines. The key feature, however, can be simplified to a two-step pathway, "danger" and "foreign" (*Figure 1*)[4] that must be completed sequentially before antibody production occurs.[5]

Step 1: The dendritic cells (antigen processing cells) look for "danger" signals on a foreign protein. If no danger is perceived, the response is tolerance, and the immune system remains in surveillance mode. If the dendritic cells identify "danger" signals on a foreign protein, the foreign protein is ingested (phagocytosis), processed intra-cellularly to display the foreign proteins on the dendritic cell surface and then transported to regional lymph nodes.

Step 2: The naive T-cell interacts with the dendritic cell. If the naive T-helper identifies the displayed surface peptides as "foreign," the immune response continues with the development of antigen-specific T-helper cells, leading to antigen-specific B lymphocyte antibody production.

Immunogenicity of purified BoNT-A

To induce NAb, BoNT-A must trigger the two-sequential non-negotiable "danger" and "foreign" steps explained above (*Figure 1*).

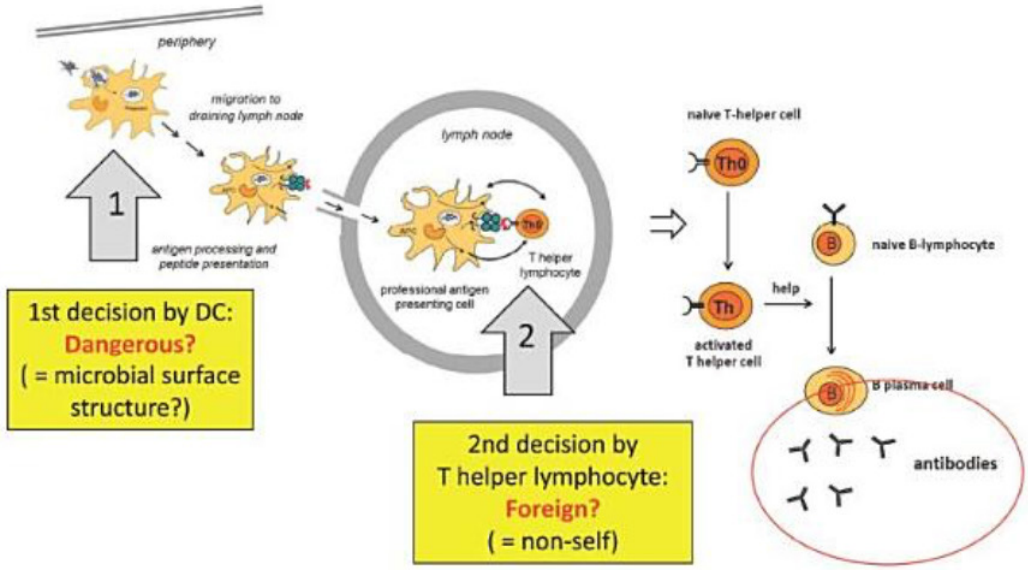

Figure 1. *Scheme of the two-criteria, two-step activation model of the human immune system leading to antibody production. Adapted from Martin.*[4] *DCs, dendritic cells; Th0, T-helper lymphocyte. Adapted from Martin.*[4]

This requires dendritic cells to identify purified BoNT-A as dangerous and present the processed BoNT-A to naïve T helper cells, who then identify BoNT-A as foreign. However, purified BoNT-A does not possess microbe-specific molecular structures and, thus, cannot activate dendritic cells. The result of the interaction between the dendritic cell and purified BoNT-A is immune tolerance (*Figure* 2).

Purified BoNT-A is still recognised as foreign by naive T helper lymphocytes. However, without dendritic cell activation, it is a weak immunogen and purified BoNT-A alone does not stimulate NAb formation (*Figure* 2).

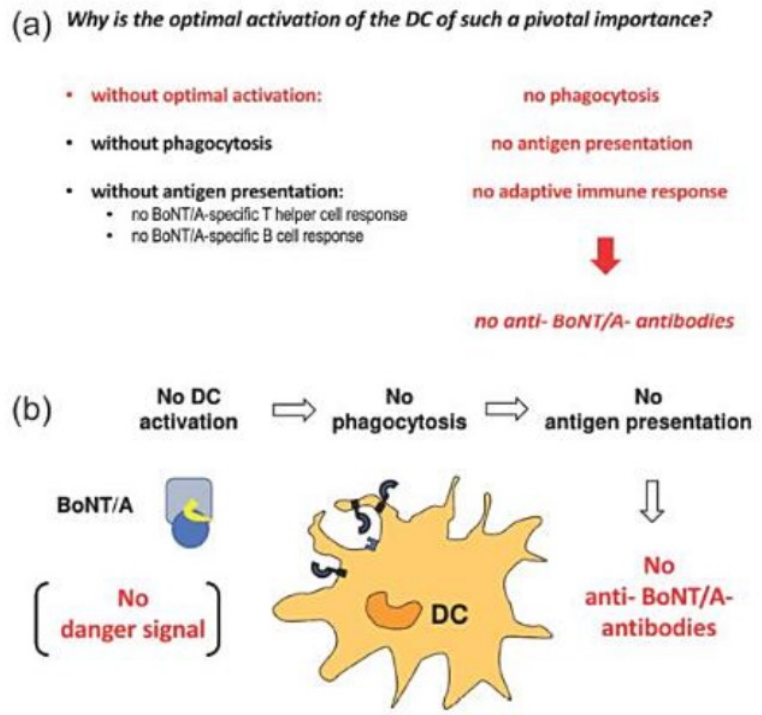

Figure 2. *(a) Only optimally activated dendritic cells can serve as professional antigen-presenting cells and initiate a full immune response. (b) Pure and bioactive botulinum neurotoxin A cannot activate dendritic cells and initiate an immune response. Adapted from Martin.*[4]

Immunogenicity of unpurified BoNT-A

The BoNT-A protein is manufactured by various pharmaceutical companies using different protocols to yield products with varying degrees of purity.[6] At the time of writing, only two products free of impurities were produced: Xeomin (Merz Pharmaceuticals, Germany) and Coretox (Medytox, South Korea). Daxxify (Revance Aesthetics, USA) contains purified BoNT-A. However, it is formulated with a 35 amino-acid peptide excipient (RTP004) whose immunogenicity remains uncertain.

The end product of the remaining pharmaceutical brands is unpurified BoNT-A, which may contain the following "adjuvants":

- haemagglutinins (complexing proteins)
- flagellin (a subunit protein of the flagella which enables C. Botulinum to move)
- denatured protein aggregates of C botulinum
- bacterial DNA remnants

All adjuvants produced during BoNT-A manufacture can activate dendritic cells, increasing the immunogenicity of the weakly immunogenic purified BoNT-A.[6–11] These adjuvants are recognised by dendritic cells as "*danger*." The activated dendritic cell then engulfs (phagocytosis) everything near the danger, including the weakly immunogenic BoNT-A. The dendritic cells then present the "co-phagocytosed" BoNT-A to naive T helper cells, who deem it *foreign* and initiate a full humoral response, leading to antibody production. *Figure* 3 illustrates the role of adjuvants in the production of neutralising antibodies against BoNT-A.

Botulinum Toxin as a Pharma Protein

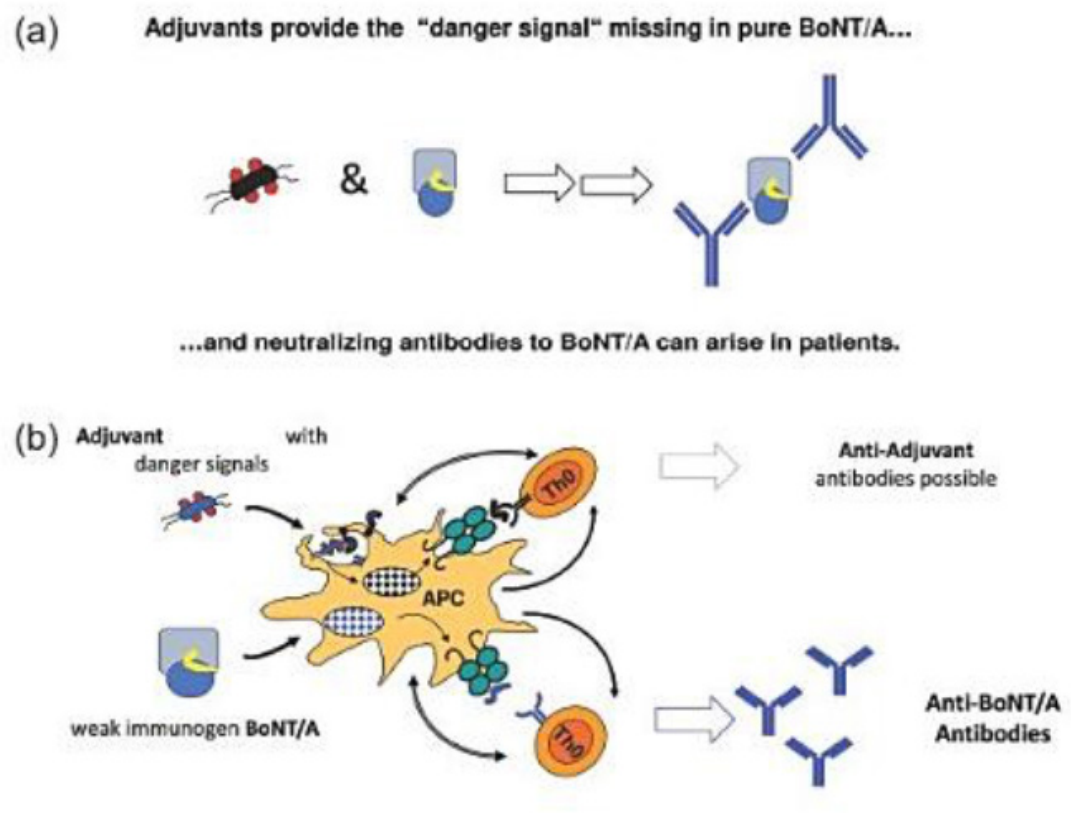

Figure 3. *(a) The adjuvant provides the "danger signal" missing in pure bioactive BoNT/A. (b) Optimal activation of the dendritic cell by the adjuvant initiates phagocytosis of BoNT/A and antigen presentation to naïve T helper lymphocytes (Th0), followed by B lymphocytic production of neutralising antibodies. Adapted from Martin.*[4]

Preventing and reducing the risk of neutralising antibody formation

First-time aesthetic BoNT-A treatment

After taking a thorough history (contraindications to treatment and previous medical BoNT-A use), the various BoNT-A pharmaceutical preparations should be explained, including reference to immunogenicity. Invariably, a purified BoNT-A will be agreed to as the best treatment option following an objective discussion.

The following steps are recommended thereafter:

- Obtaining written consent
- Baseline photography
- Meticulous product preparation of the purified BoNT-A to avoid contamination
- Injecting the smallest amount of pure BoNT-A required to obtain the desired clinical effect
- A concentrated dilution technique to minimise diffusion (dendritic cell activation)
- Intramuscular injection (to avoid the dermis and its greater concentration of dendritic cells)
- Dosage documentation (including cumulative at each visit)
- Review at 2 weeks
- Dosage intervals: 3–4 months (no dose restrictions)
- Advise against top-ups between treatments (unless for asymmetry)
- Advise against "clinic-shopping"
- At follow-up, monitor for dose and/or interval creep and the development of concurrent medical problems

If a purified BoNT-A preparation is refused due to the client's personal choice or cost considerations, then the above protocol is followed with minor adjustments as follows:

- Obtain written consent
- Baseline photography
- Meticulous product preparation to avoid contamination
- Injecting the smallest amount of impure BoNT-A required to obtain the desired clinical effect
- A concentrated dilution technique to minimise diffusion (dendritic cell activation)
- Intramuscular injection (to avoid the dermis and its greater concentration of dendritic cells)
- Dosage documentation (including cumulative at each visit)
- Dosage intervals: 3 months (<100 units), 4 months (100–200 units), ≥6 months (doses >200 units)
- No top-up treatments (except minor doses for asymmetry)
- Advise against "clinic-shopping
- At follow-up, monitor for dose and/or interval creep and the development of concurrent medical problems

Existing client established on unpurified BoNT-A formulation

Non-aesthetic BoNT-A use and concurrent medical problems should be noted during history taking. The client's notes should allow for a review of BoNT-A treatment duration, frequency, and cumulative units administered.

The aesthetic practitioner needs to be vigilant for the following warning signs of secondary non-responsiveness that may indicate the presence of NAb:

- Is the dose required for clinical effect increasing over time (dose-creep)?
- Is the treatment interval decreasing over time (interval creep)?
- Does the individual attend for regular top-up visits?
- Does the individual "clinic shop"

A discussion of purified options and the pros and cons of changing brands should ensue, and the above protocols should be followed, pending the client's preferred BoNT-A preparation.

Management of suspected secondary non-responsiveness

If there is historical and clinical (photographic) evidence of possible secondary non-responsiveness, there are several management options that can be considered:

Option 1

Continue current BoNT-A treatment initially.

Undertake antibody detection by quantitative and qualitative assessment:

- There are no commercially available tests in Australia
- Blood can be collected and sent overseas (Toxogen Germany): quantitative assessment of antibody titre via radio immune precipitation assay is available (approximate cost of 300–400 AUD), and/or a more sensitive qualitative assay via the mouse hemidiaphragm assay (approximately 2,000–3,000 AUD)

Stop treatment once high-titre BoNT-A antibodies and/or NAbs are confirmed. Discontinue treatment until NAbs have dropped below the clinically relevant level. When treatment recommences, restart with a low-immunogenic BoNT-A preparation.

OR

Option 2

Continue current BoNT-A treatment initially. Conduct a clinical confirmation and/or quantitative/qualitative assessment (Toxogen Germany). Do not stop treatment but continue treatment with a low immunogenic BoNT-A. NAb titres have been reported to reduce over time because the lower immunogenic preparation fails to activate antigen-specific memory T cells.[12]

OR

Option 3

An aesthetic BoNT-A holiday of at least 2–3 years may allow NAb titres to drop to undetectable levels.[13] The patient can then restart a low immunogenic BoNT-A free of complexing proteins and other adjuvants. This may prevent memory T cell antibody production stimulation and potentially restore efficacy.[14]

The author does not recommend concomitant administration of immunosuppressive agents such as methotrexate or prednisolone. This practice has been used in rheumatology and haematological oncology to reduce the development of neutralising antibodies.

Addressing the elephant in the room

Despite the strong scientific evidence, an expanding BoNT-A clinical landscape, the view of regulators regarding the importance of low immunogenicity proteins, aesthetic doses in many individuals now comparable to medical doses, and a compelling ethical obligation, aesthetic BoNT-A resistance and the potential for the development of NAb and reduced responsiveness continues to be vigorously dismissed by many Aesthetic Practitioners.

The author believes there is no logical reason for this "recognition lag." However, three possible explanations warrant consideration as outlined below:

Misinterpretation of studies

Non-believers claim that the low doses administered to treat facial rhytides are insufficient to trigger NAb and secondary non-responsiveness. They support their argument by referring to various clinical studies[15–17] that show the rate of antibody formation to be very low. These Aesthetic Practitioners fail to appreciate that such studies have major flaws, viz: (i) the areas treated with BoNT-A are very small and not indicative of real-world use of BoNT-A; hence, the dosages investigated are under the threshold for the development of NAb, (ii) the study follow-up period is often maximal at two years post-treatment, an insufficient duration for the development of NAb and (iii) most studies are also based on meta-analysis, which is known to have significant flaws such as publication bias, heterogeneity of data and small study effect.[18]

The perception that the risk is so minuscule it is of no significance

The second stance is dismissive, believing that even if aesthetic BoNT-A resistance is real, its occurrence is so rare that its consequences are proportionately unimportant. This tends to stereotype an individual as just "cosmetic," a potentially dangerous typecast. Individuals seeking multiple BoNT-A treatments, such as pre-rejuvenation, improvement of pores, and reduced seborrhoea, are now commencing BoNT-A treatment at a much younger age when future medical problems are unforeseen. The healthy "I want toxin" individual in the aesthetic clinic in 2023 may well become the unwell "I need toxin" patient of a Medical Specialist in 2033 with devastating consequences if the development of NAb could have been avoided in earlier life.

An inexorable mindset

It is impossible to imagine that within a busy BoNT-A aesthetic practice, no one will develop the classic signs of secondary non-responsiveness, i.e., where BoNT-A treatment no longer has the desired effect, a higher dosage is required to maintain the original benefit, and/or a there is a need for more frequent treatments. Without proper follow-up protocols, the aesthetic practitioner may fail to recognise that clients may have taken their business elsewhere, believing that a technical fault on the part of the injector or an inferior quality product is to blame for the lack of efficacy. Often, aesthetic practitioners articulate that they will believe it when they see it, but paradoxically, until they believe it, they may not see what is right in front of them.

Conclusion

As pharmaceutical companies in general medicine strive to create low immunogenic drugs, it is hoped that aesthetic pharmaceutical organisations will have a similar mindset. The supply of BoNT-A (a Schedule 4 Pharmaceutical) in Aesthetic Medicine is unique in that the Practitioner purchases, promotes, prescribes, dispenses, and administers the treatment. Avoiding media and AHPRA scrutiny in the future requires prescribing and performing such treatment to protect and maintain client/patient health by using best practice protocols and a high standard of ethics. Armed with abundant scientific facts, the Aesthetic Practitioner now has a duty of care to compare and contrast in consultation the available BoNT-A products with regard to their immunogenicity and the risk of Nab development.

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Cellular Senescence and Skin Ageing

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OUTLINE: Cellular senescence, a state of stable growth arrest in cells, is a crucial element of ageing and age-related diseases and can be triggered by various events such as DNA damage, oxidative stress, and oncogene activation. Although it can prevent cancer by halting the replication of damaged cells, it can also contribute to age-related diseases due to the accumulation of senescent cells and their secretion of inflammatory molecules known as the senescence-associated secretory phenotype (SASP). Senescent cells accumulate in intrinsic and extrinsic ageing, promoting inflammation and structural deterioration of the skin.

Senolytics are drugs that selectively induce apoptosis in senescent cells. Dasatinib and Quercetin have shown promise in eliminating senescent cells, with combination therapy being more effective. In contrast, senomorphics modify the phenotypes of senescent cells, reducing the harm caused by SASP components. Rapamycin and metformin are senomorphic drugs that have shown the potential to improve skin appearance and structure by downregulating SASP and inhibiting pro-inflammatory pathways. There is also evidence that senoreverters can reverse some hallmarks of cellular senescence, allowing senescent cells to re-enter the cell cycle. Inhibition of PDK1 has shown promise in converting senescent cells into quiescent cells, potentially boosting skin regeneration.

The senotherapeutics field is advancing rapidly, with promising preclinical results. However, further robust clinical trials are needed to assess long-term safety and efficacy.

KEYWORDS: senescence, senolytics, senomorphics, senoreverters, ageing

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What is cellular senescence?

First described in 1961, cellular senescence is a highly dynamic state of stable growth arrest where the cells can no longer divide despite optimal growth conditions and stimuli and can resist apoptosis via the upregulation of cell survival pathways.[1] It was initially demonstrated by showing that fibroblasts have a limited capacity for cell division before irreversible growth arrest occurs.[2] Therefore, cell proliferation is reduced as tissue ages, and damaged cells cannot be replaced over time.[2] There are various instigators for cellular senescence, including DNA damage, oxidative stress, telomere dysfunction, and oncogene activation.[3] Depending on the context, senescence may be beneficial or detrimental. For example, tumour-suppressive properties of senescent cells prevent damaged or malignant cells from replicating (oncogene-induced senescence).[4] However, the accumulation of senescent cells in tissue creates an inflammatory environment that contributes to age-related diseases, including cardiovascular disease, osteoarthritis, and skin ageing.[4]

Structural changes associated with senescent cells include both flattening and hypertrophy, changes to the plasma membrane, increased lysosomes, and build-up of dysfunctional mitochondria, which secrete reactive oxygen species.[5] While senescent cells are in a state of growth arrest, they are metabolically active and can affect the surrounding, non-senescent cells.[1] Despite the accumulation of damaged products, senescent cells do not undergo apoptosis; instead, they overexpress pro-survival pathways known as senescent cell anti-apoptotic pathways (SCAPs) while simultaneously suppressing apoptosis moderators.[6] Another hallmark feature of senescent cells is the development of a hypersecretory phenotype, the senescence-associated secretory phenotype (SASP), which allows senescent cells to secrete inflammatory cytokines, interleukins, and growth factors and is responsible for the majority of the pathological features of senescent cells (*Figure 1*).[5,6] The main cytokines implicated in this process are IL-6, IL8, and MCP1.[1] The SASP represents a therapeutic target for senotherapeutics against age-related diseases.

