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IN THIS ISSUE

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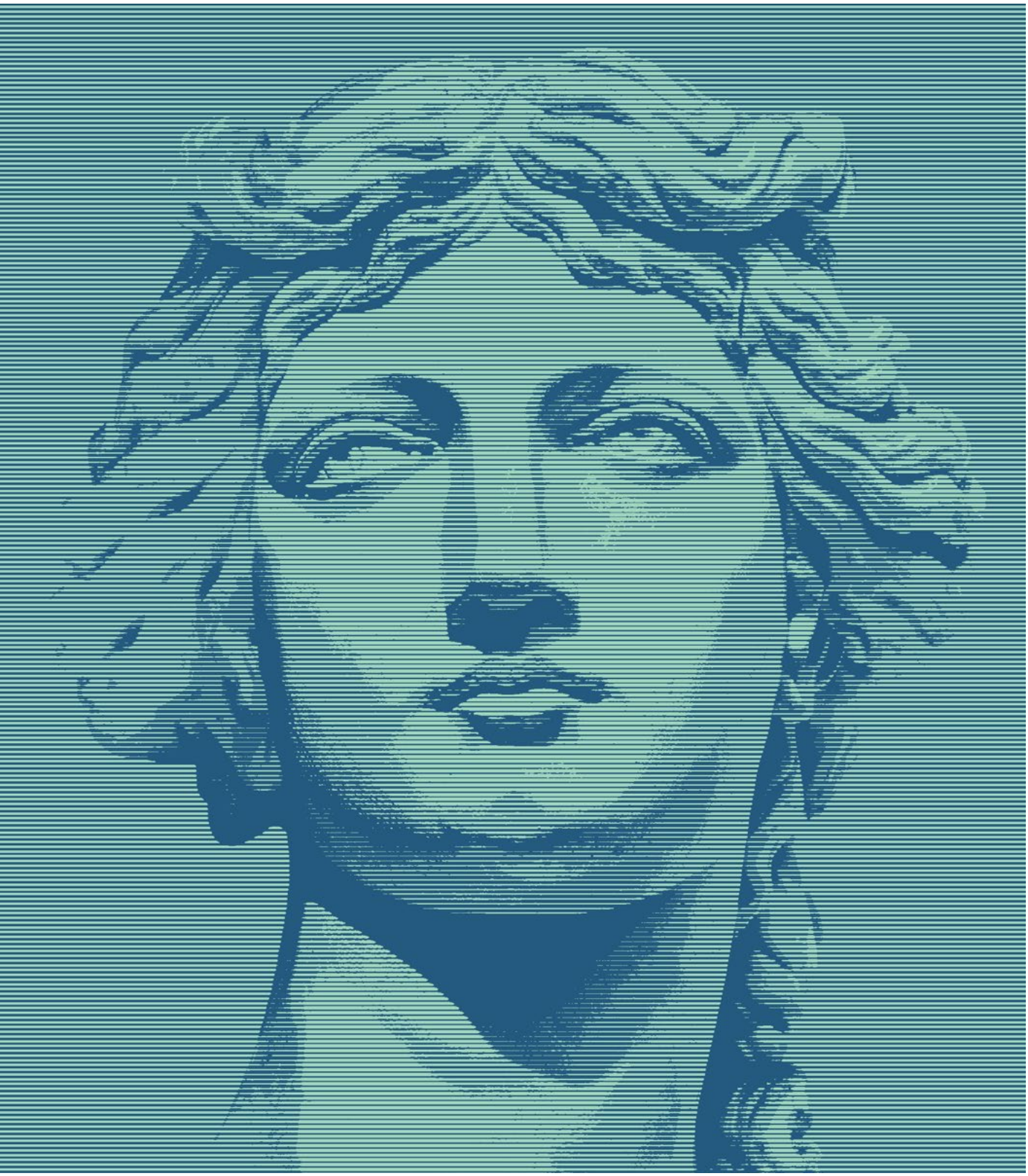

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OPINIONS AND PROGRESS IN
Cosmetic Dermatology
VOLUME 02 / ISSUE 01 / FEBRUARY 2022

Welcome to **Photodamage 2 – the final instalment on sun damage, skin cancers and photoageing.**

We are honoured to have Associate Professors Stephen Shumack and Marius Rademaker join us as guest editors for this issue. They are esteemed dermatology colleagues with many research and academic interests, and former editors-in-chief of the Australasian Journal of Dermatology.