Pathologic cellular senescence feedback loop

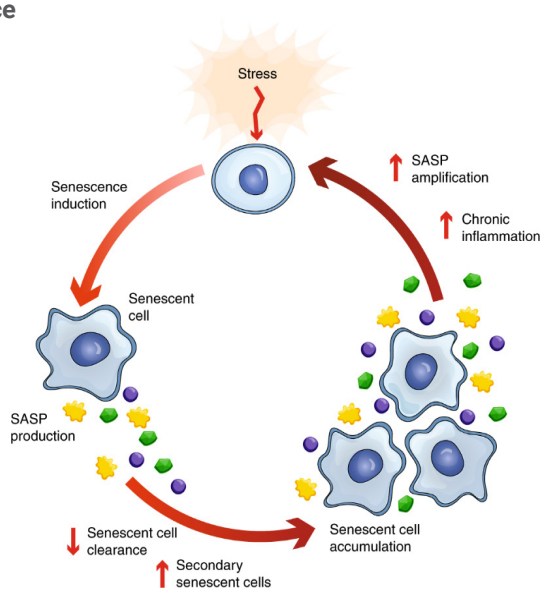

Figure 1. *Cellular senescence positive feedback loop. Adapted from Gasek et al.*[6]

Biomarkers

One of the challenges associated with cellular senescence is the lack of a universal biomarker to assess their activity. Senescence-associated β-galactosidase (SA-β-gal) is the current gold standard for identifying senescent cells. However, it is non-specific, and its detection requires ongoing enzyme activity, limiting the use in fixed/cryopreserved samples.[7,8] Cell cycle regulators such as p16INK4, p21CIP1, and p53 have also been deemed reliable markers of senescence and have been expressed in fibroblasts following UV radiation exposure.[9] In particular, P16INK4-positive cells have been found to accumulate in several ageing processes.[8] Monitoring inflammatory cytokines associated with the SASP, such as IL-6 and IL-8, may demonstrate senescence, but there is significant overlap with non-senescent inflammatory profiles.[10,11] As telomere shortening is a key element of senescence, the use of telomere length as a biomarker for cellular senescence has also been considered, however, telomere length is reflective of both senescence and chronic disease-related oxidative stress, making it a non-specific biomarker.[12]

Cellular senescence and skin ageing

Skin ageing may be categorised as intrinsic (chronological) or extrinsic. Intrinsic factors include time, genetics, and hormones.[13] Changes in the skin in intrinsic ageing occur predominantly at the basal cell layer, with reduced proliferation of cells at this layer as a person ages. This results in flattening of the dermo-epidermal junction, making the skin more vulnerable to damage. As the surface area between the dermis and epidermis is reduced, there is less surface for nutrition exchange, further propagating the reduced ability for cell proliferation, which may contribute to wrinkles.[14] Aged skin has less b-galactosidase in fibroblasts and keratinocytes, indicating increased senescent cells in older skin.[15] Intrinsic skin ageing typically manifests with fine lines, poor skin turgor, and xerosis. Extrinsic ageing is generally seen in areas with high levels of exposure, such as the face and hands, and is associated with deep wrinkles, uneven skin tone, and solar lentigines. Factors particularly implicated in extrinsic ageing include excessive UV radiation exposure, smoking, and environmental factors such as pollution, temperature, and sleeping patterns.[13] In extrinsically aged skin, the epidermis thickens due to impairment of the differentiation process of epidermal keratinocytes. There is also a reduction in type VII collagen in keratinocytes, weakening the dermal-epidermal junction, which results in deep wrinkles. The accumulation of senescent cells in both intrinsically and extrinsically aged skin has been shown.[15,16] Permanent senescence results from telomere shortening, mitochondrial impairment, and miRNA dysregulation, eventually leading to cell cycle arrest. The resulting accumulation of senescent keratinocytes and fibroblasts produces inflammatory cytokines and enzymes, which act on the extracellular matrix to reduce the structural integrity and function of the skin.[13] Senescent fibroblasts also contribute to hyperpigmentation because of phenotype switching in these cells, causing reduced expression of Stromal Derived Factor 1 (SDF1), a chemokine heavily implicated in tissue homeostasis and by stimulating the expression of microphthalmia-associated transcription factor (MITF) which regulates the development of melanocytes.[17-19] *Figure 2* contrasts the histological changes between young and aged skin.

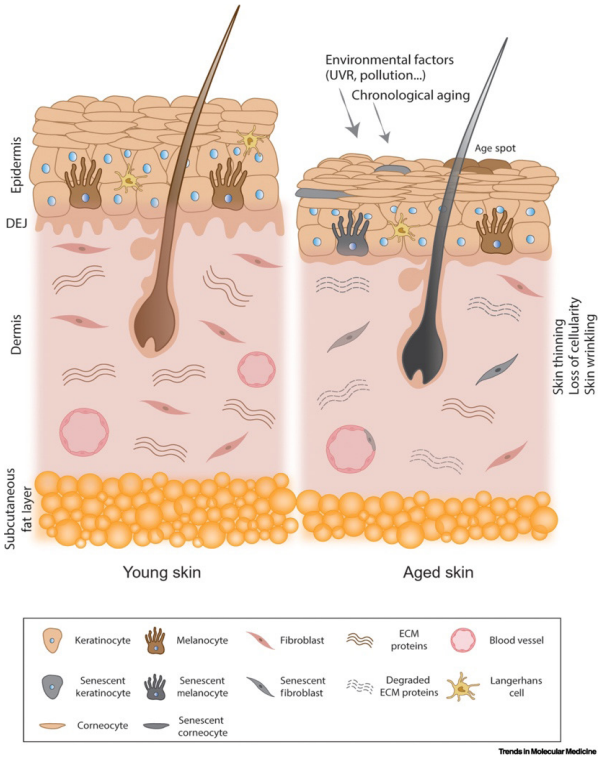

Figure 2. *Schematic of young vs aged skin. Adapted from Franco et al.*[13]

Senolytics

Senolytics are drugs that stimulate apoptosis of only senescent cells (*Figure* 3).[20] The most researched senoloytics are dasatinib and quercitin. Dasatinib has been approved for medical use (mainly for chronic myeloid leukaemia and acute lymphoblastic leukaemia) since 2006 and is a kinase inhibitor that acts primarily on the Pi3k, Akt1, and mTOR pathways. Quercetin is a flavonoid found in various plants and food with a well-established anti-oxidant, anti-inflammatory, and immunoprotective profile.[21,22]

The discovery of dasatinib and quercitin as senolytic drugs resulted from the observation that senescent cells are resistant to apoptosis and, therefore, have a survival mechanism that protects them from their own SASP.[23] Temporarily deactivating SCAPs will allow for apoptosis of senescent cells with a tissue-damaging SASP, while non-senescent cells and senescent cells without a tissue-damaging SASP will survive.[23] It has been found that some SCAPs in senescent cells can be redundant. Therefore, targeting multiple SCAPs through combination therapy rather than one treatment is beneficial. For example, murine studies have shown that senescent mesenchymal embryonic fibroblasts require combination therapy of dasatinib and quercitin for elimination, while single therapy is ineffective.[24] Furthermore, preclinical trials have illustrated that even eliminating only 30% of senescent cells has a positive impact; the efficacy is the same if administered continuously or intermittently, such as every 2–4 weeks.[25] This is attributed to the fact that senolytics directly target senescent cells, which take weeks to months to develop and do not actively divide, rather than a specific receptor or enzyme.[26] This also gives the added benefit of bypassing potential off-target effects due to uninterrupted receptor occupancy or manipulation of specific biochemical pathways.[26] Dasatinib and quercitin have demonstrated their efficacy as a senolytic combination in numerous animal studies and have now entered clinical trials to treat various age-related diseases.[20,22,27,28] Other senolytics have been described, such as inhibitors of the antiapoptotic BCL-2 family proteins (e.g., navitoclax/ABT-263, ABT-737), HSP90 inhibitors, USP7 inhibitors, and p53 modulators (e.g. inhibitors of FOXO4-p53 or MDM2-p53 interactions).[29]

Senomorphics

Rather than actively killing senescent cells, senomorphics alter the phenotypes of senescent cells to those of younger cells by suppressing the damaging effects of SASP components secreted by senescent cells (*Figure* 3).[30] Transcriptional regulators of the SASP that are typically manipulated by senomorphics include inhibitors of MAPK, JAK/STAT, and the NF-κB and mTOR pathways.[31]

Rapamycin

Rapamycin is a senomorphic drug that has demonstrated significant promise in anti-ageing due to the findings of mTOR activation as a hallmark of senescent cells and ageing tissue and its role in the IGF-1 signalling pathway, which is heavily implicated in ageing.[32,33] It has improved longevity in several animal studies and inhibits cellular senescence in various cell types, including fibroblasts.[32-35] Low dose (0.001%) topical rapamycin has been found to reduce p16INK4A expression (consistent with a reduction in cellular senescence), improving the clinical appearance of the skin and histological signs of ageing.[36] It also increases collagen VII, a major component of anchoring fibrils, and, therefore, the integrity of the basement membrane.[36]

Metformin

The biguanide, metformin, has been an oral hypoglycaemic agent for over 60 years.[37] Metformin has significant potential as an anti-ageing drug due to its pleiotropic nature and the resulting influence on metabolic and cellular processes associated with age-related diseases, as well as its safety profile and extensive clinical research.[38]

Regarding cellular senescence, metformin acts by downregulating SASP, thus reducing the senescent cell burden.[39] Continuous administration of metformin at reduced doses delays senescence in human

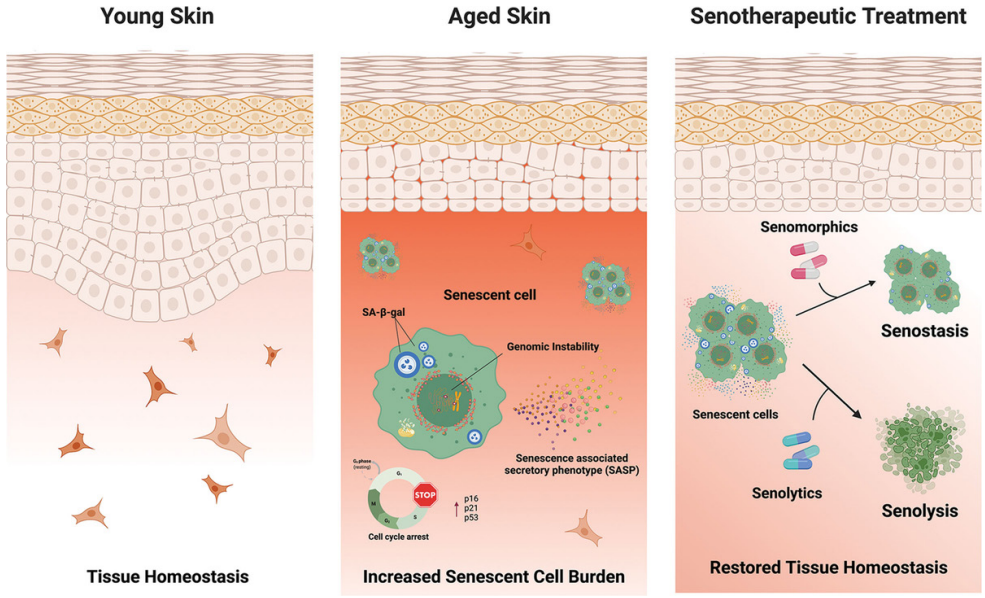

Figure 3. *Schematic of skin ageing and treatment with senotherapeutics. Adapted from Thompson et al.*[20]

fibroblasts and mesenchymal stem cells. It also reduces pro-inflammatory cytokines and oxidative stress markers by inhibiting the NF-KB pathway (particularly IL-6 and IL-8 in human fibroblasts), reducing p16 and p21 levels.[40] Conversely, metformin has also been shown to induce a pro-senescent state in some malignancies by stimulating SASP gene expression and p53-dependent senescence.[41,42] Therefore, further research is needed to elucidate the conditions allowing metformin to create an environment of anti-senescence in ageing tissues rather than promoting cellular senescence in malignant tissue. The Targeting Aging with Metformin (TAME) trial, a series of six-year clinical trials across 14 research institutions in the United States, is due to commence this year and promises to answer this critical question.[43] Figure 4 summarises the natural and synthetic compounds demonstrating senotherapeutic properties.[44]

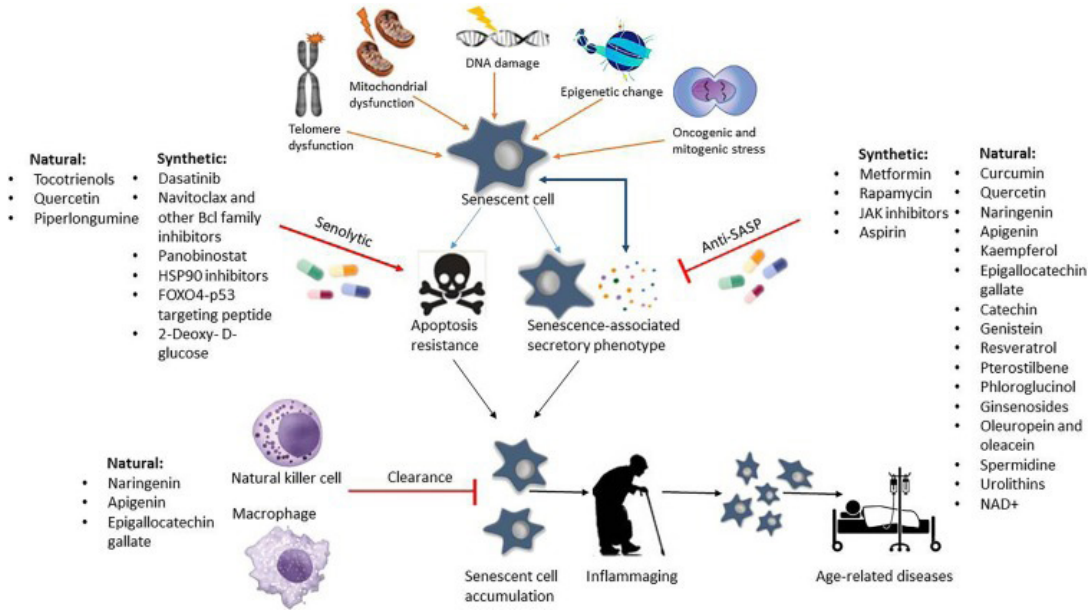

Figure 4. *A variety of natural and synthetic compounds have demonstrated senotherapeutic properties. Adapted from Gurău et al.*[44]

Senoreverters

Although cellular senescence has been viewed as an irreversible process, studies suggest that there may be potential for senescent cells to lose hallmarks of senescence and re-enter the cell cycle, becoming quiescent cells.[45] 3–phosphoinositide–dependent protein kinase 1 (PDK1 – an oncogene frequently overexpressed in multiple cancers) is a promising target in human dermal fibroblasts to convert senescent cells into quiescent cells. By inhibiting PDK1, the hallmarks of cellular senescence can be eradicated via the suppression of NF-KB and mTOR signalling by deactivating a positive feedback loop consisting of PDK1, AKT, IKBKB, and PTEN, resulting in increased skin regeneration capacity.[46]

Conclusion

The field of senotherapeutics is developing rapidly, and while preclinical trials are promising, robust clinical trials must be undertaken to determine the potential adverse effects of long-term administration before these can be adopted into clinical practice. Drugs with well-established safety profiles, such as metformin, have had positive senotherapeutic effects, so this field is anticipated to continue to expand with more drug combinations found.

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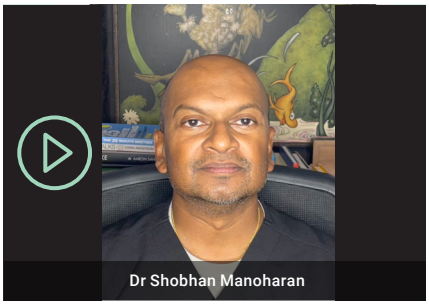
Resurfacing With Energy-based Devices For Facial Ageing



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Disclosures: None

OUTLINE: THIS article provides an overview of various energy-based techniques used in facial skin rejuvenation. We outline the evolution of facial skin rejuvenation techniques in aesthetic medicine, focusing on energy-based devices. With the introduction and development of laser resurfacing technology, beginning with the carbon dioxide laser in the mid-1990s, this technology, including ablative and non-ablative lasers as well as fractional and non-fractional lasers, has been diversified to improve skin tone, texture, dyschromia, scarring, and field change. Energy-based treatments such as radiofrequency, plasma resurfacing, and microdermabrasion are additional therapeutic options. The article underscores the importance of energy-based devices in non-surgical facial rejuvenation, detailing the various technologies and their applications in treating aged facial skin. It emphasises the need for careful patient selection and counselling regarding realistic expectations and potential risks associated with these procedures.

KEYWORDS: energy-based devices, laser resurfacing, ablative fractional resurfacing, non-ablative fractional resurfacing

Balendran T, Manoharan S. Resurfacing With Energy-based Devices For Facial Ageing. Opin Prog Cosmet Dermatol 2023;3(2):19–23.

Ageing is a unique process for every individual, which depends on a complex interplay between genetic, epigenetic, and environmental factors. Various molecular and structural changes occur during ageing, manifesting as volume loss, rhytids, skin laxity, dyspigmentation, and telangiectasia.[1–3] The face is the most cosmetically sensitive region of our body where the ageing process is clearly visible and makes it the centre of attention in rejuvenation.[1,4] Though the perception of beauty varies with gender, culture, and psychosocial preferences, facial skin ageing may cause major psychological impacts.[3]

Various facial skin rejuvenation techniques in aesthetic medicine have been practised for centuries, including skin care and cosmeceuticals, chemical peels, injectable agents, and surgical techniques. Recently, energy-based devices (EBDs) have become another potent modality.[2,3,5]

Following the introduction of carbon dioxide laser for skin rejuvenation and resurfacing in the mid-1990s, laser resurfacing technology represents an exciting development that has been modified and diversified over the years to improve skin tone, texture, dyschromia, scarring, and field change.[1,3] In addition to the laser, other EBDs, including plasma and radio frequency devices, have also been developed to help in a similar manner.

This article summarises various energy-based techniques used in facial skin rejuvenation.

Facial Skin Rejuvenation with Laser

Laser-based skin rejuvenation techniques currently account for 33.2% of the skin resurfacing techniques in aesthetic dermatology. There are ablative and non-ablative lasers, as well as fractional and non-fractional lasers. Indication, depth of effect, desirable outcomes, downtime, and side effects depend on targeted chromophores, delivering energy, depth of penetration, and surrounding tissue thermal injury.

Full-field Ablative Laser Resurfacing

The full-field ablative laser treats the targeted skin area by vaporising tissue, removing the epidermis, and penetrating the dermis, producing significant, often

dramatic, rejuvenating results. It is more suitable for ageing skin, deep rhytids, and photodamaged skin. The two most utilised ablative lasers are the carbon dioxide (CO2) and Erbium:YAG (Er:YAG) lasers.

CO2 lasers (10,600 nm) target cellular water as a chromophore and have been used in medicine since the 1960s in a continuous wave mode to destroy lesions. In the 1990s, high-energy pulsed CO2 devices evolved to provide field cutaneous resurfacing.[6]

Absorption of this wavelength by the epidermal cells' intercellular water ablates and vaporises 50–100 µm epidermal tissue.[7] This promotes subsequent re-epithelialization from residual dermal skin appendages and adnexal structures. Below the zone of ablation, thermal injury produced by the laser induces heat-mediated collagen contraction and subsequent collagen remodelling in the dermis, which, in turn, causes skin tightening. Also, the heat produced by CO2 laser causes greater coagulation of small blood vasculature in the dermis, leading to substantially less bleeding even though a large surface area is ablated.[1,4,6–9]

Although CO2 lasers have a long history, they remain the gold standard for facial resurfacing for more advanced ageing and photo-damaged skin.

Due to the risk of dyschromia post-treatment, it is mainly used for skin phototypes I-II; however, in the right setting, with adequate preparation and aftercare, it may also be used effectively in darker skin types. Careful patient selection is vital, as is detailed pre-procedural counselling about realistic treatment timelines and the risk of complications.

The Erbium:YAG (Er:YAG) laser (2940nm) was introduced in 2000 for superficial laser resurfacing. It has a 16 times greater absorption coefficient than the CO2 laser and thus provides more precise tissue ablation with less surrounding thermal tissue damage. This has a potentially less severe risk of complications and post-procedural downtime compared to its CO2 cousin.[8,9]

Fractional ablative laser resurfacing

Fractional ablative lasers are newer generation ablative lasers delivering the CO2 or Erbium:YAG laser energy in microscopic columns to provide controlled thermal damage in 'micro-thermal zones. As fractional ablative lasers treat only a small fraction of skin at each session and leave evenly spaced gaps between each treatment zone, there are shorter healing times and a lower risk of complications.[6–8,10]

Fractionated controlled thermal injury results in tissue contraction, collagen production, and remodelling. Tissue regeneration results from adjacent non-damaged tissue. It generally requires multiple treatment sessions to achieve significant results for aged skin with deep rhytids, dyspigmentation, and skin laxity.

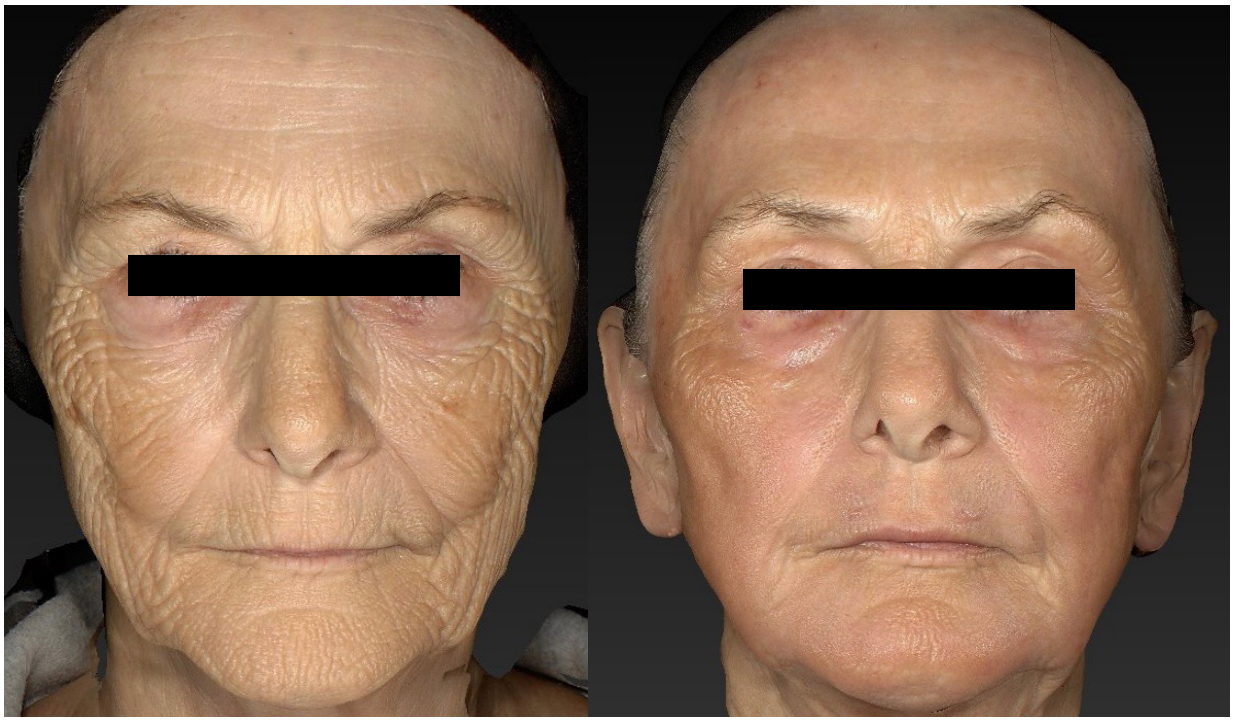

Figure 1: *70-year-old woman treated with a combination of CO2 and Erbium:YAG laser resurfacing to improve age-related changes.*

Non-ablative Fractional Laser Resurfacing

Non-ablative fractional laser resurfacing (NAFR) combines the best aspects of both fractionated and non-ablative laser technology. NAFR delivers fractional energy in microscopic columns with evenly spaced spare areas between the microthermal zones from 300 -1200µm depth. Water is the target chromophore. Commonly used wavelengths in NAFR are listed in Table 1.[2,3,5]

Commonly used NAFR include 1,540 nm and 1,550 nm Erbium:Glass and 1,927 nm Thulium. Due to favourable post-procedure outcomes such as low downtime (typically 1–7 days) and less risk of dyspigmentation, NAFR is highly popular in treating aged skin to improve skin texture, mild to moderate rhytids, and dyschromia.

NAFR may also be utilised in darker skin types, with less risk of post-inflammatory hyperpigmentation. As only a fraction of tissue is treated in a less invasive form, multiple sessions are required for the best outcomes.

Table 1. *Commonly used non-ablative fractional lasers.*

Non-ablative fractional lasers (wavelength)	Type	Key features
1,410 nm	Erbium	• Safe on skin type I-VI • Epidermis is not compromised • 70 µm depth • 20 mJ/MTZ
1,440 nm	Nd: YAG	• Includes 1,540 nm handset
1,540 nm	Erbium Glass	• Includes 1,440 or 2,940 nm fractional ablative handset
1,550 + 1,927 nm	Erbium + Thulium	• 1,550 nm: 1.4 mm depth and 70 mj/MTZ

MTZ, microscopic treatment zone.

Figure 2: *A 50-year-old female treated with a combination of IPL and 1,550 nm NAFR with synergistic improvements in vascularity, pigmentation, tone, and skin texture. Three sessions spaced four weeks apart.*

Hybrid Lasers

Hybrid lasers are increasing in demand as they incorporate both ablative and non-ablative laser technology in partially automated customisation of resurfacing settings in a single device. These allow treating both epidermis and dermis together for a wide variety of indications with less post-procedural downtime.[11]

A device with synergistic energy of fractional Erbium:YAG and 1,470 nm treats deep dermal collagen remodelling and superficial dyspigmentation.

Most of the newest devices are incorporated with advanced technologies such as automated power adjustment in response to treated skin temperature, automated depth estimation, and density of effect.

The recent hybrid device in the market combines an ablative CO2 laser and a non-ablative 1,570 nm laser. This energy is designed to deliver simultaneously, sequentially, or individually and incorporated with customised ratios to deliver both lasers depending on the required response.[12,13]

Hybrid lasers marry the intensity of fractional ablative lasers with the lower risk profile of non-ablative fractional resurfacing in a tuneable fashion, enabling significant results as an alternative to traditional resurfacing techniques.[12–15]

Radiofrequency in Facial Skin Rejuvenation

Radiofrequency (RF) is a non-invasive technology used in facial rejuvenation. RF waves are part of the electromagnetic spectrum wavelength range from 3 kHz to 300 MHz. RF devices are available as monopolar, unipolar, bipolar, or multipolar based on the number of electrodes, or they may be combined with physical treatment methods like fractional RF with micro-needling (FMR). Insulated and non-insulated microneedles are used in FMR, which aid direct dermal delivery of energy in the dermis with minimal epidermal injury.[16,17]

RF energy produces heat, stimulating collagen remodelling, contraction, and rejuvenation. It also increases elastin density, which can aid in skin tightening. Post-inflammatory depigmentation may be less likely with this technology than traditional energy-based resurfacing devices.

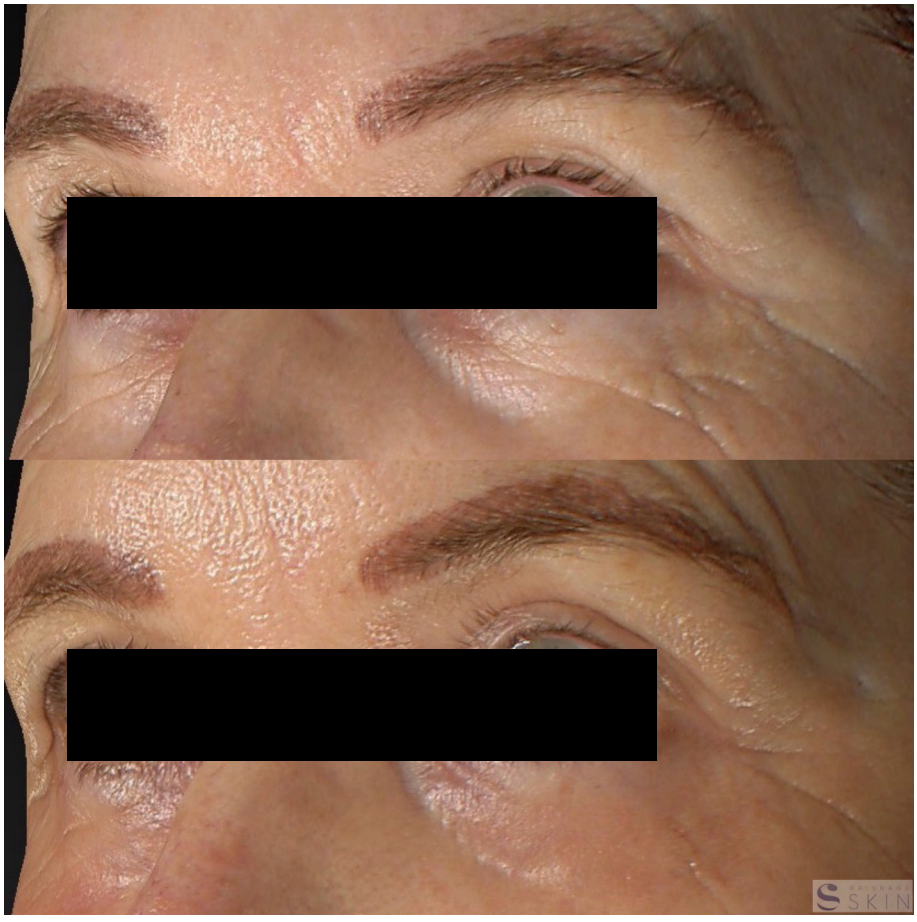

Figure 3. *Improvements in periorbital wrinkles using six radio frequency microneedling treatments and botulinum toxin injections.*

Plasma Skin Resurfacing

Plasma skin resurfacing technology is used for skin rejuvenation, typically in skin types I–IV, by thermal energy produced by a positively ionised gas. A gaseous nitrogen resource has positively ionised plasma, which results in heat and eliminates oxygen from the target tissue. This eventually desiccates the epidermis and causes heat-related denaturing of collagen in the upper dermis. The desiccated epidermal layer stays on the surface as a natural biological skin barrier, which promotes epidermal regeneration and accelerated healing. Thermal injury leads to neocollagenesis, increased fibroblast activity, and skin tightening.[18]

PSR is generally reserved for lighter skin types, and complications include scarring, prolonged redness, and dyschromia.

Microdermabrasion

Microdermabrasion is a minimally invasive skin rejuvenation technique to treat uneven skin tone, dyspigmentation, and skin laxity. This technique exfoliates the corneal layer of the epidermis by the propulsion mechanism of solid microparticles through a handpiece with a vacuum to remove removed cellular debris. Microdermabrasion devices can have crystal or crystal-free systems. Aluminium oxide crystals are commonly used microcrystals. Diamond-embedded systems are used in crystal-free microdermabrasion techniques. Hydra dermabrasion is the newest modality in which oxygen and aqueous solutions exfoliate the cells.[19]

Summary

Various skin rejuvenation technologies are being used to treat aged facial skin. Energy-based devices have cemented a role in non-surgical facial rejuvenation. Different energy-based devices are currently in use with the help of rapidly evolving advanced technologies. Laser-based technology, including ablative, non-ablative, and fractional lasers, remains prevalent in energy-based technologies. Ablative technology targets the epidermis and dermis, resulting in more postprocedural downtime. Non-ablative lasers targeting dermal rejuvenation with a sparing effect on the epidermis lead to quick recovery. Hybrid lasers are novel modalities that deliver precise energy to the skin tissue to be treated with the synergistic effect of ablative and non-ablative lasers. Other energy-based treatments, including radiofrequency, plasma resurfacing, and microdermabrasion, are also used to address facial ageing with promising outcomes.

Careful patient selection based on skin type, concern, downtime, and budget should be considered essential before treatment. Counselling regarding realistic expectations of outcomes, potential complications, and risks should also be undertaken.

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Assessing the Efficacy and Use of Biostimulatory Injectables for Facial Ageing: A Review

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Disclosures: *None*

OUTLINE: Facial ageing is a natural and complex process influenced by intrinsic and extrinsic factors. This process results in the development of physical characteristics such as wrinkles, volume loss, skin laxity, and reduced skin hydration. Traditional dermal filler injectables have historically been used to address these concerns by providing instantaneous results as a less invasive means than surgical and invasive interventions. However, such therapeutic outcomes work periodically and require repeated treatments. The recent emergence of biostimulatory filler injections has proven to be a highly efficient means of addressing facial ageing with longer-lasting clinical effects than traditional dermal fillers. Although having a more gradual onset, they help to stimulate the biological and cellular processes involved in counteracting facial ageing to provide a more natural cosmetic effect. Biostimulatory fillers include hyaluronic acid, calcium hydroxyapatite, polycaprolactone, poly-L-lactic acid, poly-D-lactic acid and most recently, polynucleotides. Each biostimulatory injectable has its unique way of counteracting facial ageing. Choosing a biostimulatory injectable depends on several factors, including cosmetic goals, cost, targeted facial structures, and side effect profiles.

KEYWORDS: facial ageing, biostimulator, Injectable, collagen

Fordham SA, Lim D. Assessing the Efficacy and Use of Biostimulatory Injectables for Facial Ageing: A Review. Opin Prog Cosmet Dermatol 2023;3(2):24–31.

Introduction

In recent years, there have been advances within medicine to target the sources of facial ageing. There are intrinsic and extrinsic factors causing facial ageing. Intrinsic factors include decreased hormone levels, anatomical variations, and genetic alterations, while extrinsic factors include exposure to ultraviolet (UV) light causing photoageing, smoking, and malnutrition.[1] There are several different treatments for facial ageing, including chemical peels, energy-based devices, and surgical augmentation.[2,3] Filler injections are a minimally invasive means of treating facial ageing by targeting its many variables.

Historically, dermal fillers have been used primarily to target volume and structural restoration. However, they lack the compounds to address other issues that contribute to the physical attributes of facial ageing.[4] The recent generation of novel biostimulatory injectables offers a means to improve skin rejuvenation, skin texture, skin hydration, neocollegenesis, angiogenesis, skin tightness, and dermal cell proliferation, which are properties that traditional dermal fillers cannot address.[5]

Biostimulatory injectables work through various compounds injected within the dermis and subcutaneous layer. These agents increase collagen, elastin, and ground substances via upregulation of the immune system, termed biostimulation.[6] This helps to create a long-lasting effect, as the endogenous cellular processes involved in the production of collagen, elastin and dermal cell proliferation are stimulated over a prolonged period.[6] The pathophysiology of biostimulatory injectables varies across each type.

Biostimulatory injectables can be differentiated into hyaluronic acid (HA-based, non-HA-based, and hybrid injectables.[7] HA-based biostimulators can be further differentiated into high (H-HA) and low molecular weight (L-HA) subtypes. The trade name for the Australian combined H-HA and L-HA product is Profhilo.[8] Non-HA biostimulators include calcium

hydroxyapatite (CaHA), polycaprolactone (PCL), poly-D and L-lactic acid (PDLLA), poly-L-lactic acid (PLLA), and most recently, polynucleotide injectables.[9]

Biostimulatory products can be further delineated into hybrid injectables, which employ a combination of biostimulatory products.[10] The advantage of such products is that they allow each biostimulatory product to exert its unique mechanism of action to produce the corresponding aesthetic outcome. As a result, clinicians can target distinct aspects of facial ageing, such as hydration and volume replacement, within the same treatment area. Examples include hybrid fillers comprising an HA and CaHA combination and polynucleotide and HA formulations.

Each biostimulatory injectable has unique characteristics, including biological properties, clinical technique delivery, dilutant properties, aesthetic outcomes, side effect profiles, clinical duration, and practice points. Evaluation and review of such biostimulatory injectable properties are required to formally assess its value and place in modern cosmetic medicine.

An Overview of Biostimulatory Injectables

The cellular and molecular mechanism of action of each type of biostimulatory injectable differs.

Hyaluronic Acid Biostimulators

HA is a naturally occurring glycosaminoglycan that helps to bind and retain water molecules due to its hydrophilic properties; it is also known as hyaluronan.[11] The hydrophilic properties are secondary to the highly charged carboxylic residues and the absence of sulphate substitutions.[10] The innate form of hyaluronan has a high molecular weight, while the low molecular weight forms are fragments from cellular turnover.[10] L-HA forms can relay receptors involved in stimulating fibroblasts and keratinocyte proliferation. In contrast, H-HA forms can interact with water molecules, collagen, and proteoglycans to promote dermal proliferation.[8] As a result, HA is known to have a vital function in tissue repair, regulating inflammatory signalling to fibroblast and epithelial response.[10] reduced HA expression ultimately results in dehydration, loss of elasticity, and epithelial atrophy.[10]

Combining both H-HA and L-HA is known as NAHYCOTM technology, which helps integrate endogenous HA levels with hybrid and stable complexes.[8] The synergistic effects of both H-HA (defined as 110–1400 kDa) and L-HA (defined as 80–110 kDa) are regulated by a process that is initiated at high-temperature, followed by a low-temperature step to help yield a thermally stabilised HA hybrid complex.[10] Linear forms of HA involve intradermal injection of ingredients into surrounding tissue over a prolonged duration that helps with stimulating water retention and fibroblasts while reducing the expression of inflammatory cytokines and matrix metalloprotease.[10] Linear HA injections can be further supplemented with additional compounds, such as amino acids, lipoic acid, retinol, ascorbic acid, and tocopherol, which lead to additional cellular benefits.[10] Crosslinked HA fillers address the poor mechanical support seen with native HA.[10] This consists of chemical modifications and crosslinkers, smaller molecules comprising a spacer and two functional groups to bridge different HA chains.[12] HA concentration and the degree of crosslinking are crucial to product duration.[10] The primary crosslinking agent used, 1,4-butanediol diglycidyl ether (BDDE), is durable since ether bonds are more stable than ester or amide bonds.[10,11] Moreover, BDDE is biodegradable and less toxic than other crosslinking formulations, making it an optimal crosslinking agent.[10] The use of crosslinked HA compounds helps to address the short half-life and poor elastic properties of native HA.[11]

Calcium Hydroxyapatite Biostimulators

CaHA biostimulatory fillers primarily work by supplementing volume replacement and collagen biostimulation.[6] Known by its trade name Radiesse, the biostimulatory filler contains CaHA microspheres carried through a carboxymethylcellulose (CMC) gel, which acts as a vector for such microspheres. Eventually, after several months, the CaHA particles are degraded into calcium and phosphate, which are excreted renally.[6] The long-lasting effects of CaHA are attributed to a controlled inflammatory process that helps to stimulate a fibroblastic and histiocytic reaction. This helps scaffold new tissue formation while collagen replaces the aqueous gel.[6]

The main type of collagen stimulated is type I collagen, which helps fortify the skin's mechanical properties and reduces skin laxity as a result.[6] Type III collagen, which plays a role in fibrotic processes, is predominantly produced during the initial stages, but type I collagen has a more significant effect over time.[6] CaHA has been observed to have a more significant effect in producing type I collagen, elastin and fibroblasts than HA compounds.[6] Compared with other biostimulatory compounds, there is minimal adaptive immune cell recruitment and a lack of chronic inflammation with CaHA.[13] Ultimately, this helps to create a brighter, more hydrated, more elastic, and less wrinkled appearance of the skin.[12]

Polycaprolactone Biostimulators

PCL compounds primarily have collagen-stimulating properties. PCL is a polymer that belongs to aliphatic polyesters, with slower degradation properties than other compounds.[14] Fillers, like CaHA, contain microspheres delivered through a gel carrier that provides an immediate effect, whereas PCL

microspheres lead to a prolonged effect with collagen stimulation and scaffold formation.[13] The response to the injection induces a tissue repair process characterised by inflammation, proliferation, and remodelling.[13] Early granulation tissue production and type III collagen recruitment are then led by long-term type I collagen production during the remodelling phase.[13] Inflammatory reactions are characterised by macrophage recruitment and protein coating of foreign material, which aid in the inflammatory and wound healing processes.[13] Phagocytosis depends on the size of microspheres, with smaller particles leading to a faster rate of phagocytosis.[13] PCL microspheres are generally 25–50 μm, helping protect them from phagocytosis. Further, the smooth surfaces of the microspheres decrease inflammatory processes.[13]

A new particle-free PCL biostimulator was developed recently.[15] The absence of microspheres adds an advantage where particles may otherwise become coagulated by carrier gels or block injection needles.[16] The carrier gel found in PCL fillers in products such as Ellanse may also result in mild swelling and erythema due to the glycerine contents. DLMR01 is a microparticle-free PCL-based filler.[16] DLMR01 contains particle-free PCL, which is homogenously solubilised in water to exert the collagen-based remodelling process without causing phagocytosis and is currently undergoing approval under the Therapeutic Goods Administration (TGA) in Australia.[17] The exact process of neocollagenesis induced by DLMR01 needs further examination, as it is not fully understood.[16] Known as Gouri In Australia, it is a liquid PCL that acts as a biodegradable polymer in the lower dermis that breaks down PCL through hydrolysis without microparticles. PCL products may be presented with microspheres suspended in an aqueous CMC gel carrier or administered as liquid PCL homogenously solubilised in water.[16]

Poly Lactic Acid Biostimulators

The PDLLA and PLLA biostimulatory injectables primarily work by stimulating neocollegenesis.[17] PLLA, also known as Sculptra in Australia, works by stimulating a foreign body reaction secondary to the injected material, resulting in an inflammatory response surrounding the injected microspheres. This ultimately stimulates the formation of new connective tissue.[18] PDLLA microspheres, known as Aesthefill fillers in Australia, have a sponge-like composition compared to PLLA microspheres, which have an irregular composition.[19] The sponge-like composition allows pores to act as a three-dimensional framework that helps articulate new connective tissue formation.[16] PDLLA is more porous than PLAA, which helps to deliver a higher volume of filler, leading to a more pronounced volume-restoring effect in the early stages of filler delivery.[16]

Polynucleotide Biostimulators

One of the latest biostimulatory injectables available in Australia is polynucleotides, known by its trade name, Rejuran. These purified DNA molecules are extracted from male salmon gonads to create a collagen-stimulating filler.[20] This is the product of polynucleotides highly purified technology (PN-HPT™) incorporating a mixture of DNA polynucleotides at various lengths.[21] Exposure of PN-HPT™ has demonstrated increased deposition of collagen and elastin fibres along with renewal of collagen and elastin networks within the superficial layers of the skin.[22] The potential of PN-HPT™ extends beyond preventing facial ageing as it effectively treats knee osteoarthritis through intra-articular injections, lower limb venous ulcers, and postmenopausal atrophic labia majora.[22] They may also be used to treat atrophic acne scars, as they stimulate an immune response that allows collagen to replace areas of atrophy.[22] Many forms of polynucleotides can help address different goals. Rejuran hybrid formulation with HA helps promote collagen synthesis while having a hydrating effect. Further, Rejuran S can be used to rejuvenate atrophic scars by using a volumising effect, while Rejuran I can be used to reduce crow's feet and wrinkles around the eyes.