As we launch this issue, Australia and New Zealand are navigating the Omicron wave and adapting to a COVID-normal world. This issue has been timed to coincide with the Australasian Society of Cosmetic Dermatologists (ASCD) Symposium in Melbourne as it welcomes both face-to-face and online delegates.

We are pleased to be a part of your continuing education activities and hope you enjoy this issue.

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

Contents

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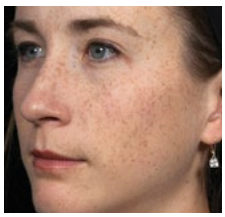
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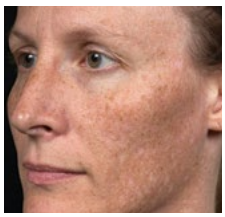
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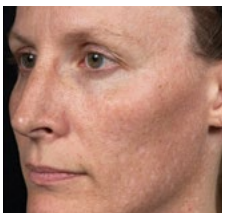
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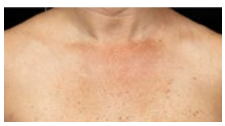
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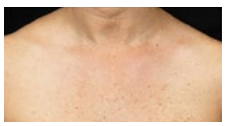
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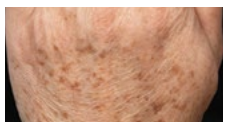
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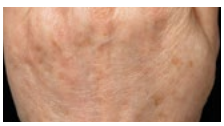
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Photodamage 2 — Guest Editorial

Guest Editors: Marius Rademaker[1] and Stephen Shumack[2]

1. Waikato Clinical Campus, University of Auckland, Pembroke Street, Hamilton 3240, New Zealand
2. Department of Dermatology, Royal North Shore Hospital, St Leonards, NSW, Australia

Correspondence: Marius Rademaker rademaker@xtra.co.nz

Rademaker M, Shumack S. Photodamage 2 — Guest Editorial. Opin Prog Cosmet Dermatol 2022;2(1):1.

We are delighted to present the second of a two-part series on photodamage in Opinions and Progress in Cosmetic Dermatology.

Cosmetic and beauty procedures are on the rise, along with the ageing global population. It is therefore timely to consider the issues, attitudes, and motivation around aesthetic work, with the topic of ageing, and ageism provocatively explored by Lim and Pham in this issue.

In the preceding issue, oral preventative therapy for sun damage was reviewed. In this issue, the spotlight is once again on nicotinamide and its role in skin cancer prevention. The dermatology toolbox is further explored with reviews on lasers and photodynamic therapies for actinic induced dysplasia.

Dermatologists, and all practitioners looking after patients with skin issues, will welcome Armour's insights on the use of cosmeceuticals for photoageing. Richards and colleagues have produced an updated review on chemical peels with an excellent step-by-step guide for photodamage.

In this issue, skin cancer surgery is addressed: starting with scar prevention and management in facial surgery; followed by Mohs micrographic surgery as an aid to optimising cosmetic outcomes in skin cancer surgery. For non-dermatologists, the Mohs surgery paper is accompanied by helpful illustrations to better explain key procedural concepts.

The debate topic for this issue is on: "injectables versus lasers for photodamage – which is better?". The paired articles from Roberts and Bekhor are equal parts education and entertainment and hopefully serve to expand the reader's perspective and therapeutic viewpoints.

We thank the journal editors for their invitation to serve as guest editors for this issue. As former chief editors of the Australasian Journal of Dermatology, we are very aware of the "tears and toil" of authors, researchers and reviewers in their dealings with scientific journals – issues challengingly discussed by Goodman.

It has been a pleasure for us both to work on this issue and congratulate the Journal editors and the editorial team for compiling and publishing Opinions and Progress in Cosmetic Dermatology as an important and relevant new publication in this ever-expanding area!

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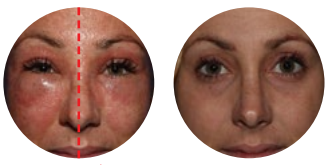

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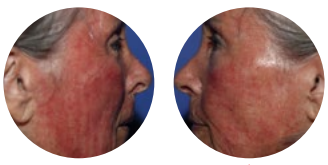

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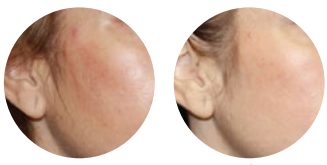