Hybrid Biostimulators

Combining different biostimulatory agents enables different cellular pathways to be targeted. A common hybrid biostimulatory injectable is the combination of HA and CaHA, which is known as HArmonyCa®. Therefore, the hydrating effects induced through proteoglycan interactions combined with dermal proliferation induced through immune-mediated inflammatory responses with neocollagenesis can be provided with one treatment.[10] CaHA-mediated neocollagenesis helps yield tissue-lifting and skin tightening, while its rheologic properties, such as high viscosity, help with further bone definition.[23] The combination of HA and CaHA also has synergistic effects, as HA can further augment the effects of CaHA by providing additional volumisation while securing tissue softness.[23] When premixing HA and CaHA together, HA can also compensate for early volume loss that may occur secondary to rapid absorption of the CMC gel with CaHA treatment areas.[24] Premixing CaHA with HA may also prolong the duration of the effect.[23] Layering the products within the same treatment area, however, can alter each product's rheological properties.[24]

Another recent hybrid product that has been described is the combination of both a polynucleotide and HA, which helps stimulate collagen production and provide a hydrating effect clinically.

Dilutions of Biostimulatory Injectables

The delivery of biostimulatory injectable products differs regarding clinical goals and the mechanism of action for each compound.

HA Hybrid Biostimulators (Trade Name: Profhilo)

Injections of L-HA and H-HA hybrid compounds usually have a HA concentration of 3.2% with 32 mg each of H-HA and L-HA suspended in 2 mL of buffered sodium chloride.[8] The product is provided in a pre-filled 2-mL syringe and is injected within the deep dermis with a bolus technique. Injections can be repeated four weeks after the initial injection over two to three sessions.[8]

The Bio Aesthetic Points (BAP) technique identifies five different points on each side of the face to allow for fewer injection points, syringes, and side effects.[23] The low viscosity and increased spread of the hybrid complex compounds allow the BAP technique to create a homogenous result once injected in five boluses.[17] The first point is identified as the zygomatic protrusion, at least 2 cm away from the lateral canthus of the eye.[17] The second point is 1.5 cm anterior to the inferior margin of the tragus.[17] The third point is 1.5 cm above the mandibular angle.[17] The fourth point is 1.5 cm away from the middle of the chin.[17] The fifth point is 1.5 cm away from the nasal base, located at the intersection between the pupil line and the horizontal line starting from the nasal base.[17]

Other injection techniques involve a dual plane delivery via cannular in addition to dermal injections.[25] The dual plane technique involves filling the addressed component, targeting the subdermal element by subcision, and then inserting a small amount of HA.[26] This can be done by filling the dermis with 0.02–0.1 mL of HA in a 29G syringe. In contrast, the following injection pass is done immediately afterwards with a 25G cannula inserted into the superficial hypodermis.[26] Using the blunt cannula helps interrupt the subcutaneous fat in cases of injected scars.[26] In the case of treating atrophic acne scars, this can then be repeated at four weeks, where 70% of the initial corrective volume is used.[26] A study that investigated the efficiency of treating atrophic acne scars with the dual-plane HA injection method found overall improvement at one-, three--, and six-month reviews with minimal complications.[26]

CaHA Biostimulators (Trade Name: Radiesse)

CaHA fillers can be delivered in several ways. The degree of dilution can affect clinical outcomes, as an undiluted or slightly diluted solution will offer instant correction, followed by neocollagenesis and elastin production.[6] A hyper-diluted formula will have a lesser or absent effect of instant volume correction, as the CMC gel will tend to disperse, allowing for more superficial injection and the treatment of larger areas.[6]

Dilution levels can also be further titrated depending on variables such as skin thickness and degree of tissue laxity.[6]

Due to the pain attributed to injections, a dilution of lidocaine at 0.3% concentration can help with patient comfort during the procedure.[6] Needles or cannulas may also be used, as needles offer more precision while cannulas minimise trauma and allow for treatment of larger areas.[6] A study that compared the two methods used frozen cephalic forehead specimens injected with radiopaque substances by both needles and cannulas.[26] After using fluoroscopy imaging, they found that 60% of needle injections resulted in an injected material altering its plane.[17] This indicated that cannulas may be more precise and recommended using a blunt cannula or a sharp needle. However, using a sharp needle may result in a higher risk of superficial placement of injected material.[17] CaHA can be inserted by retroinjection by using cannulas with fanning (i.e., redirecting needle in multiple angles) and asterisks techniques, as 2–4 entry points may be applied on each side of the face.[6] A dilution of 1:1 (i.e., 1.5 mL of dilutant) with one syringe per session is also recommended.[6]

PCL Biostimulators (Trade Name: Ellanse, Gouri)

Particulate PCL fillers are prepared in a CMC gel (comprising 70% of the volume), where the PCL microspheres (comprising 30% of the volume) are homogeneously suspended.[3] Such fillers are administered via 3 mL syringes that include the PCL filler, which can be reconstituted with 0.5 mL of lidocaine and 2 mL of normal saline.[3] The mixture can then be passed through different syringes several times to create a homogenous mix of the diluents.[3] The injection depth is ideally the deep dermis for facial treatment.[3] However, under correction is recommended in areas with low soft-tissue coverage (i.e., nose, melomental folds, and pre-jowl sulcus).[27]

The recommended techniques for subcutaneous injections are linear threading, fanning, or cross-hatching. The bolus requires injecting small amounts (≤0.2 mL) to build a low-pressure gradient. Overcorrection is unnecessary as the subsequent collagens synthesis will be sufficient to obtain the desired result.

The ideal injection delivery method for particle-free liquid PCL has not yet been standardised. Both cannula and intradermal injections have been described.[16]

PLLA Biostimulators (Trade Name: Sculptra)

The delivery of PLLA is presented as 150 mg per vial. It should be prepared for hydration with 7–8 mL of sterile water for injection or bacteriostatic water for more than 24 hours at room temperature.[15] However, a study demonstrated the effectiveness of immediate reconstitution of facial PLLA injections.[15] A single PLLA

vial was added to 5 mL of sterile water and mixed vigorously for 1 minute. The suspension was then aspirated into a 20 mL luer lock syringe with 5 mL sterile water and 2 mL of 2% lidocaine.[15] The result was a 12 mL suspension of PLLA, which was transferred to four 3 mL syringes. The injections were given with cannulas via fanning through retrograde injection with two different insertion points on each side of the face.[15] PDLLA is delivered through a CMC vector gel and is available as a lyophilised powder.[28] Reconstitution with a dilutant, such as sterile water for injection, is generally used with 200 mg of PDLLA lyophilised powder.[18]

A study investigated the 'back-and-forth method' to help accelerate the reconstitution process of PDLLA injectables.[18] It is recommended that PLLA is given over three to six sessions with injections spaced six weeks apart. Different dilutants used included sterile water, normal saline, lidocaine, lidocaine with epinephrine, sodium bicarbonate, and mannitol.[18] Typically, suspension concentrations can be made through reconstitution of 200 mg PDLLA per 8 mL (i.e., a thin suspension) or 1.4 mL (i.e., a thick suspension).[18] The back-and-forth method was done by using two 3 mL syringes, including the PDLLA product, and the other was used to prepare a thin or thick suspension using the required diluent volume.[18] The two syringes were connected via a three-way stopcock with a luer-lock, where the PDLLA product and diluent were pushed back and forth between the two syringes for one minute.[18] This method allowed all diluents to be successfully reconstituted, and a homogenous suspension was created without PDLLA microsphere aggregation.[18] This contrasts with the standard method of hand-shaking the product, as only sterile water for injection can be used as a diluent due to other diluents having inadequate particle separation, which does not create a homogenous suspension.[18] PDLLA is generally given over two to three sessions with injections spaced six weeks apart.

Polynucleotide Biostimulators (Trade Name: Rejuran)

The consensus of injection technique for polynucleotide injections includes three to four sessions using a thin needle (30–32 G) and anaesthetic gel with microdroplet, linear or fanning methods. The microdroplet method targets the dermal layer with great precision, pushing the needle slowly until a bleb can be appreciated in the skin. Such injections are spaced 1–1.5 cm apart, causing blebs in the treatment area. The most common methods used clinically are the microdroplet and linear retrograde techniques. The highest concentration for facial treatment is an intradermal injection of 40 mg per 2 mL. In contrast, those with sensitive skin or receiving treatment in more delicate areas, such as the periorbital area, may receive low-concentration injections. Low-concentrated injections include 1–2 mL intradermal injections of 7.5 mg/mL polynucleotide formulations for a maximum concentration of 15 mg per 2 mL. The microdroplet method is the preferred technique for sensitive skin and delicate facial areas. Priming is also recommended, which refers to using polynucleotide injections before using another facial rejuvenation stimulus, such as HA or energy and light-emitting devices.[21]

Aesthetic Outcomes

The aesthetic outcomes achieved in clinical practice with biostimulatory injectables have been demonstrated in studies.

One study that explored the clinical effects of Profhilo evaluated the degree of hydration and viscoelasticity.[29] One treatment demonstrated a significant increase in skin hydration and viscoelasticity after two treatments.[26] Another study employed Profhilo to assess facial parameters, including wrinkles and skin surface microrelief.[8] Such parameters were assessed at four weekly intervals after the first injection.[8] All parameters demonstrated a statistically significant result, as skin surface relief (measured by imaging) decreased at each interval and wrinkles (assessed by the Wrinkle Severity Rating Scale) demonstrated a decrease in severity.[8] However, it must be noted that the volume replacement effect of Profhilo is minimal compared with other biostimulatory injectables due to its low impact on collagen stimulation.[30]

Non-HA fillers do not hydrate the skin as much as HA filers but provide prolonged collagen-stimulating properties. This helps provide skin tightening, volume distribution, and contour alteration. PCL fillers have demonstrated clinical efficacy in a study following several study participants for 6–24 months.[13] There were significant improvements in the Global Aesthetic Improvement Scale and Wrinkle Severity Rating Scale scores with PCL fillers.[13] Moreover, PCL fillers demonstrated 18–24 months longer than HA-based fillers, namely CaHA fillers.[13] Another case study demonstrated improvement in facial volume in several tissue layers through Vectra 3D imaging.[31] Further, a study using ultrasonography to assess the dermal thickness after PCL injections demonstrated that the mean rate of temporal skin thickness increased by 26.74 ± 9.26% after one year of treatment due to neocollagenesis.[3] This was also associated with improvement in skin texture and fine wrinkles.[3] Overall, the primary clinical outcomes include volume restoration, contour redefinition, skin rejuvenation, and wrinkle reduction. PCL fillers have the most significant collagen stimulation potential compared with other biostimulatory injectables.[13] PCL fillers, however, do not provide as much of a volumising effect as CaHA, PLLA, and PDLLA fillers.[3]

Table 1. An overview of biostimulatory injectables.

Biostimulatory Filler	Dilution Ranges	Aesthetic Outcomes	Mechanism of Action	Duration of Effect	Side Effect Profile
Hybrid High and Low Molecular Weight Hyaluronic Acid Trade Name: Profhilo	2 mL pre-packaged syringe	• Skin hydration • Improve skin laxity • Reduction in wrinkles	Synergistic effects of H- HA (dermal proliferation through collagen and proteoglycan interactions) and L-HA (fibroblast stimulation and keratinocyte proliferation) help to produce a hydrating effect. • Minimal effect on collagen stimulation • Great hydration effect • Minimal volumisation	Up to 12 months	• Erythema (less frequent than non-HA fillers) • Ecchymosis (less frequent than non-HA fillers) • Oedematous tissue (less frequent than non-HA fillers) • Non-inflammatory nodules (not common) • Inflammatory nodules (not common) • Vascular compromise (rare)
Calcium Hydroxyapatite Trade Name: Radiesse	1.5 mL pre-packaged syringe with or without xylocaine • The dilution ratio varies between 1: 1 to 1: 6	• Volume restoration • Reduction in wrinkles • Acne scarring treatment	Early initiation of Inflammatory processes influenced by microspheres that stimulate collagen and fibroblastic production to generate new tissue formation. • Mild effect on collagen stimulation • No hydration effect • Moderate volumisation	Up to 18 months	• Erythema • Ecchymosis • Oedematous tissue • Non-inflammatory nodules (not common) • Inflammatory nodules (not common) • Vascular compromise (rare)
Polycaprolactone Trade Name: Ellanse Trade Name: Gouri	Ellanse 1.0 mL pre-packaged syringe • Up to 0.2mL dilution with xylocaine off-label Gouri 1.2 mL pre-packaged syringe • Dilution not recommended	• Reduction in wrinkles • Improve skin laxity	Introduction of microspheres that cause prolonged collagen stimulation through inflammatory processes and tissue remodelling. • Great effect on collagen stimulation • Minimal hydration effect • Minimal volumisation	Up to 24 to 48 months depending on product	• Erythema • Ecchymosis • Oedematous tissue • Non-inflammatory nodules (not common) • Inflammatory nodules (not common) • Vascular compromise (rare)
Poly-L-Lactic Acid Trade Name: Sculptra	367.5 mg dose vial • Reconstitution volume range 6 to 20mL	• Volume restoration	Microspheres cause a foreign body inflammatory response that stimulates new connective tissue. • Moderate effect on collagen stimulation • Minimal hydration effect • Moderate volumisation	Up to 24 months	• Erythema • Ecchymosis • Oedematous tissue • Non-inflammatory nodules (not common) • Inflammatory nodules (not common) • Vascular compromise (rare)
Poly-D and L-lactic Acid Trade Name: Aesthefill	200 mg dose vial • Reconstitution volume ranges from 1.4–8 mL saline	• Volume restoration • Reduction in wrinkles	The sponge-like composition of microspheres helps articulate new tissue formation, while the porous characteristics of microspheres add a volume-restoring effect. • Moderate effect on collagen stimulation • Minimal hydration effect • Moderate volumisation	Up to 24 months	• Erythema • Ecchymosis • Oedematous tissue • Non-inflammatory nodules (not common) • Inflammatory nodules (not common) • Vascular compromise (rare)
Polynucleotides Trade name: Rejuran	2 mL pre-packaged syringe • Up to 40 mg of polynucleotide product	• Reduction in wrinkles • Improve skin laxity • Improves skin texture and pores • Atrophic scarring	Extracted salmon DNA uses polynucleotide chains at different lengths to stimulate collagen production. • Mild effect on collagen stimulation • Minimal hydration effect • Minimal volumisation	Up to 12 months	• Erythema • Ecchymosis • Oedematous tissue

A study assessing the clinical efficiency of polynucleotides for treating facial ageing demonstrated significant improvement in pore size and skin thickness in 30-year-old consumers.[32] Moreover, skin tone, melanin, wrinkles, and skin sagging were significantly improved in 40-year-old consumers.[32] Although the clinical effects regarding volume replacement and tissue hydration were minimal, combining HA formulations helped target these variables.

Clients must be aware of the different profiles associated with each biostimulatory filler (*Table 1*) to make an informed decision on what filler is best indicated for their needs.

Conclusion

When evaluating the management of facial ageing, clinicians can consider using biostimulatory injectables. The type of biostimulatory agent used is based on selective patient outcomes, goals, cost, availability, clinician training, intended injection site, and safety profiles. Biostimulatory injectables differ in mechanism of action, injection technique, safety profile, and clinical outcomes. Studies have demonstrated the clinical effectiveness of these fillers, which offer a minimally invasive and highly effective method of treating facial ageing and other areas of aesthetic medicine.

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Commentary – Do Biostimulatory Injectables Hold the Promise of Optimising Results From Lasers Whilst Potentially Reducing Adverse Effects?

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Lim D. Commentary – Do Biostimulatory Injectables Hold the Promise of Optimising Results From Lasers Whilst Potentially Reducing Adverse Effects? Opin Prog Cosmet Dermatol 2023;3(2):32–34.

Lasers are frequently employed in skin rejuvenation to improve skin quality, address laxity, reduce wrinkles, and treat photodamage. It is widely accepted that ablative resurfacing provides superior neocollagenesis compared with non-ablative lasers. However, the results come at the cost of increased adverse outcomes, such as dyspigmentation, prolonged erythema, scarring, and infection. These side effects are proportional to the aggression of resurfacing, namely the amount of energy delivered, density, and number of passes performed.[1,2]

Biostimulatory injectables offer an alternative to energy-based devices (EBD) as they provide a cellular-centric approach to neocollagenesis. Depending on the dilution and injectable properties, biostimulatory injectables are employed as a treatment for facial laxity, volume enhancement, and improvement of skin quality. Injectables such as poly L lactic acid (PLLA), calcium hydroxyapatite (CAH), hybrid hyaluronic acid (HA) complexes, and polycaprolactone (PCL) have robust studies on the effects of cellular bio-remodelling with differentiation of fibroblasts, adipocytes, keratinocytes, and the dermal matrix.

Targeting different levels and pathways

Ablative lasers stimulate collagen production via the generation of heat shock proteins.[3] Their depth of action extends from the epidermis to the reticular dermis. In contrast, injectables, such as PLLA, PCL, and CAH, induce collagen production through foreign body reactions.[4] In the context of bio-remodelling, these substances are most frequently injected in the hypodermis. It appears reasonable to stimulate cellular activity through two pathways rather than one. Moreover, stimulating collagen in dermal and hypodermal layers may offer more favourable outcomes than focused biostimulation of a single layer. Thus, combining biostimulatory injectables during or shortly after energy devices may provide an adjunct to cellular differentiation.

Combination treatments may offer advantages over monotherapy with either energy devices or injectables. The main goal of combination treatment is to deliver more conservative treatment parameters without compromising clinical outcomes. This translates to faster recovery and reduces adverse outcomes. Additionally, depending on the properties of the biostimulator employed, we can improve skin elasticity, pliability, volume deficits, and dermal hydration.

A pivotal study by Casabona et al.[5] demonstrated that combination treatments with high-intensity focused ultrasound (HIFU) immediately before calcium hydroxyapatite and hyaluronic acid injectables resulted in the highest level of neocollagenesis compared with standalone treatments. This study highlights a possible synergy with combination therapy.[5]

Over the past two years, my team and I have cautiously delivered various biostimulators immediately before ablative CO2 lasers as a novel rejuvenation method with the notion of achieving good clinical results using conservative energy settings and passes.

Treatment combinations with CO2 laser resurfacing and biostimulators

Case 1

This patient wanted skin tightening, improved skin quality, and reduced periocular and forehead wrinkles with subtle improvements in volume. A total of 2.4 ml of liquid polycaprolactone mixed with 0.4 ml xylocaine was delivered via a 22 G cannula to the hypodermis in the temples, forehead, and lateral cheeks, including the marionette lines. Liquid PCL was chosen as the biostimulant due to the limited volume enhancement since it is carboxymethylcellulose-free. Conservative fractional CO2 with a 5-day re-epithelisation timeframe was performed in the same session. The patient underwent one session only.

Case 2

A fully ablative CO2 resurfacing procedure is indicated for more severe facial laxity and ageing cases. PLLA was selected for its volumising and skin-tightening effects. Two vials of PLLA (18 ml saline dilution per vial) were injected with a 22 G cannula into the midface and temple areas. The injections were performed immediately before resurfacing.

Re-epithelialisation was achieved within nine days. The before and after photos were taken ten weeks apart. The degree of erythema post-resurfacing is less than expected, corresponding to the more conservative resurfacing approach. Although we had planned for another two sessions of PLLA injectables, the patient was happy with the results from one session.

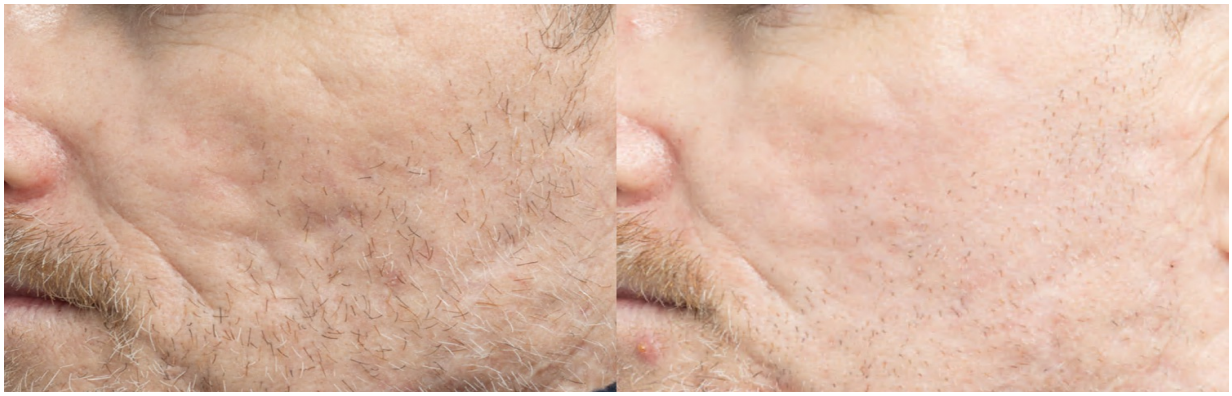
Case 3

In patients with mature acne scars, we must account for the ageing process, including depletion and migration of fat compartments, collagen loss, and a reduction in hyaluronic acid. Although CO2 lasers remodel dermal pathology, injectables can be advantageous for patients with high-volume atrophic scarring with clinically evident subcutaneous atrophy.[6,7]

NAHYCOTM technology based HA, commercially available as ProfHilo®, was employed in this case. Hybrid HA complexes have a biostimulatory effect on fibroblasts and keratinocytes and potentiate adipose stem cell differentiation. Moreover, the anti-inflammatory effects of HAs anti-inflammatory can potentially accelerate laser-induced wounding.[8,9] The 'after' image was achieved with a single session of CO2 resurfacing procedure and 2 ml of hybrid HA biostimulator, followed by an additional 2 ml administered eight weeks later. The biostimulator

Case 1: *Light CO2 resurfacing combined with liquid polycaprolactone injectable.*

Case 2: *Two vials of CO2 medium to heavy settings plus poly-L-lactic acid.*

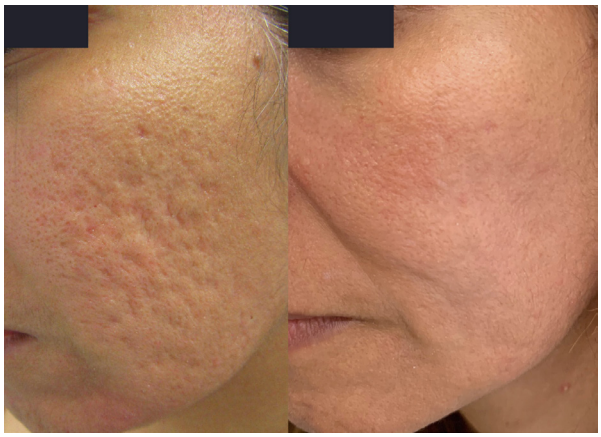


Case 3: *Treatment of acne scars: fully ablative CO2 resurfacing coupled with HA-based biostimulator.*

was placed in the hypodermis and mid-subcutaneous layer using a 22 G cannula with a blunt subcision to the scar field.

Case 4

Given this patient's darker skin type, fractional CO2 was chosen to reduce the duration of post-inflammatory hyperpigmentation. Calcium hydroxyapatite 1.5 ml plus 2.0 ml xylocaine 2% was delivered with a 22 G cannula before resurfacing. Only two sessions were conducted. The 'after' photo was taken six months after the last treatment.



Case 4: *Fractional CO2, calcium hydroxyapatite. Two sessions.*

Critical questions regarding combined biostimulators and energy devices

Timing

What is the ideal timing for each modality?

Optimal combinations

What biostimulator should be used for what device?

What is the mechanism of cross-talking behind neocollagenesis pathways?

Will hybrid biostimulators with different molecules (e.g., CAH + HA) give better outcomes?

Will the delivery of energy change the properties of non-HA-based injectables?

How do we apply the algorithm to variations in chronological age?

What is the contribution of genetics to combination treatments?

How does racial variation come into play with devices and injectables?

What is the ideal dilution of biostimulatory?

Will multiple injections with more diluted products be better than higher concentrations?

Safety issues

Will the rate of infection be increased with concurrent treatments?

Would combined treatments increase the PLLA and PCL rate of nodules?

Will the pro-inflammatory nature of liquid polycaprolactone lead to fibroplasia?

Will the dystrophic calcification rate be increased with calcium hydroxyapatite and energy devices?

The future

Several new biostimulators will be available in Australia in 2024, including poly-D-lactic acid, liquid polycaprolactone, and HA with CAH. These agents add to our current PLLA, CAH, PCL, hybrid HA complexes and polynucleotides repertoire.

The prospect of skin rejuvenation holds promise as we explore the integration of biostimulators and energy-based devices. Nevertheless, caution is warranted, given the numerous unanswered questions. With time, we may uncover innovative combinations of injectables and energy devices that foster synergistic biostimulation, ultimately enhancing clinical results and concurrently diminishing adverse events.

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Non-surgical Body Contouring

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OUTLINE: Non-surgical body contouring has become an increasingly popular procedure sought by patients hoping to achieve localised fat reduction without undertaking the risks of a surgical procedure. This article provides an overview of the five main energy devices used for non-invasive body contouring: cryolipolysis, laser therapy, radiofrequency, ultrasound, and high-intensity focused electromagnetic field/electromagnetic muscle stimulation technology. Additionally, this article discusses minimally invasive body contouring with chemical lipolysis via deoxycholic acid injections.

KEYWORDS: body contouring, deoxycholic acid, laser, cryolipolysis, subcutaneous fat

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Non-surgical body contouring that is an increasingly popular cosmetic procedure that patients seek to achieve localised fat reduction, skin tightening or increased muscle tone without the risks of a surgical procedure. Devices for non-surgical body contouring include five main modalities: cryolipolysis, laser therapy, radiofrequency, ultrasound and high-intensity focused electromagnetic field/electromagnetic muscle stimulation technology. Many of these devices are not regulated by the Therapeutic Goods Administration (TGA), owing to their classification as cosmetic procedures, and given they are non-laser devices. Besides using energy devices, fat reduction can be achieved using chemical lipolysis with deoxycholic acid injections.

With all non-surgical body contouring methods, patients must be adequately counselled for realistic expectations regarding outcomes, with discussion of individual variability in results, potential side effects, time course of treatment response, and the need for multiple treatment cycles in most cases. Judicious patient selection is required for patient satisfaction, as global obesity and certain medical conditions preclude the use of non-surgical body contouring.

Cryolipolysis

Cryolipolysis is a well-established non-invasive body contouring procedure targeting the flanks, abdomen, thighs, submental areas, periaxillary fat, and buttocks. It involves using approximately 10°C cooling applicators on a targeted treatment area for 25–60 minutes. Cryolipolysis takes advantage of lipid-rich adipocytes' higher freezing temperatures than the surrounding water-rich cells, allowing for selective fat targeting. Low temperatures and crystallisation of adipocytes result in lobular panniculitis (inflammation of the subcutaneous fat), and adipocyte apoptosis. Postprocedural massage is recommended to increase tissue reperfusion after cooling.

Based on data from 4,792 cryolipolysis treatments over the flanks, back, thighs, submental area and banana roll region, cryolipolysis reduces ultrasound fat layer thickness by an average of 20.6% and 3.9 mm (Range: 10.3–25.5%; 1.9–8.3 mm).[1]

A cryolipolysis treatment session typically spans one hour. Each treatment area involves one to three sessions spaced 2–3 months apart. Results are appreciable as early as three weeks following treatment, with final results demonstratable 2–4 months after the treatment session. Cryolipolysis should be used only in areas with a subcutaneous fat layer thickness greater than 1 cm. They should not be performed in areas with superficially located nerve branches, arteries, or veins.

Cooling via applicators can be associated with tingling, stinging, and discomfort that usually resolves after the area goes numb. Patients can commonly experience

erythema, bruising, swelling and dysaesthesia following a cryolipolysis session, which resolves within one month of treatment (*Figure 1*).[2] Rarely, cryolipolysis can result in paradoxical adipose hyperplasia (PAH) where patients develop a tender, hardened subcutaneous mass 3-6 months after treatment (*Figure 2*). The incidence of PAH has been reported to vary between 0.025% and 0.39%, with a reduced incidence in newer cryolipolysis units and application models.[3] PAH does not routinely spontaneously resolve and may require either chemical lipolysis or surgical intervention. Other rare adverse events reported with cryolipolysis include prolonged/severe pain and frostbite, particularly with inappropriate operator use.[4]

Cryolipolysis should not be used in patients with cold-induced metabolic disorders such as Raynaud's disease, cryoglobulinaemia, and cold agglutinin disease, as well as in individuals with amorphous fat, global obesity, hernias and pregnant or lactating women.

Laser therapy

Laser therapy uses wavelengths of either 635 or 1060 nm for body contouring involving areas such as the abdomen, back, thighs, or submental area. Low-level laser light therapy (LLLT) utilises a non-contact 635-nm diode laser, which is thought to disrupt the cell membranes of adipocytes non-thermally.[5,6] This membrane disruption facilitates triglycerides to leak out of cells but does not cause adipocyte apoptosis.[5] The absence of adipocyte apoptosis calls into question the permanence of this fat reduction method, and there are no long-term studies following patients over 12 months.[2,7] LLLT usually requires six to twelve treatment sessions at targeted areas. It has been demonstrated to be efficacious for body contouring over several treatment areas, including the waist, hip, thighs, abdomen, and upper arm (*Figure 3*).[8] LLLT is associated with pain during the procedure due to tissue heating and, uncommonly, the formation of tender subcutaneous nodules.

The more recently developed 1060-nm diode laser is a contact device that causes thermally induced adipocyte apoptosis. The dermis is protected from overheating with contact cooling, whilst the adipose tissue is exposed to temperatures of 42–47°C. The 1060 nm wavelength has an affinity for adipocytes, contributing to the efficacy and relative safety of this device. Laser therapy with the 1060-nm diode laser is also relatively fast, requiring only 25 minutes per treatment session. Each treatment area needs between 1–2 treatment sessions, and while results are appreciable at 6 weeks, they are optimal at 12 weeks post-treatment (*Figure 4*).

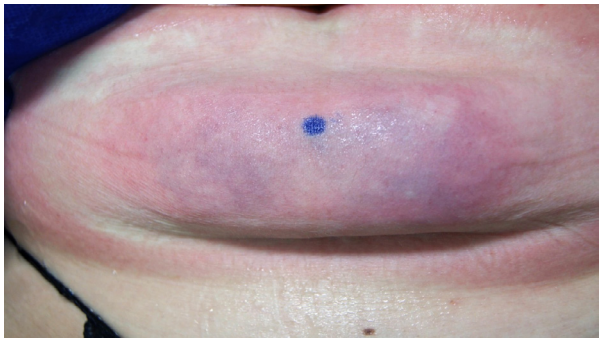

Figure 1. *Photograph demonstrating common side-effects of erythema, swelling and variable purpura immediately after removal of cryolipolysis suction cups. Adapted from Sebaratnam DF et al.[9]*

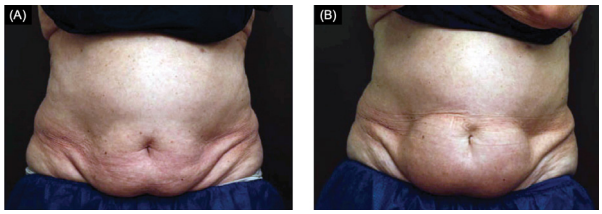

Figure 2. *(A) Photograph prior to treatment with cryolipolysis (B) Paradoxical adipose hyperplasia demonstrated five months after a single cryolipolysis session. Adapted from Stroumza N et al.[10]*

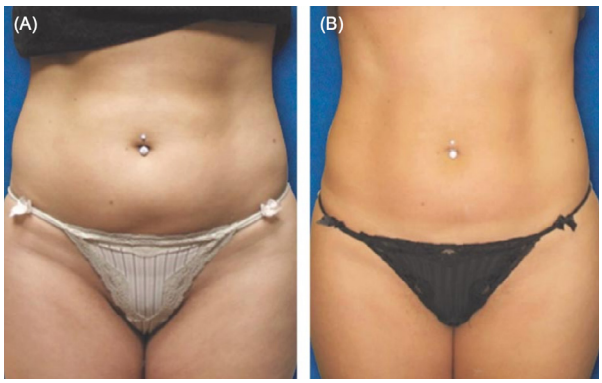

Figure 3. *(A) Photograph prior to treatment with low-level laser light therapy (LLLT) (B) Following treatment with six sessions of LLLT. Adapted from https://www.myzerona.com/what-is-zerona/before-after/*

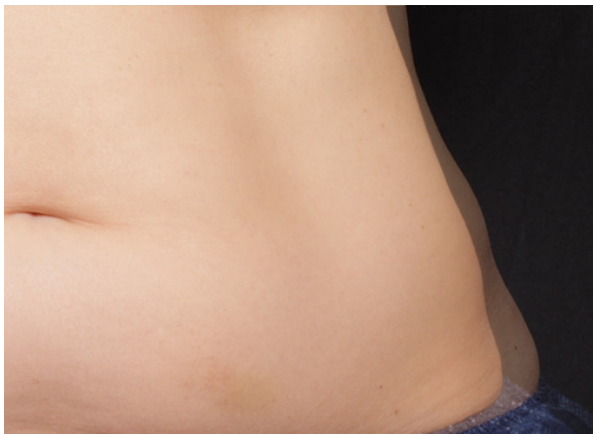

Figure 4. *An overlay of pre-treatment and 12 weeks post-treatment photographs of the flank area following one session of 1060-nm diode laser therapy targeting the flanks. Adapted from Kang A et al.[11]*

Treatment with the 1060-nm laser is associated with mild-to-moderate pain associated with tissue heating, and commonly, oedema, tenderness, and induration that resolves by 3 weeks post-therapy.[12,13] Less commonly, laser therapy was associated with nodules, burns/blisters, prolonged or severe pain and scars.[4] More recently, devices that combine both wavelengths have been developed with good safety and efficacy.[14]

Laser therapy should not be used over tattoos, scars, or hernias. It is contraindicated in patients who are pregnant, lactating or have metal implants.

Radiofrequency

Radiofrequency (RF) devices are used to reduce adipose tissue and tighten the overlying skin (*Figure 5*). RF devices can be either monopolar or bipolar. RF uses the inherent difference of each skin layer's resistance to electrical energy or impedance. When the oscillating electrical current produced by an RF device then interacts with tissue impedance, volumetric heating of the skin and subcutaneous tissue results.[15] The heat induces collagen contraction and remodelling, resulting in skin tightening. Thermal injury also induces apoptosis of adipocytes, resulting in the clinical endpoint of fat reduction.[6] Fat reduction depends on the setting and RF device used. RF involves contact cooling to prevent burns, scarring and pigmentary changes.

Similar to other energy devices used for body contouring, the number of treatment sessions required depends on several factors, including the settings and RF device used, the treatment area and the patient's aesthetic goals. Up to four treatments are performed per treatment area, scheduled approximately two weeks apart.

RF is most commonly associated with oedema, erythema and swelling that resolves days after an RF session. However, improper use, ranging from excessively slow handpiece movement to aggressive parameters, can result in burns and blisters.[4,6]

RF should not be used in patients with pacemakers or metal implants, or in patients who are pregnant or lactating.

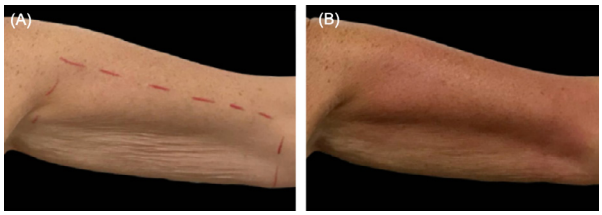

Figure 5. *(A) Photograph prior to treatment with monopolar radiofrequency treatment (B) Observable fat reduction and decreased skin laxity after four treatment sessions with monopolar radiofrequency. Adapted from https://btlaesthetics.com.au/for-providers/exilis-providers*

Ultrasound

Ultrasound devices for body contouring can be divided into lower energy devices, i.e., micro-focused ultrasound (MFU), and higher energy devices, i.e., high-intensity focused ultrasound (HIFU).

MFU is indicated for use in patients with mild-to-moderate skin and soft tissue laxity. MFU uses ultrasound waves to target the reticular dermis and sub-dermis to produce small, discrete thermal coagulation points. This causes collagen fibres in these areas to denature, stimulating tissue contraction, tissue remodelling and de novo collagen production, resulting in skin tightening.[16] MFU is most frequently used to target the superficial musculoaponeurotic system (SMAS) for more natural and durable skin tightening (*Figure 6*). MFU uses lower ultrasound energy than HIFU, and heats tissue to a focal depth of only 1.5–4.5 mm.[17]

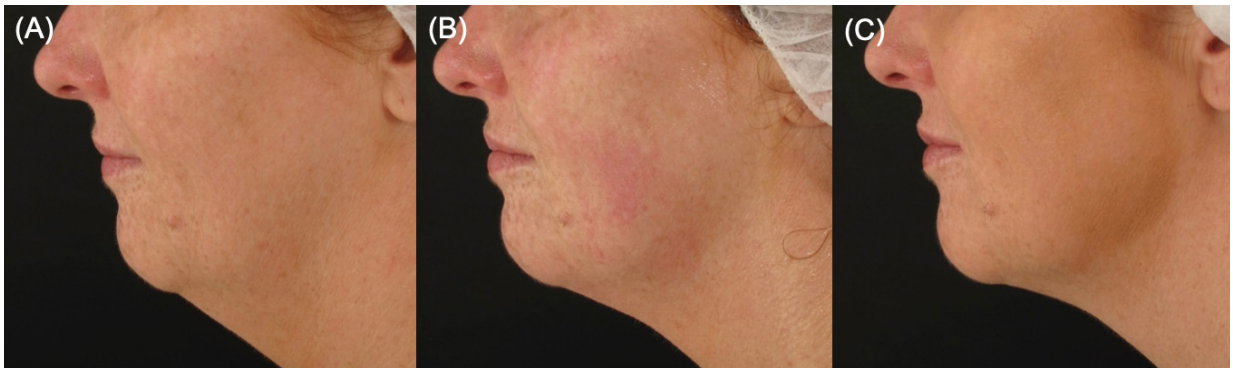

Figure 6. *(A) Photograph prior to treatment with microfocused ultrasound (MFU) (B) Immediately after treatment session (C) Three months after treatment, demonstrating skin tightening and submental fat reduction. Adapted from https://medicinetoday.com.au/mt/2023/september/regular-series/nonsurgical-body-contouring-energy-devices*

If MFU is used in conjunction with high-resolution ultrasound imaging (MFU-V), the practising clinician can visualise tissues up to a depth of 8 mm.[16]

MFU and MFU-V are associated with discomfort during treatment, transient erythema, and oedema.[16] To minimise discomfort, topical anaesthetic or pre-treatment simple analgesia can be administered. Rarely, MFU may be associated with dysasthesia, bruising, mandibular burns, striations, and contact dermatitis.[18]

HIFU uses higher ultrasound energies to a greater depth (1.1–18 cm) to target adipose tissue directly and achieve non-surgical body contouring.[16] Besides the thermocoagulation seen in MFU, HIFU devices use a mechanical process to cause adipocyte apoptosis. High-intensity acoustic pulses delivered by HIFU devices cause tissue cavitation, high shear stress and subsequent cell death.[19] HIFU for body contouring requires multiple treatments 3–4 weeks apart, with gradual improvement demonstrated over 2–6 months.[2]

The adverse events associated with HIFU are similar to those reported for MFU. HIFU generally causes more procedural discomfort than MFU. HIFU has rarely been associated with skin surface irregularities following treatment and nerve symptoms, particularly with operator error.[4]

HIFU and MFU should not be used in patients with severe skin laxity, metal implants, or in pregnant or lactating women.