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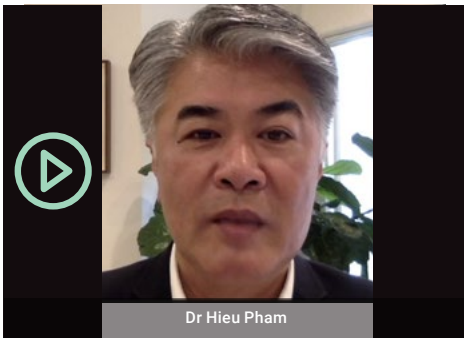
Ageing, ageism and cosmetic procedures

Adrian Lim[1,2], Hieu Pham[3]

1. Department of Dermatology, Royal North Shore Hospital, St Leonards, NSW, Australia
2. uRepublic Cosmetic Dermatology and Veins, Sydney CBD, NSW, Australia
3. Department of Mental Health Services, Mildura Base Public Hospital, Mildura, Victoria, Australia

Correspondence: Adrian Lim adrian@urepublic.com.au

Disclosures: *none*



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OUTLINE: Chronological and photoageing changes in humans are well recognised and documented. Ageing tends to be negatively perceived and associated with undesirable traits such as loss of beauty, youth, vigour and competence. Ageism is defined as biases and preconceived attitudes towards individuals because of age, particularly older adults. Individuals targeted by ageism report suffering both physical and psychological harm and consequently, avoidance and corrective strategies are sought to minimise this. Ageism can also be internalised to cause loss of self-esteem and depression. The COVID-19 pandemic has dramatically highlighted the ubiquity of ageism in our community, particularly the compassionate or "care-mongering" form of ageism. The current popularity of cosmetic procedures underscores our motivation to look younger in order to avoid the stigma of ageism. Anti-ageing procedures can ameliorate some aspects of ageism, but also paradoxically fuel it, through (old) age escapism. We discuss the inter-related themes of ageing, ageism and the perceptual issues associated with anti-ageing procedures.

KEYWORDS: ageing, ageism, beauty, cosmetic procedures, healthy ageing

Lim A, Pham H. Ageing, ageism and cosmetic procedures. Opin Prog Cosmet Dermatol 2022;2(1):3-6.

Ageing – physiological process or disease?

In many parts of the world, the population is disproportionately ageing, with increasing life-expectancy coupled with better health at older age. The visible signs of ageing are most discernible on the skin and its appendages. Whilst most consider ageing to be an expected biological progression through the human life cycle, some have expressed the view that ageing is a disease state that is increasingly treatable and ultimately curable.[1] Semantics aside, chronological and physiological ageing is universally recognised, even if less well-accepted. The age-related hallmarks of wrinkles, sagging skin, mottled complexion, grey and thinning hair are well studied and documented in both the arts and sciences, as are the surgical and non-surgical corrective options.[2,3] Ageing is also accompanied by psychosocial changes where the unwelcome signs of ageing and the emerging spectre of declining health and death can be confronting and threatening to one's confidence and sense of self.

Ageing and beauty

With increasing chronological age, older adults are more frequently perceived as infirm, incompetent and unattractive.[4] Studies investigating what constitutes a beautiful and aesthetically desirable appearance have identified youth as one of the key beauty signals.[5] In females, the "youthfulness" (neoteny) category is characterised by classic juvenile features such as fullness of cheeks, large bright eyes and smooth skin, which are sexually attractive to heterosexual males and the preferred aesthetic goals for many females.[5] Conceivably, "youthfulness" as an aesthetic goal may be a co-motivating factor for females undergoing cosmetic procedures – to ultimately look more youthful as well as more attractive. Cosmetic procedures can also improve facial symmetry and complexion clarity, which are the other beauty signals.[5-7] Ageing also narrows the physical difference between genders (sexual dimorphism) typified by the masculine "v"-shaped torso and the feminine "hour-glass" figure[8], resulting in further loss of attractiveness with advancing age.

Ageism

Ageism is defined as bias against individuals due to age, particularly older-looking adults.[9, 10] Simplistically, ageism operates along the lines of: "youth is good, desirable and beautiful; old-age is bad, repulsive and ugly".[11] Ageism can be encountered socially, at work, with potential intimate partners, and within healthcare; ageism targets may commonly experience a sense of devaluation, rejection and social exclusion.[10, 12] Older females may also experience sexism along with ageism.[11] This double assault has been consistently documented as a potential cause of physical and psychological stress for female targets.[9, 10, 12, 13] When older adults experience ageism, there is a reported increase in serum cortisol levels with a greater likelihood of illness; unpartnered individuals living alone are especially vulnerable.[10] Perceived age discrimination is associated with lower self-esteem, lower self-rated health and greater apprehension about growing old.[10] Certain minority groups may additionally suffer other types of group prejudice such as racism. Compared to sexism and racism, ageism is relatively less well studied, with retrievable PubMed articles of 8756 for racism, 3630 for sexism and 1696 for ageism (accessed 31 Jan 2022). Curiously, this reflects a blind-spot we have for growing old; a situation most of us will eventually encounter, sooner or later.