High-intensity focused electromagnetic technology

High-intensity focused electromagnetic (HIFEM) or electromagnetic muscle stimulation (EMMS) technology is the most recent addition to non-invasive body contouring. HIFEM/EMMS technology uses alternating magnetic fields to induce electrical currents in muscle tissue, triggering motor neurons and resulting in muscle contractions.[6] Magnetic resonance imaging has demonstrated that HIFEM/EMMS results in muscle growth and facilitates localised fat reduction and reduction of abdominal diastasis.[20] The exact physiological mechanism explaining localised fat reduction remains controversial.

The typical target areas for HIFEM/EMMS are the buttocks and abdomen (*Figure 7*), and the pads can be either directly applied onto the abdomen or incorporated into a seat to target the buttocks and perineum. Using the latter application method, HIFEM/EMMS has been demonstrated to benefit women with pelvic floor dysfunction.[21] Other emerging uses of HIFEM/EMMS include application to the biceps, triceps and gastrocnemius muscles.[22]

Treatment with HIFEM/EMMS involves at least four 30-minute sessions spaced 2–3 days apart. Following this, one treatment every 3–6 months is recommended to maintain results. During the session, the strength of contractions can be adjusted from 0 to 100% depending on patient tolerance. Although most patients can tolerate stimulation intensities above 90% without much discomfort, some patients may experience painful muscle contractions or brief electric shocks.[2] HIFEM/EMMS has rarely been associated with third-degree burns, attributable in most cases to operator error.[4] Very rarely, ovarian symptoms have been reported in association with HIFEM/EMMS use.[4]

HIFEM/EMMS should not be used in patients with a high BMI, metal, or electronic implants, and in pregnant or lactating women.

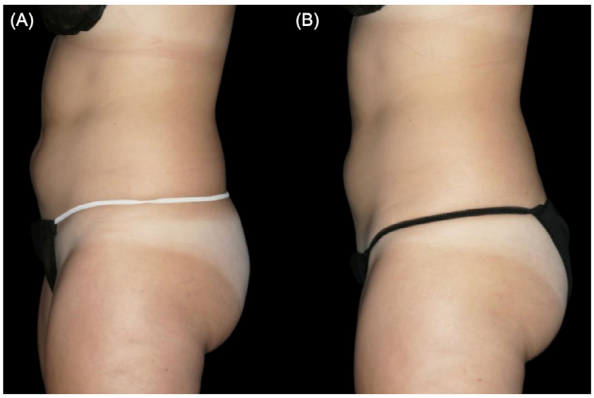

Figure 7. *(A) Photograph prior to treatment with high-intensity focused electromagnetic (HIFEM)/ electromagnetic muscle stimulation (EMMS) technology (B) 30 days after four HIFEM/EMMS treatment sessions. Adapted from Murgia RD et al.*[23]

Chemical lipolysis

Chemical lipolysis using injectable deoxycholic acid (DCA) is a minimally invasive body contouring method, although only TGA-approved for submental fat (SMF) reduction. DCA is an endogenous bile acid that emulsifies dietary fats in the gastrointestinal system. When injected in subcutaneous adipose tissue, DCA causes membrane rupture of adipocytes and subsequent irreversible lysis of adipose tissue. This cell lysis causes an inflammatory response, and after 28 days, fibroblast recruitment and induction of neocollagenesis follow.[24] DCA has a low affinity for protein-rich tissues such as muscle tissue, blood vessels and skin, and a higher affinity for adipose tissue, which is protein-poor.[24]

DCA is typically administered at 1–2 mg/cm^2 with a 30-gauge needle (or smaller) at multiple sites within the area of desired fat reduction. DCA is injected into the preplatysmal fat, superficial to the platysma muscle, and is injected away from key structures: the marginal mandibular branch of the facial nerve, arteries, and salivary glands. An adequate depth is required to prevent intradermal injection complications, including skin necrosis. Aspiration should precede every injection to avoid intravascular injection of DCA. A maximum of six sessions can be performed, with a minimum interval of one month between sessions.[25]

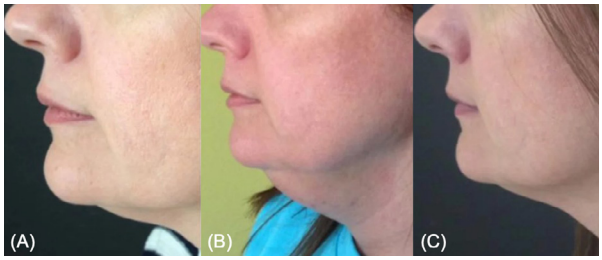

Figure 8. *(A) Photograph prior to treatment with chemical lipolysis using deoxycholic acid (DCA) injections (B) Transient swelling and oedema 24 hours after DCA injections to submental fat (C) Post-treatment photograph. Adapted from https://www.healthline.com/health/kybellaswelling#pictures*

The common adverse events associated with DCA injection into SMF include transient oedema, bruising, pain, numbness, erythema, induration and pruritus, all of which have been shown to resolve within the one-month interval between sessions (*Figure* 8).[26] These adverse events can be managed using topical and injectable anaesthetics, oral analgesics, and ice packs before and after the injection.[25,27]

Less common adverse events include damage to the surrounding structures (marginal mandibular nerve, lymph nodes, salivary glands and muscles), dysphagia, localised alopecia and skin necrosis.[25,28] Rarely, sequelae of permanent scars,[29] neutrophilic dermatosis[30] and submental abscess,[31] have been reported in the literature. Patients should be adequately informed about the potential risks associated with DCA before therapy begins.

Chemical lipolysis with DCA should not be used in pregnant or lactating patients, patients aged >65 or <18 years, and those with bleeding diathesis, coagulation disorders, or those with antiplatelets/anticoagulants. Clinicians should not inject in sites where beard alopecia would be unacceptable for a male patient.

There are a number of off-label applications for DCA, including use in anterior and posterior periaxillary fat, lower abdominal subcutaneous fat, jowls, paradoxical adipose hyperplasia, and lipomas.[32] Whilst some of these treatment areas may be ideal due to the lack of surrounding major nervous or vascular structures, the evidence recommending off-label DCA use remains weak to very weak.[32]

Conclusion

Non-surgical body contouring encompasses many options to achieve targeted fat reduction, including energy devices and chemical lipolysis. Its increasing popularity is due to its proven efficacy with a side effect profile that is preferable to surgical liposuction. However, clinicians and therapists should ensure that patients are adequately counselled regarding potential adverse events such as burns and scarring, and establish realistic patient expectations.

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High-speed Low-pain Micro-focused Ultrasound Tightening of the Lower Face and Neck*

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** This research paper is based on Ultraformer 3. From 2024, an updated version, Ultraformer-MPT, will become available.*

AIM: To investigate the safety, efficacy, and patient satisfaction of Ultraformer 3, a micro-focused ultrasound (MFU) device for tightening the skin of the lower face and neck.

METHODS: Twenty consecutive patients were selected based on specific criteria and underwent the Ultraformer 3 treatment. Their satisfaction and the treatment's efficacy were prospectively evaluated through standardized photography, patient surveys, and assessments by blinded dermatologists.

RESULTS: Most patients observed immediate skin tightening post-treatment, and a high satisfaction rate was reported by 75% of patients at follow-up (4-26 weeks). The procedure was well-tolerated, requiring only topical anesthesia and occasional nitrous oxide supplementation. Transient post-treatment erythema was common but there were no long-term adverse events.

SUMMARY: The Ultraformer 3 device is an effective, safe, and well-tolerated method for non-surgical skin tightening of the lower face and neck, with a high patient satisfaction rate.

KEYWORDS: Ultraformer 3, micro-focused ultrasound, skin tightening

Lim A, Mulcahy A, Patel A, Lowe P, Shumack S. High-speed Low-pain Micro-focused Ultrasound Tightening of the Lower Face and Neck. Opin Prog Cosmet Dermatol 2023;3(2):41–46.

Introduction

There is a strong demand for non-surgical tightening procedures, especially to the jowl and neck areas, for a more youthful mandibular and neck contour (jawline). Popular procedures such as filler and botulinum toxin injections mainly target the face, leaving the jowl and neck areas increasingly lagging with time. Non-surgical jowl and neck lifting procedures include skin resurfacing and various skin heating devices such as infrared, radiofrequency and micro-focused ultrasound (MFU).[1–4] Ablative resurfacing can tighten the skin but is primarily limited by the recovery time and potential complications such as pigmentary alteration and scarring. In contrast, non-invasive skin tightening devices are limited by subtle and inconsistent results, long treatment times, and significant procedural discomfort.[5] In 2016, the Australian Therapeutic Goods and Services (TGA) approved a new high-speed, low-pain MFU device (Ultraformer 3) for skin tightening. This study, conducted in 2016, evaluates the safety, efficacy, and patient satisfaction rate of Ultraformer 3 on lower face and neck laxity.

Mechanism of action of Ultraformer 3

MFU visibly tightened skin laxity in more than 80% of cases.[6–8] MFU targets the superficial muscular aponeurotic system (facelifting plane) for more natural

and durable skin tightening. The delivery of the MFU is not associated with any epidermal injury and, therefore, does not require any recovery or downtime. The focused and precise energy delivery is associated with significantly fewer side effects such as burns, blisters, and diffuse heating with collateral damage to adjacent epidermis or adipose tissue.

The Ultraformer 3 has a patented ultrasound focussing and delivery method that precisely targets tissue at adjustable depths of 4.5 mm, 3 mm, and 1.5 mm depending on the transducer cartridge selected, with corresponding frequencies of 4 MHz, 7 MHz, and 7 MHz, respectively. According to ultrasound physics, the higher frequency transducer cartridge corresponds to a more superficial focal depth. The Ultraformer 3 uses a proprietary mechanism enabling targeting a depth of 1.5 mm without exceeding 7 MHz compared with conventional non-Ultraformer technology. The thermal injury zone (TIZ) is spaced between 1 and 2 mm apart, and the energy can vary from 0.1 to 1.5 J. The pulse duration for the 4.5 mm cartridge ranges from 22–33 ms (0.1–1.5 J), while the pulse duration for the 3mm cartridge ranges from 43–65 ms (0.1–1.5 J). The relatively low pulse duration combined with adjustable energy allows precise and focused energy delivery without excessive collateral damage beyond the TIZ. The patented technology also enables faster treatment times with less procedural discomfort.

The objective of this study is to prospectively evaluate the efficacy and safety of the latest MIFU (Ultraformer 3) for mandibular and neck contouring in patients with age-related laxity. We also undertook a patient satisfaction survey on the Ultraformer 3 procedure.

Methods

All twenty enrolled patients satisfied the inclusion/exclusion criteria: age ≥40 years, no previous skin tightening treatment in the last 12 months, and no neck or lower face botulinum or filler injections during the prior six months and the follow-up period. Standardised face and neck photography was taken at baseline, immediately post-procedure, and subsequent follow-up at four weeks or more post-procedure. A standardised survey was performed at a subsequent post-treatment follow-up visit (4–20 weeks post-procedure) to assess patient satisfaction. Procedural efficacy was rated by two blinded dermatologists examining baseline and post-procedural photos.

Two trained registered nurses administered the skin tightening treatment using the Ultraformer 3 (Classys, Korea). All patients were pre-treated for 60 minutes with compound anaesthetic to the lower face and neck, intra-operative chilled air cooling (Cryojet), and the additional option of using inhaled nitrous oxide if required. The treatment areas were: (A) lower face and (B) upper neck: submental and submandibular regions (avoiding thyroid). The method of treatment is as follows: (A) lower face: two passes – two columns down and two columns across – first pass is parallel to the jawline and second pass is perpendicular (90°) to the jawline, and (B) upper neck: two passes parallel to the mandibular jawline (bilateral) and submental region.

Results

A total of 19 females and 1 male, aged 49–76 years (mean: 58.5 years) took part in this study. Almost all the patients commented on some degree of skin contraction and facial and neck contour improvement immediately after the procedure. At follow-up (4–26 weeks), 75% of patients continued to report a high degree of satisfaction. A total of 95% of patients found the procedure tolerable, requiring only topical anaesthesia and chilled air (Cryojet) for pain control during treatment. None of the patients required oral or injectable anaesthesia, and only one-third of patients requested additional inhaled nitrous oxide, which was freely offered throughout the procedure. A total of 85% of patients would consider having the Ultraformer 3 again in the future, with 75% reporting they would recommend the procedure to a friend. *Table 1* summarises the results from the patient satisfaction survey.

Two blinded dermatologists studied a series of participant images: baseline images, immediate post-procedure images, and final follow-up images from 4 to 26 weeks post-procedure (*Figures* 1–5). On average, the two blinded dermatologists (D1, D2) were able to identify initial improvement immediately after treatment in 72.5% of cases (data not presented). The two blinded dermatologists correctly identified the final follow-up images in 72.5% of cases (mean post-procedure follow-up: 12.9 weeks, range: 4–26 weeks). Post-treatment, the mean aggregate tightening score was 1.63 on the rating spectrum of mild tightening (score = 1) to moderate tightening (score = 2). One patient markedly improved, scoring 3 from both assessors (*Figure* 4). The blinded dermatologists' survey results are summarised in *Table* 2.

No long-term adverse events were noted. Mild to moderate transient erythema was commonly seen post-procedure, lasting approximately 30 minutes. One patient on fish oil developed mild bruising that resolved fully after a few days. There were two transient but notable post-treatment effects: one patient had transient mild linear erythematous plaques for 24 hours after treatment, and another patient had a subtle asymmetry of smile for a few days after treatment, which fully resolved after one week.

Table 1. *Ultraformer patient satisfaction survey.*

	Strongly disagree (-2)	**Disagree (-1)**	**Uncertain (0)**	**Agree (1)**	**Strongly agree (2)**	**Weighted mean (-2 to 2)**	**Median score**
Q1. **I am satisfied with the outcome of the procedure**							
	0 respondent	1 respondent	4 respondents	7 respondents	8 respondents	1.1	Strongly agree
Q2. **I would consider having the procedure again in the future**							
	0 respondent	0 respondent	3 respondents	7 respondents	10 respondents	1.35	Strongly agree
Q3. **I would recommend this procedure to a friend**							
	0 respondent	0 respondent	5 respondents	6 respondents	9 respondents	1.2	Strongly agree
Q4. **I find the comfort level of the procedure to be:**							
	'very uncomfortable' 1 respondent	*'uncomfortable but bearable'* 7 respondents	*slightly uncomfortable'* 7 respondents	*'comfortable'* 4 respondents	*'very comfortable'* 1 respondent	-0.15	Slightly uncomfortable but bearable
Q5. **I find the duration of treatment:**							
	'much longer than expected' 0 respondent	*'longer than expected'* 1 respondent	*'about right'* 14 respondents	*'shorter than expected'* 3 respondents	*'much shorter than expected'* 2 respondents	0.3	About right

Table 2. *Blinded physician (dermatologists D1 and D2) survey.*

Case	Age (years)	Sex	Profile	Post (weeks)	D1*	D1** Rating	D2*	D2** Rating
1	49	F	L	22	Yes	1	Yes	2
2	67	F	L	4	Yes	1	No	--
3	58	F	L	4	Yes	2	Yes	3
4	57	F	L	13	Yes	0	No	--
5	59	F	R	26	Yes	2	Yes	3
6	49	F	L	22	No	--	No	--
7	61	F	R	4	Yes	1	Yes	1
8	67	M	L	8	No	--	Yes	0
9	63	F	R	17	No	--	No	--
10	69	F	L	21	Yes	1	Yes	2
11	50	F	front	13	Yes	2	Yes	3
12	56	F	L	26	No	--	Yes	2
13	76	F	Front	4	Yes	1	No	--
14	53	F	L	12	No	--	Yes	1
15	52	F	L	16	Yes	1	No	--
16	63	F	L	7	Yes	2	Yes	2
17	68	F	L	8	Yes	1	Yes	1
18	56	F	L	10	Yes	1	Yes	2
19	54	F	L	9	Yes	1	Yes	2
20	43	F	L	12	Yes	3	Yes	3
	mean = 58.5yo (range 49-76yo)	19F	L 15/20	mean = 12.9w (range 4-26w)	15/20 (75%)	20 (/15) =1.33	14/20 (70%)	27 (14) =1.93

* **correctly identifies the baseline and post-treatment images. D1, D2 mean = 72.5%**

** **Rating scale (0, 1, 2, 3). D1, D2 mean = 1.63**

- **0 = no change**
- **1 = mild tightening**
- **2 = moderate tightening**
- **3 = marked tightening**

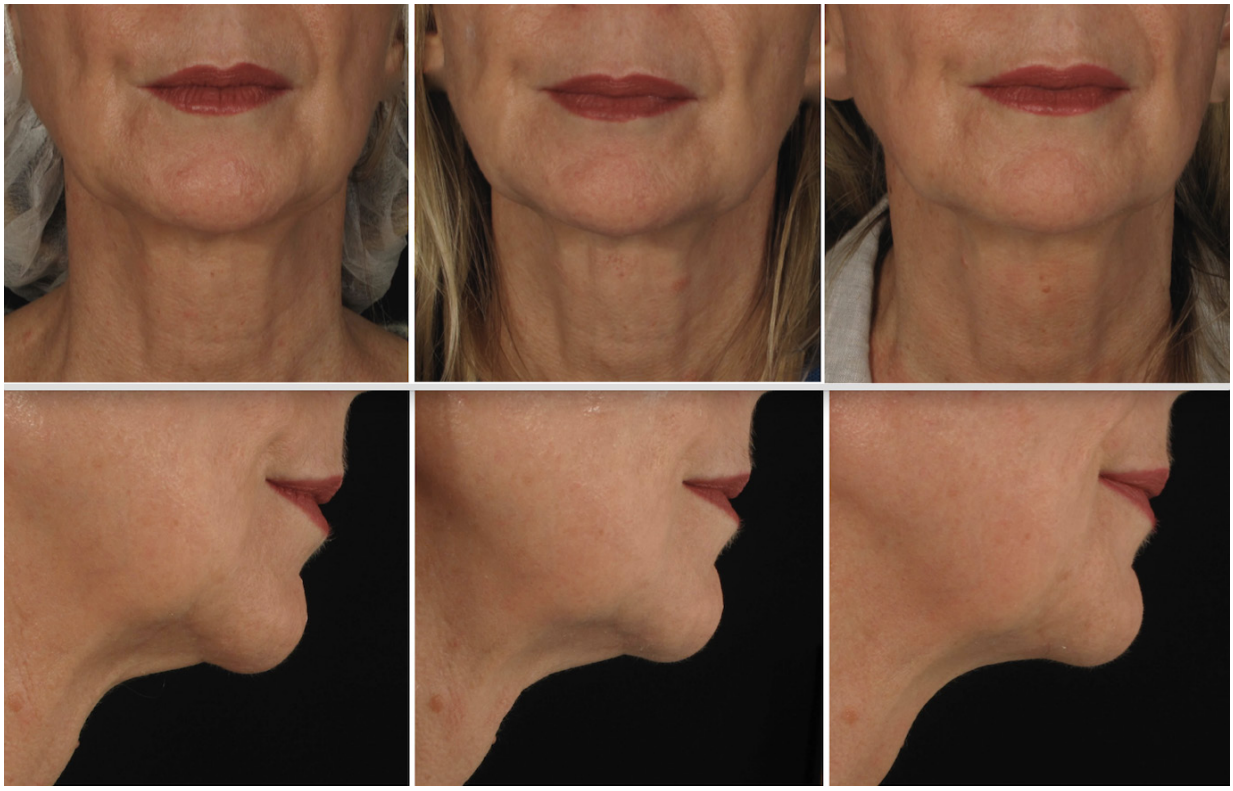

Figure 1. *59-year-old female at baseline and 1 month and 2 months post-procedure (left to right).*

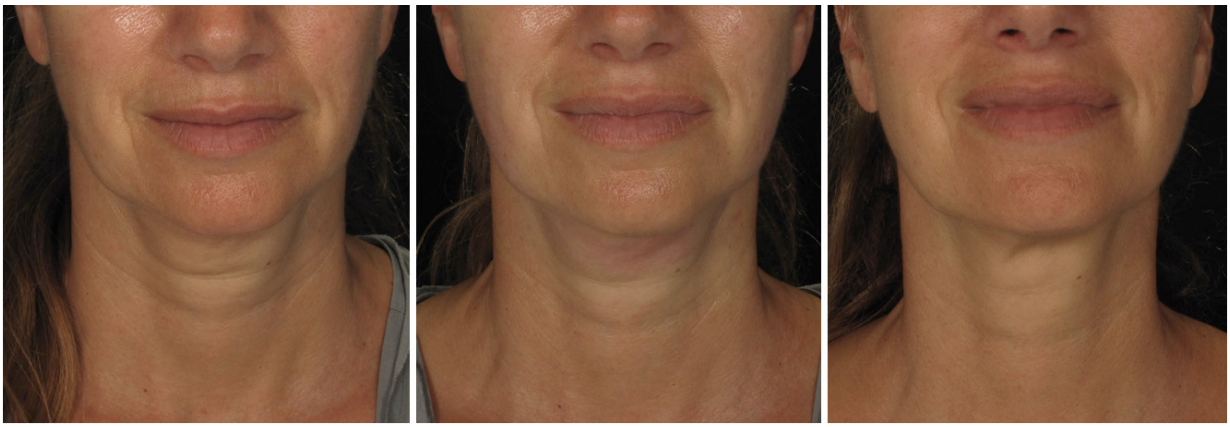

Figure 2. *50-year-old female at baseline, immediately post, and 3 months post-procedure (left to right).*

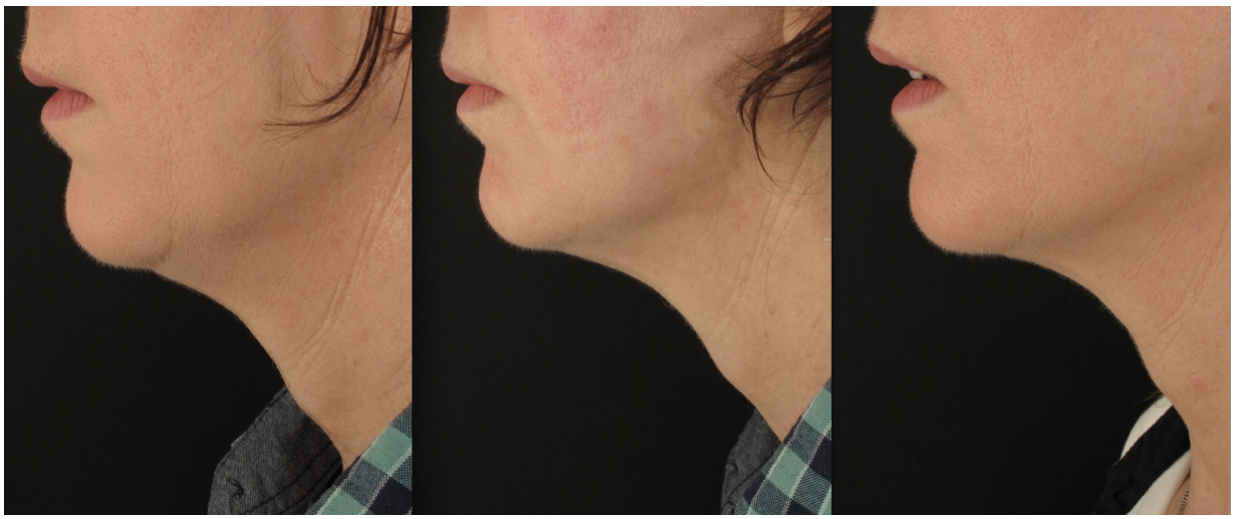

Figure 3. *50-year-old female at baseline, immediately post, and 3-months post-procedure (left to right).*

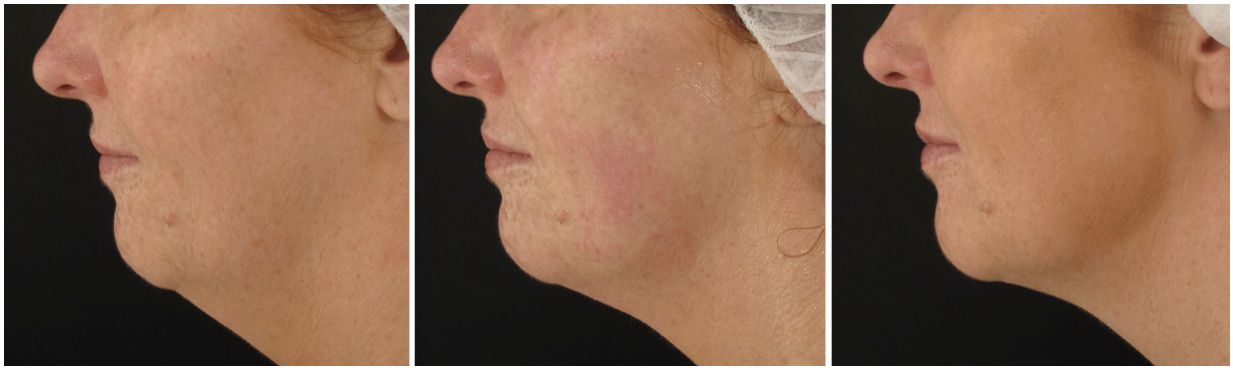

Figure 4. *43-year-old female at baseline, immediately post, and 3-months post-procedure (left to right).*

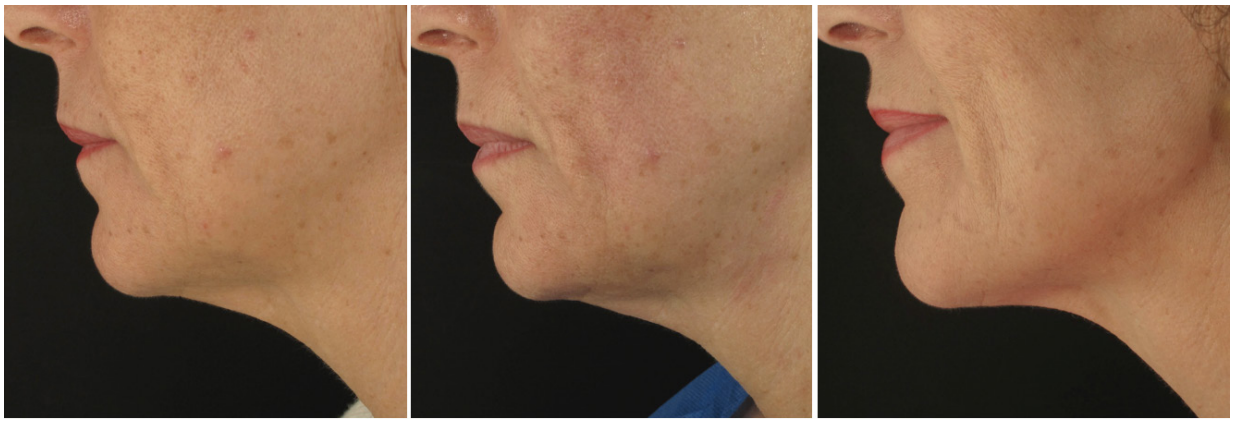

Figure 5. *A 50-year-old female at baseline, immediately post- and 1-month post-procedure (left to right), highlighting gradual neck and jawline tightening, even though there was no observable change immediately post-procedure (centre image).*

Discussion

MFU has been used for skin tightening in facial and non-facial sites.[5,6,9,10] Upper face tightening for brow and eyelid laxity is more straightforward to measure objectively using fixed landmarks such as pupils and eyebrows. It has been subjected to studies with various skin tightening procedures, including MIFU.[6] The jowl and neck areas are more challenging to measure without a consistent objective grading scale or identifiable landmarks. Studies must rely on photographic changes and subjective patient self-assessment. We elected to study jowl and neck tightening because this area is not easily treatable by other non-invasive techniques such as cosmetic injectables and non-MIFU skin tightening procedures. Therefore, the ageing jowl and neck are of great concern to all cosmetic patients, with progressive lagging in these areas relative to the mid-to-upper face, resulting in strong patient demand in our practice for jowl and neck tightening procedures.

The limitations of skin tightening devices include inconsistent results, the need for multiple treatments, procedural discomfort, durability of results, and costs.[5] Patient satisfaction rate for skin tightening procedures ranges from 31% for monopolar radiofrequency to 80% for MFU.[8,11] In our study, 75% of patients are satisfied with the treatment outcome. This high patient satisfaction rate partly translates to a desire for repeat procedures (85%) and referring the procedure to others (75%). Procedural tolerability is another important patient consideration for return visits. In this regard, Ultraformer 3 is notably different from non-Ultraformer MFU in that it is well tolerated, with 95% of patients reporting the experience as either 'very comfortable', 'comfortable,' or 'slightly uncomfortable but bearable'. The average treatment time was less than 20 minutes, and 70% of patients rated the treatment time as 'about right,' while 25% rated the treatment time as 'shorter' or 'much shorter' than expected. Pre-Ultraformer devices tend to be associated with significant discomfort, requiring oral anxiolytics and oral/intramuscular narcotic analgesics. They are a substantial barrier to the uptake of pre-Ultraformer MFU treatments.[4]

The safety of MFU is well established, with a very low incidence of reported adverse events. Overheating of the skin with inappropriately high energy settings can result in blisters and reticulate scars. Associated pain usually prevents this from happening, and there are no reports of MFU-related scarring.[4] In our study,

two transient post-treatment effects deserve further comment. Two patients experienced transient mild linear erythematous plaques lasting less than 24 hours. There has also been a report of these lasting for days with a subsequent full resolution with topical steroids. When linear plaques become noticeable during treatment, a decrease in fluence is recommended. Another patient had transient thermal neuropraxia from inadvertent MFU targeting of the left marginal mandibular nerve, resulting in subtle transient lip weakness. The temporal and marginal mandibular nerves are vulnerable to MFU effects at the temple and lateral chin, respectively, and are 'caution areas' during MFU therapy. Transient sensory thermal neuropraxia presenting as tingling and numbness can also uncommonly occur.

Blinded physician assessment of the before and after photos show a noticeable change post-procedure (at 4–26 weeks; mean: 12.9 weeks). Although there was an initial non-response rate of up to 27.5%, based on blinded two-dimensional photo-ratings, these initial 'non-responders' may show a noticeable tightening response later (*Figure* 5), consistent with delayed collagen remodelling effects. Initial post-procedural improvement is correlated with subsequent improvement in 71.4% of cases (data not presented). The durability of results has not been well studied, and there is no data on the effects of regular MFU treatment on skin ageing. Although MFU is generally considered a short-term single-session treatment, others have anecdotally observed better results with up to three treatment sessions at 4–6-month intervals, followed by annual maintenance sessions (personal communication, Korea). We hypothesise that regular maintenance MFU treatments may slow down skin laxity and ageing. We will examine this with longitudinal data on the effect of regular MFU on skin laxity over time.

Our commercial experience with Ultraformer 3 has been very favourable. A market gap exists for a non-surgical lower face and neck tightening procedure that delivers consistent results without being too uncomfortable or protracted. Patients are often very receptive to procedural recommendations for jowls and facial sagging. They will be prepared to have repeat treatments and recommend the procedure to others if it meets their efficacy and tolerability expectations. From a practitioner's perspective, the Ultraformer 3 is easy to handle and drive. The procedure can be performed by doctors, nurses, dermal therapists, and other trained allied health practitioners. Ultraformer 3 can be delegated to suitably trained staff because of its dependable, non-laser technology and low incidence of adverse events. Further, its affordability and low running cost make it an attractive business and commercial proposition, which adds value for the patient.

The limitations of this study are the small sample size, older age group (mean: 58.5 years), preponderance of females (all but one), relatively short follow-up period of up to 6 months, and potential investigator bias from using an industry-sponsored device (Cryomed Australia).

Conclusion

MFU therapy with the Ultraformer 3 is a safe, effective, high-speed, low-pain procedure that meets a clear need among patients seeking skin tightening. The procedure induces noticeable skin tightening post-procedure with a 75% patient satisfaction rate that is independently verifiable. Patients tolerated the procedure well with only topical anaesthesia and chilled air cooling. The favourable procedural experience and results convert to an 85% reported desire for repeat procedures and a 75% referral rate to others.

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Clinical Comparison of Results Using Fraxel 1927™ Compared With the Novel Frax 1940™ in the Treatment of Facial Solar Dyschromia

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OUTLINE: The study compares Frax 1940™ against the Fraxel 1927™ for treating solar dyschromia, based on a review of 25 patient files (24 females and one male). Patients with Fitzpatrick skin type III or greater, melasma, or a high proportion of seborrheic keratoses were excluded. The participants were treated either with the Frax 1940™ or Fraxel 1927™, and areas of dark solar lentigo were pre-treated with Picoway 532nm. Post-treatment assessments included digital clinical photography and evaluations using the Global Aesthetic Improvement Score (GAIS) and a 5-point Likert scale for patient satisfaction. Both treatment modalities were well-tolerated, with similar recovery profiles and no adverse events. Dermatologist assessors gave an average GAIS score of 3.28 (range 2-5) for Frax and 3.51 (range 2-5) for Fraxel at one month, signifying slightly higher than "improved" for both systems. Average Likert scores were 3.93 (range 3-5) for Frax and 3.55 (range 2-5) for Fraxel, signifying a greater than moderately satisfied result for both systems but marginally higher for the Frax. The study suggests that a single treatment of either Frax 1940™ or Fraxel 1927™ resulted in equivalent moderate improvements in facial solar dyschromia.

KEYWORDS: solar dyschromia, Fraxel 1927™, Frax 1940™

Bekhor P, Lim D, Richards S, Robertson S, Webb A, Pangbourne L. Clinical Comparison of Results Using Fraxel 1927™ Compared With the Novel Frax 1940™ in the Treatment of Facial Solar Dyschromia. Opin Prog Cosmet Dermatol 2023;3(2):47–51.

Introduction

Solar dyschromia results from chronic sun exposure, presenting as irregular pigmentation, solar lentigo and background skin dullness as part of the spectrum of photoaging. Non-ablative fractional 1927 nm laser is a well-established and effective treatment for solar dyschromia. In our practices, it has been the standard of care for this condition.[1]

The 1927™ wavelength corresponds to an absorption peak in the mid-infrared range. Using 1927 nm at the appropriate fluences, the epidermis is mummified but remains a protective covering such that bleeding or serous exudation will not occur. The persistence of a nonviable but protective epidermis dramatically improves the recovery quality post-treatment compared with fully ablative fractional lasers. The therapeutic effect in the 1927™ range is, in simple terms, halfway between full ablation as seen with CO2 lasers and fractional fully non-ablative as occurs with the use of 1550nm fractional non-ablative.[2]

Candela has produced a handpiece that delivers 1940 nm – Frax 1940™. The novel 1940 nm wavelength is close to 1927 nm and hits the same mid-infrared water absorption peak. It has a similar water absorption coefficient (124 cm^{-1} compared with 131 cm^{-1} at 1927 nm). Therefore, one may expect a similar therapeutic effect and recovery profile.2 Our histology confirms apoptotic keratinocytes in the epidermis with mild oedema in the papillary dermis to a depth of 200 microns (*Figure 1*).

The Fraxel 1927™ is a fractional thulium. The Frax 1940™ handpiece is an advanced fractional diode laser system that delivers 1940nm wavelength and can be used as part of the Candela Nordlys Platform or on a more specialised

Frax Pro platform. Both lasers deliver their fractional beams via a moving, random-firing handpiece.

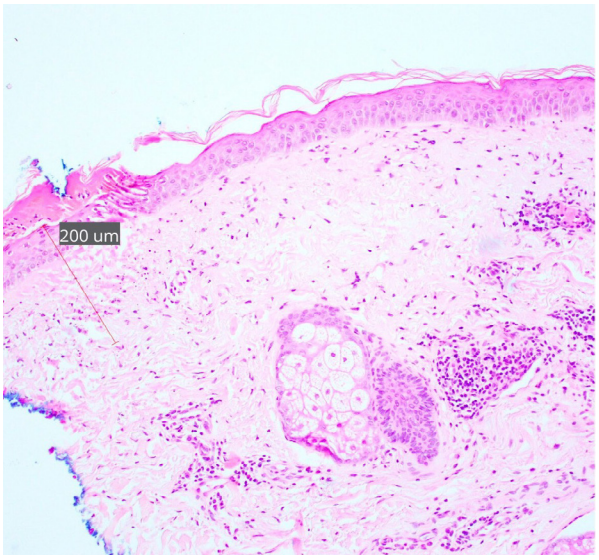

Figure 1. *Histology taken from facial skin shows the penetration depth for the Frax Pro 1940™ non-ablative laser at 20 mj, 50% coverage. Note apoptotic keratinocytes in the epidermis with mild oedema in the papillary dermis to a depth of 200 microns.*

Aim

To compare the performance of the Frax 1940™ handpiece against the Fraxel 1927™ standard of care for solar dyschromia.

Materials and methods

Patients

The files of twenty-four female patients and one male patient with solar dyschromia were reviewed. Our standard practice policies exclude patients with Fitzpatrick skin type (FST) III or above, melasma, or a high proportion of seborrheic keratoses. We do not treat pregnant patients because of the risk of inducing melasma.

Treatments

Treatment was delivered with either Frax 1940™ or Fraxel 1927™. All patients received prophylactic Valtrex 500 mg bd and Keflex 250 mg qid, starting the morning before treatment and continuing for five days as is standard at both practice sites.

Reviews were carried out for fifteen consecutive patients treated with Fraxel 1927™ treatment and ten consecutive patients treated with Frax 1940™ in total.

Any prominent areas of dark solar lentigo were treated with Picoway 532 nm 3 mm spot to achieve a soft grey endpoint just before the fractionated treatment at the same session, as is our standard protocol.

Topical anaesthetic gel was applied and left on the skin for 30–60 minutes. This was followed by six passes using the Frax 1940™ over the treatment area at 20 mj 50% density (maximum setting) for the Frax group and eight passes with the Fraxel 1927™ at Energy 10 to achieve 50% density for the Fraxel 1927 group, which is our standard Fraxel 1927 setting.

All patients received prophylactic Valtrex 500 mg bd and Keflex 500 mg qid or doxycycline 100 mg daily, beginning the morning before treatment and continuing for five days as is standard at both practice sites.

Blinded evaluation assessments

Digital clinical photography with standardised conditions was performed pre-treatment and at daily intervals up to five days post-treatment. Final photos were taken at one month post-treatment.

The treating dermatologists and two independent dermatologists completed a Global Aesthetic Improvement Score (GAIS) scale (1 = worse to 5 = Very much improved; *Table* 1) based on the initial photograph (before treatment) and a photograph one month after initial treatment. The photographs were presented as before and after but were otherwise blinded.

Patient assessments

Subjects reported their satisfaction and graded their overall cosmetic improvement at the one-month follow-up appointment using a 5-point Likert scale (1 = Not satisfied to 5 = Very satisfied; *Table* 1).

Table 1. *GAIS and Likert scales were used for blinded evaluation and patient assessments.*

GAIS (Global Assessment improvement score)	LIKERT SCALE
1 Worse	1 Not satisfied
2 No change	2 Minimally satisfied
3 Improved	3 Moderately satisfied
4 Much improved	4 Satisfied
5 Very much improved	5 Very satisfied

Results

All patients tolerated the treatment well, with no adverse events (*Figures* 2–5). All experienced erythema and mild oedema that resolved rapidly over one week to 10 days, similar to both systems (*Figures* 6 *and* 7).