It is interesting to consider whether cultures that promote respect for elders (e.g., amongst certain Asian and non-Anglo European countries) may attenuate the degree and prevalence of community ageism. Somewhat surprisingly, the relevant studies indicate the reverse may be true; older adults in East Asia draw more resentment from younger adults compared to the West – possibly because of competition for limited resources and a widening gap between elder expectation and what the younger cohort is able and willing to deliver.[14, 15]

Ageism can further be defined as occurring in one of two settings: structural or individual. Individual ageism refers to the situation where older adults assimilate the derogatory attitudes about ageing from their culture, in the context of negative stereotyping and negative self-perception.[13]

Structural ageism occurs within societal institutions where there is systematic bias against older adults e.g., access to health services and medical treatments. In a systematic review involving 45 countries over 25 years, Australia fared relatively poorly on the structural ageism association score: Africa (100.0%); Australia (97.4%); Asia (94.4%); Europe (79.9%); North America (65.9%); South America (66.7%) – where a higher percentage is associated with higher levels of structural racism.[13] This study examined the following domains: access to health services, work opportunities, mental illness, physical illness, exclusion from health research, quality-of-life and wellbeing, risky health behaviours, social relationships, longevity, cognitive impairment and devalued lives of older adults.

Health impact and other costs

Individual ageism has been the focus of the majority of ageism studies especially the adverse health impacts – including longevity reduction – all of which have been well documented.[13] Ageism regardless of settings (structural or individual) can result in personal, public health and economic costs.[13] The detrimental physical and psychological effects include: more negative self-assessment, more hospitalisation and more dependency and disability.[9] When older adults are subjected to ageism, they tend to internalise the bias which results in impairment of their functional ability and performance resulting in social isolation and lowered mood.[9, 13, 16] For example, when older adults are subjected to performance stereotyping e.g., age-related memory loss, the measured performance outcomes will consistently worsen.[14] Further, ageism targets are not only more likely to feel older but will also exhibit lower peak respiratory flow rate, weaker grip power, and a higher waist circumference.[12] In other words, ageism directed at older adults may make them act and feel even older. It has also been estimated that ageism is linked to 6.33 million cases of older adult depression worldwide.[13] Not surprisingly, all this comes with significant monetary costs. The economic cost of ageism has been estimated to be around US$63 billion or 15.4% of the annual health care expenditure for the eight most common medical conditions for Americans aged 60 and above.[17]

Compassionate ageism

It is well established that conventional or "hostile" ageism (overt or covert) can cause emotional and physical harm, including learned helplessness and incompetence.[16] During the COVID-19 pandemic, the "compassionate" form of ageism has come to the fore. Compassionate or benevolent ageism tends to be less obvious and more under-the-radar because of the generally positive accompanying intentions. However, compassionate ageism can also compromise the health and wellbeing of older adults. The bias of compassionate ageism involves a warm and positive perception of older adults concurrent with the negative perception of incompetence, dependence and frailty. Compassionate ageism – as typified by the pervasive care mongering during the COVID-19 pandemic – can cause harm by eroding the target's self-worth and sense of agency and through homogenisation of the needs of older adults.[16]

Coping strategies against ageism

Older adults experiencing individual ageism may sometimes choose to age-dissociate i.e., identify with a younger age group ("they" are old but "I" feel younger) as a protective mechanism that has been shown to ameliorate the harm of ageism.[4] Age-group dissociation can be seen as a defensive strategy adopted by older adults to combat negative stereotyping of old age through self-imposed psychological separation from similarly aged peers. Older adults adopting a younger outlook tend to experience better psychological wellbeing and higher levels of self-esteem.[4, 12] Ageing adults may also elect to alter their appearance through measures such as hair colouring, make-up and even undergo cosmetic procedures to more closely match their younger subjective age "to look how I feel", which in turn can boost physical and psychological health.[4]