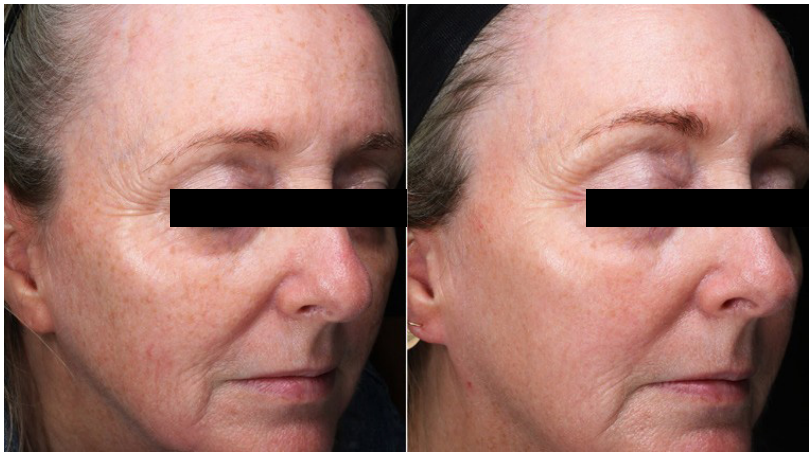

Figure 2. *Patient in Frax 1940™ group. Likert score: 5 (very satisfied); Average GAIS score: 4.25 (much improved).*

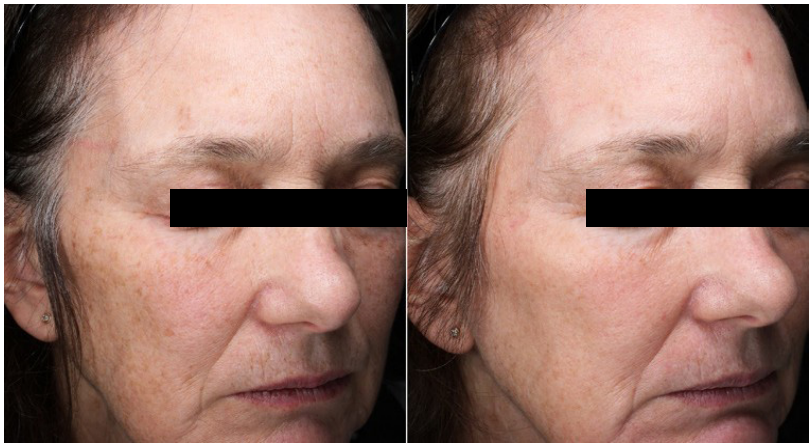

Figure 3. *Patient in Fraxel 1927™ group. Likert score: 5 (very satisfied); average GAIS score: 4 (much improved).*

Figure 4. *Patient in Fraxel 1927™ group. Likert score: 3 (moderately satisfied); average GAIS score: 3 (improved).*

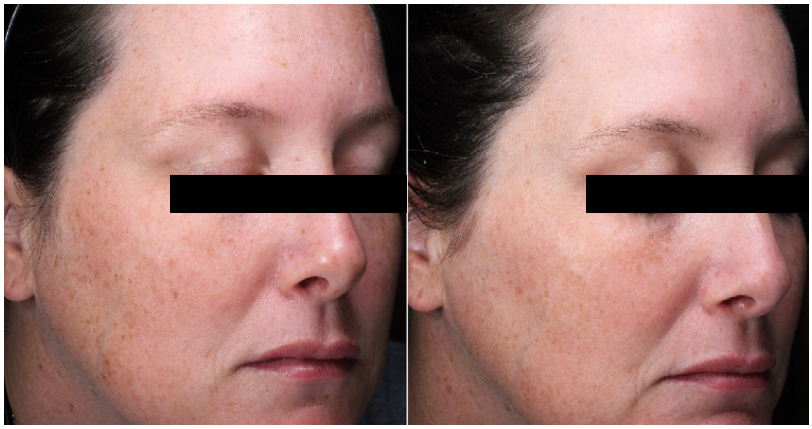

Figure 5. *Patient in Fraxel 1927™ group. Likert score: 3 (moderately satisfied); average GAIS score: 3.25 (improved).*

Table 2. *GAIS scores.*

		Assessor DL	Assessor SR	Assessor PB	Assessor SRo	GAIS All evaluators
Frax 1940™ Analysis Total 15	Worst	2	2	2	2	2
	Average	**3.07**	**3**	**3.33**	**3.73**	**3.28**
	Best	4	4	5	5	5
Fraxel 1927™ Analysis Total 10	Worst	2	2	3	3	2
	Average	**3.10**	**3.20**	**3.90**	**3.80**	**3.51**
	Best	4	4	5	5	5

Table 3. *Likert scores.*

			GAIS				LIKERT
Subject	Initials	System	Assessor DL	Assessor SR	Assessor PB	Assessor SRo	
1	BE	Fraxel	4	4	5	4	5
2	AH	Fraxel	3	3	3	3	3
3	HM	Fraxel	4	4	5	5	4
4	JW	Fraxel	4	3	4	5	4
5	JR	Fraxel	4	3	4	4	4.5
6	EA	Frax	4	4	4	5	5
7	AB	Frax	3	2	3	3	4
8	DB	Frax	4	4	4	5	5
9	LB	Frax	2	2	3	3	4
10	TB	Frax	3	3	4	4	3
11	JB	Frax	4	3	3	4	4
12	CH	Frax	3	3	3	4	3
13	SL	Frax	2	2	3	2	3
14	PM	Frax	4	3	3	4	5
15	KT	Frax	4	3	4	4	4
16	GL	Frax	2	3	3	3	5
17	JB	Frax	3	4	5	5	5
18	JW	Frax	2	2	2	2	3
19	MM	Frax	3	4	3	4	3
20	SH	Frax	3	3	3	4	3
21	CH	Fraxel	3	3	4	3	3
22	EW	Fraxel	3	4	4	4	4
23	HM2	Fraxel	2	3	3	3	3
24	KP	Fraxel	2	3	4	4	3
25	LB2	Fraxel	2	2	3	3	2

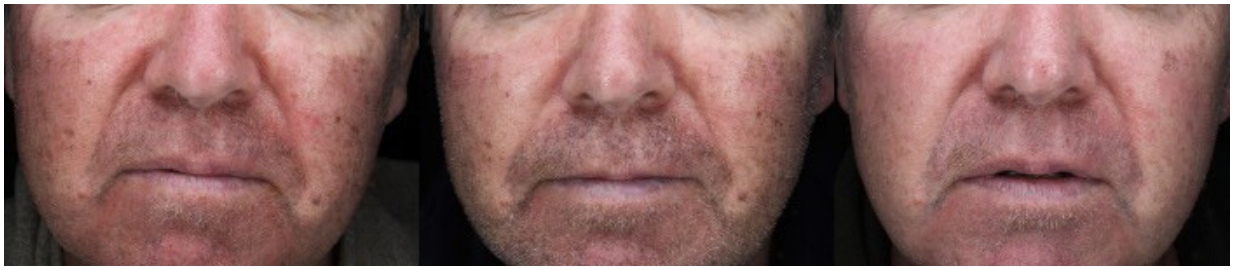

Figure 6. *Healing post-Frax 1940™ treatment.*

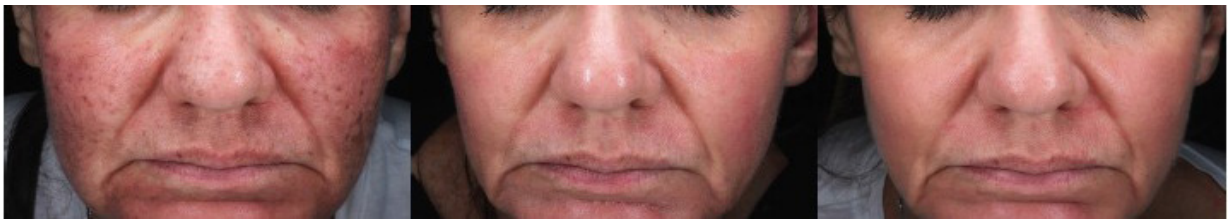

Figure 7. *Healing post-Fraxel 1927™ treatment.*

Dermatologist assessors gave an average GAIS score of 3.28 (range 2–5) for Frax and 3.51 (range 2–5) for Fraxel at one month, signifying slightly higher than "improved" for both systems (*Table* 2).

Average subject Likert scores were 3.93 (range 3–5) for Frax and 3.55 (range 2–5) for Fraxel, signifying a greater than moderately satisfied result for both systems but marginally higher for the Frax. No subject in the Frax arm self-assessed at less than "moderately satisfied." The lowest of the ten assessed Fraxel-treated patients was "minimally satisfied." No patient in either group assessed themselves as "not satisfied" (*Table* 3).

Discussion

This study confirms that single treatment Picoway 532 to spot lentigo treatment followed by either Fraxel 1927™ or Frax 1940™ produced an equivalent moderate improvement in solar dyschromia as assessed by both subject and dermatologist assessors. However, it is important to note that most centres offer more than one treatment, likely lifting the achievable improvement level. While the Picoway Laser was used in this study, equivalent results would be seen with any Q-Switched laser using 532 nm.

Limitations of the study include low patient numbers and the fact that more Fraxel than Frax treatments were assessed. It is also possible that the assessment was influenced by the benefit of the Picoway spot treatments, which were the same in both groups. However, an improvement in background dullness was evident in both groups, which cannot be related to the spot treatments.

The study confirmed that the Frax 1940™ treatment matched the outcome achieved with our Fraxel 1927™ standard of care.

Conclusion

This study suggests using the Frax 1940™ results in equivalent moderate improvement in facial solar dyschromia to that achieved by the Fraxel 1927™ standard of care. It is important to note that this study involved a single treatment. Many centres employ multiple treatments, which would likely lift the level of improvement.

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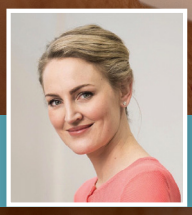
FOR HEALTHCARE PROFESSIONALS ONLY

Treating photoageing with ReTrieve® (Tretinoin 0.05%) in a changing environment



Not actual patient.

A case study and discussion from **Dr Cara McDonald**

Dr Cara McDonald is a highly trained specialist dermatologist and cosmetic injector. She is the co-director and principal dermatologist at Complete Skin Specialists. She holds a public hospital consultant position at St Vincent's Hospital Melbourne. She is a fellow of the Australasian College of Dermatologists.

Dr McDonald's special interests in her field include skin cancer prevention and treatment, acne scarring, laser, surgical and cosmetic dermatology. Her extensive knowledge and experience in cosmetic dermatology and anti-ageing treatments lets her combine her specialist knowledge of the skin and anatomy to offer medical treatment of the skin with a natural looking cosmetic outcome.

Advice and tips for treating photoageing with ReTrieve

There is a growing patient interest in treating photoageing[1] coupled with a changing regulatory landscape around cosmetic treatments. Here Dr McDonald offers a review of the evidence and practical use of ReTrieve to enhance clinician confidence in prescribing in light of this evolving environment.

> *In Australia where we have an outdoor lifestyle, we see photoageing in quite young people.[1] Topical retinoids such as tretinoin are a mainstay to treat photoageing[2] and ReTrieve is the only topical tretinoin approved for use in photoageing in Australia.[3,4] Tretinoin has a long and strong evidence base for its efficacy in the signs of photoageing.[2]*

Unmet needs in photoageing

A market research survey of over 1000 people conducted in 2022 revealed that over half of Australian adults across all age groups are concerned about sun damage to the skin. In fact, 9 out of 10 participants agreed that it is important to look after, treat and prevent sun damage.[1]

When it comes to what motivates people:[1]

- Women were more concerned about wrinkles
- Men were more concerned about rough or dry patches and solar keratoses
- Older patients (40+) were more concerned about solar keratoses, age spots or liver spots, melasma and lentigines

> *We see signs of photoageing throughout the Australian population in both men and women. Often women express more concern about their skin type and their skin health, but men are also concerned about the signs of photoageing. They might not be as willing to voice their concerns as women, but evidence shows they are equally affected. While we know that patients want to improve their skin quality, they may not be aware that they have the signs of photoageing and early sun damage.[1]*

TOPICAL RETINOIDS ARE A MAINSTAY FOR MANAGING PHOTOAGEING[2]

The term retinoid covers the natural and synthetic forms of biologically active vitamin A.[5] When applied topically, retinoids promote keratinocyte proliferation and collagen synthesis as well as inhibiting collagen degradation and transepidermal water loss and metalloproteinase activity.[2] These activities are what make retinoids ideal ingredients to combat photoageing.

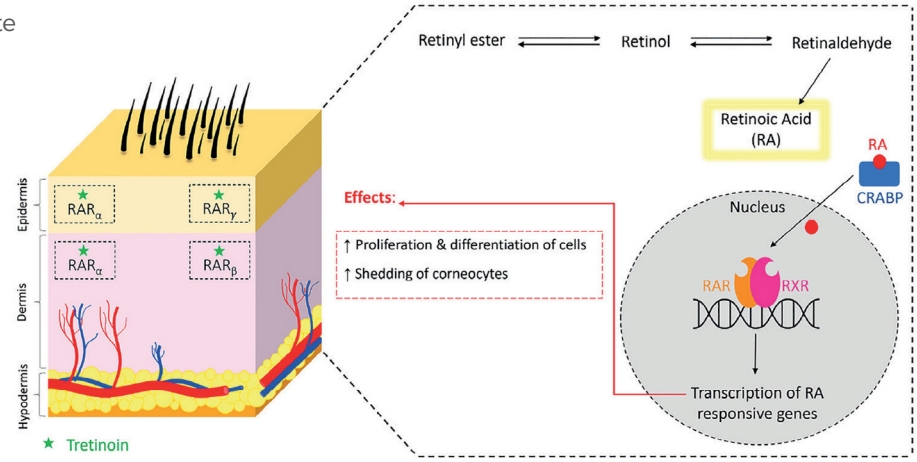
All-trans-retinoic acid is a synthetic form of retinoic acid also known as tretinoin.[5] **Tretinoin is considered the gold standard to treat photoageing as it is the most studied of the topical retinoids.**[2]

Tretinoin is the active ingredient in the prescription only cream **ReTrieve 0.05% – the only prescription tretinoin cream approved for photoageing in Australia.**[3,4]

ReTrieve offers an evidence-based, non-invasive, self-management (i.e. apply at home) option for the treatment of photoageing.[2,3]

How tretinoin works to treat photoageing

Retinoids bind to and activate retinoic acid receptors in the nucleus, inducing transcription of retinoic acid-responsive genes.



Adapted from Motamedi et al. 2022.[6]
CRABP=cytosolic retinoic acid-binding protein; RA=retinoic acid; RAR=retinoic acid receptor; RXR=retinoid X receptor.

The gold standard to treat photoageing[7,8]

A 2022 systematic review of 7 randomised, controlled clinical trials found 0.05% tretinoin provided:[8]

Smoother, clearer, firmer skin compared to baseline	Tretinoin reduced the clinical appearance of: • Fine and coarse wrinkling • Sallowness • Mottled hyperpigmentation • Lentigines
Molecular and histological improvement compared to baseline	Tretinoin improved histological signs of photoageing, including: • Increased epidermal thickness • Formation of new collagen fibres • Reduced epidermal melanin content
Visible improvements from 4 months to 2 years	Improvements in the visible signs of photodamage seen after 4 months of treatments and maintained for 2 years of treatment
Established safety and tolerability	Most common adverse effects were mild to moderate local site skin reactions such as: • Erythema • Itching • Dryness • Peeling • Burning/stinging

PRACTICAL TIPS FOR PRESCRIBING RETRIEVE

ReTrieve should be applied sparingly to affected areas once daily at night-time.[3] Treatment should be individualised according to tolerance and response, starting slowly. Recommended dose titration is:[3]

Wash the affected areas before application with mild soap-free cleanser and pat dry

NIGHT 1	NIGHT 2	NIGHT 3	NIGHT 4	NIGHT 5	NIGHT 6
					
Apply **Leave on for 5 mins** Wash off	Apply **Leave on for 10 mins** Wash off	Apply **Leave on for 30 mins** Wash off	Apply **Leave on for 1 hour** Wash off	Apply **Leave on for 1.5 hours** Wash off	Apply **Leave on for 2 hours** Wash off

If no redness or irritation is seen the day after the two hour application, then ReTrieve may be left on overnight and washed off the following morning. If there is redness or irritation, then adjust the schedule to alternate nights until the skin accommodates.[3]

> *What's really amazing about ReTrieve is the patient resources and information that are available. I find my patients love to be educated and they want information to help them understand the product, what benefits they're going to get and how to use it in the long term. I can also give my patients the authority and flexibility to manage their dosing regimen to suit their skin type. I like to make sure all my patients have written information which is readily available with ReTrieve.*

ReTrieve is contraindicated in pregnancy and women planning a pregnancy[3] – consider discussing this possibility with female patients of child-bearing age before commencing treatment.

Not actual patient.

FREQUENTLY ASKED QUESTIONS WITH DR CARA MCDONALD

Q. What are the side effects of ReTrieve?

A. *"It's really important to discuss side effects with your patient and assess their skin type to decide on the optimal dosing. Side effects with topical tretinoin are common in the early days such as redness and slight peeling, or sometimes a tight burning or even stinging feeling. I like to tell my patients that this is expected but not a serious side effect that will improve with time and can be overcome with the correct dosing. ReTrieve does increase susceptibility to sun damage so sun exposure must be minimised, and sun protection measures utilised (e.g., slip slop slap seek slide)".*[3]

Q. What adjunct skincare can/should be recommended to patients?

A. *"If my patients are really sensitive, I will use a plain moisturiser over the top of the product. But if their skin is tolerating it well, they can use this as their sole night-time cream. We want to avoid using other active ingredients on top of ReTrieve, so make sure that their skincare routine is otherwise fairly basic at night. In the morning, I'd recommend that patients use other actives such as niacinamide and antioxidants. But of course strict daily sun protection is a must because ReTrieve can make people more sensitive to the sun".*[3]

Q. What kind of follow-up and ongoing monitoring is needed?

A. *"When prescribing ReTrieve, I do like to make sure that my patients understand that this is a long term treatment for prevention and treatment of their photoageing, but it's still important that they see their GP or doctor regularly to have skin checks and ensure they don't have any abnormal lesions or other signs of sun damage that needs alternative treatment. And also I like to make sure patients know to come back if they're having troubles tolerating the ReTrieve. Some patients do have underlying conditions such as rosacea, irritant dermatitis, or even allergy. And so if my patients don't tolerate the treatment over time, then they should come back and have that assessed as well. Given the known teratogenicity with oral retinoids, I like to make sure that my patients understand that this treatment should be stopped if they are planning pregnancy or become pregnant*[3] *– although it is important to note that we have no evidence that topical application has the same risk. Lastly, it's important to manage their expectations, as improvements can take around 4 months to be visible".*[8]

Q. How long can ReTrieve be used for?

A. *"When I prescribe ReTrieve, it's really important that my patients understand what this means for the long term. So first and foremost, unless the patient is planning pregnancy, this should be considered a long-term treatment. I explain that if you're using ReTrieve and strict sun protection, you're really getting almost all the benefits you can for long term prevention and treatment of photoageing".*

Q. Can ReTrieve be used more than once?

A. *"I like to make sure that patients know that they can have a short break from treatment then restart, to let their skin recover, if they are getting significant side effects. Some people need to go slower than the recommended titration regimen. If patients have sensitive skin or are prone to irritation or dermatitis, I will advise them that they will still be able to tolerate ReTrieve in time, but they just need to go very slowly. It doesn't mean they need to stop; they just need to persist because they will usually overcome the side effects. And almost everybody will tolerate it if they build up that regime slowly with time".*

RETRIEVE CASE STUDY


Not actual patient.

Meet Justine*

Justine is 36 years old and presents with concerns about pigmentation on her face following her second pregnancy. Her friends have told her about 'prescription skin creams' that can help, so she has gone to her GP seeking treatment.

- Not planning any more children
- On the oral contraceptive pill
- Also concerned about visible signs of sun damage – mentions fine lines, wrinkles and rougher skin texture
- She enjoys spending time in the sun – but is aware of the damage it can cause her skin
- Hasn't come in before as her skin 'wasn't bad enough'

Goals and previous skincare:

- Goal is to remain looking youthful
- Uses a range of over-the-counter cosmeceutical products – but doesn't know much about them or their active ingredients
- Occasionally has a facial or other minor procedure
- Has tried anti-wrinkle injections but concerned about cost and ongoing effort required

Examination of her skin:

- Relatively minor photodamage – pigmentation, rough skin texture, fine wrinkling around mouth and eyes
- No serious pathology detected

ReTrieve is an appropriate treatment for Justine to treat the photodamage and help improve her skin quality and appearance

Justine is told about:

- The contraindications - pregnancy, women planning pregnancy and hypersensitivity to tretinoin or other ingredients[3]
- How to apply – starting with a small amount left on her skin for a short time and working her way up to overnight use
- What adverse effects she may expect and how to manage them
  – Mild irritation, redness, peeling in the first few weeks of treatment – which can be managed by changing the amount/frequency of ReTrieve applied[3]
- Sun protection measures
- When she should come back for follow-up and how her skin will be monitored going forward

> *I find that people are concerned about the signs of photoageing more than they like to admit. It's actually a simple conversation to have with your patient because we can look at it as a preventative, protective treatment which goes along with the sun protection that everyone in Australia is well aware of. So if a patient is coming in for a skin check, it's a great time to just mention photoageing and decide whether or not ReTrieve is appropriate for them.*

*Hypothetical patient.

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FACIAL AGEING 2

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