Cosmetic procedures

Cosmetic procedures – both surgical and minimally invasive – are more popular than ever; on top of anti-ageing medical treatments such as prescription topical retinoids, low dose systemic isotretinoin, hormone replacement and nutraceutical supplementation. Cosmetic injectables (e.g., botulinum and filler injections) and other minimally invasive procedures are offered widely by a range of practitioners and practice settings. Remarkably, the uptake of cosmetic procedures remained relatively strong in 2020 compared to 2019 despite the COVID-19 pandemic. In the US, 2020 saw a COVID-19-related death toll of over 500,000, yet cosmetic surgery and minimally invasive procedures dropped by only 14% and 16% respectively.[18] The resilience of the cosmetic industry during the pandemic is mirrored in Australia, with anecdotal accounts of some cosmetic practices even busier during COVID-19 than pre-pandemic years. Possible reasons for the anomalous demand for cosmetic services include: greater expendable income (working more with fewer holidays); limited spending opportunities (less travel, shopping and entertainment); more time and opportunity to focus on personal appearance (the "Zoom" effect); and greater opportunity to recover from procedures (social isolation and working from home).

Although it can be argued that having cosmetic procedures to escape ageism is ultimately fuelling ageism, the surrounding issues and themes are certainly more nuanced. Earlier studies on patient motivation for cosmetic procedures tended to focus unduly on psychopathology and vanity.[19] Contemporary studies on the same issue have identified the relevant factors as: improving employment prospects; better relationship opportunities; combatting the invisibility of old age; and countering age-based discrimination.[10, 11] Pearl et al. found women undergoing cosmetic procedures in a single-centre aesthetic plastic surgery clinic (n=47) had heightened perception of age-based discrimination, but that study was not case-controlled.[10] Another larger multicentre survey of cosmetic dermatology patients (n=511) revealed that the desire to look more youthful and attractive are the most commonly cited motivations, with the key reason of the majority being to please themselves (66.2%) rather than others (27.2%).[19] Conceivably, fundamental drivers for older adults seeking cosmetic work could be the intrinsic human appreciation of beauty[5], coupled with internalised ageism fuelling the drive to look younger.[10–12] The older person's subjective age – with or without ageism – can also be a motivating factor "to look how I feel".[12]

Much has been written about the link between cosmetic work and the pressures of an ageist and patriarchal society.[11, 20] Women can be harshly critical of the implications of cosmetic work, and at the same time, partake in it; paralleling the anti-ageing paradox: where the act of escaping ageism only serves to fuel it. It has been observed that women undergoing cosmetic procedures are typically neither deluded nor "cultural dopes" but are insightful, autonomous and agentic.[11] This ambivalence and mixed-messaging around ageing and anti-ageing measures was recently brought into focus by the widely publicised *Allure* editorial – a celebrity, beauty and fashion magazine – calling an end to ageist language by banishing the term "anti-ageing".[21]

Potential perils of looking younger

An unintended consequence of older adults looking younger is violation of the expectations of younger adults on how older adults should look and behave.[22] Prescriptive ageism describes this preconceived notion held by younger adults that older adults should act or behave in a certain manner; older adults are expected to act their age and not attempt to conceal it through manipulation of appearance or cultivated interests such as fashion or musical tastes.[22] Trying to pass as younger is seen as deceptive and appropriation of younger-age fashion or music is perceived as an intrusion across the generational gap.[22] Interestingly, younger adults perceive no difference in attractiveness in older adults trying to look younger compared to those who do not.[23] Perhaps the established pattern of secrecy around cosmetic procedures is derived from the intuitive understanding by older adults that others, upon finding out, will judge them negatively.[14, 23] When specifically asked, cosmetic patients tend to explain their motivation for cosmetic procedures as "looking younger" rather than to "conceal" their age.[10]

Age-group dissociation has been proposed as a defence mechanism against the harm of ageism.[4] Older adults who age-dissociate and identify with younger adults

tend to rate their psychological and physical health more positively;[4] have better psychological, physical and cognitive health, and live longer.[12] However, the long-term benefits of this behaviour have not been properly explored and arguably, with time, psychosocial complications may subsequently arise from rejecting the reality of ageing and its associated challenges.[4] Indeed, hiding one's group identity (e.g. social class, sexuality) has been shown to result in psychological harm. However, it has also been suggested that older adults attempting to escape ageism through identification with younger adults may not necessarily suffer any ill-health as long as there remains other well-defined generational or cultural identification, as these can provide a comforting sense of belonging and connectedness from shared socio-cultural experience over time.[14]

Healthy ageing

Resilience in the face of adversity and loss has been suggested as a crucial attribute for healthy ageing and wellbeing in the older age group.[24] Older adults maintaining a high level of functioning in the absence of adversity are ageing healthily, whereas older adults who are functioning well even in the face of adversity are both resilient and ageing healthily.[24] Importantly, healthy ageing is not a prerequisite for positive wellbeing in older adults. The wellbeing paradox describes resilient older adults experiencing high levels of wellbeing despite (or perhaps because of) age-related deterioration.[24, 25] Indeed, a greater sense of wellbeing may result from a challenging life well-lived. Importantly, there is no evidence to suggest that older adults undergoing cosmetic procedures are less resilient or have less opportunity to navigate the multi-dimensional vicissitudes of growing old.

Conclusion

Ageism carries significant personal and societal costs and directly impacts on the health, opportunities and wellbeing of older adults. In an increasingly ageing but youth-oriented society, cosmetic procedures will continue to be pursued by a significant sector of the community. Cosmetic practitioners should be aware of the key ageism issues and related dynamics, including patient motivation factors and perceptual issues around anti-ageing cosmetic procedures.

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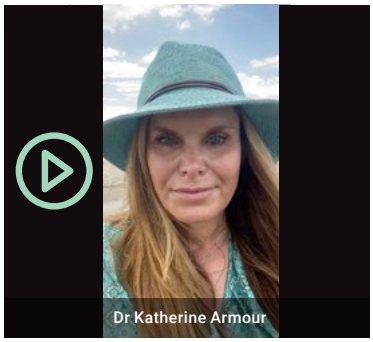
Cosmeceuticals to address cutaneous photoageing

Katherine Armour[1, 2, 3]

1. Dermatology Institute of Victoria, Melbourne, Victoria, Australia
2. The Alfred Hospital, Melbourne, Victoria, Australia
3. Skin Health Institute, Melbourne, Victoria, Australia

Correspondence: Katherine Armour katherinearmour@gmail.com

Disclosures: *Dr Armour is the founder and director of Bespoke Skin Technology*



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OUTLINE: The cosmeceutical industry is growing at an exponential rate. The majority of the signs of facial skin ageing are due to photodamage. Ultraviolet, visible and infrared radiation are all responsible for the development of photodamage in human skin. Therefore, it is important to address all of these factors in a skincare regime. The ever-expanding number of cosmeceutical options to address photoageing can be overwhelming for clinician and patient alike. In this article, a systematic approach to cosmeceuticals to address this problem will be provided. These skincare products integrate well with in-clinic procedures and medical therapies to effectively manage photoageing in our patients.

KEYWORDS: Cosmeceuticals, photoageing, photodamage, antioxidants

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Background

Photodamage is an all too familiar problem in Australasia. Sun exposure is thought to account for approximately 80% of facial ageing, with the remaining extrinsic causes being ascribed to pollution, smoking, poor nutrition and alcohol consumption.[1] Clinical features of photoageing include fine lines and wrinkles, skin laxity and poor light reflection, dryness, fragility, dryness, textural roughness, decreased elasticity and dyspigmentation including lentigines.

The majority of the clinical signs of photodamage are due to a loss or dysfunction of collagen, elastin, and/or hyaluronic acid.[2] Unwanted melanogenesis also plays a role. The main goals of cosmeceutical ingredients which target photodamage are to prevent the loss of collagen, elastin and hyaluronic acid, as well as to increase the production of hyaluronic acid and collagen. There are currently no available skincare products which are able to increase production of elastin.[2]

Chronic ultraviolet (UV) exposure leads to photocarcinogenesis and photoageing. DNA within epidermal cells absorbs UVB (290–320 nm), inducing DNA mutations such as cyclobutane pyrimidine dimers and pyrimidine cross-linked dimers, and activating skin melanogenesis.[3] UVA (320-400 nm) radiation penetrates more deeply into the skin, primarily causing oxidative damage to DNA, and indirectly through chromophores that act as endogenous photosensitisers.[4]

It is now appreciated, that, in addition to the crucial role of cutaneous UVA and UVB exposure in the development of photoageing, visible light (400-700 nm) and infrared radiation play a significant role. Visible light accounts for 40-45% of the solar radiation reaching the earth's surface.[5, 6] It is important in pigment induction, numerous dermatoses such as porphyrias, and in phototoxic, photoallergic, and chronic actinic dermatitis. Visible light also contributes to oxidative damage, and photoageing via this mechanism.[7] Infrared radiation in the IR-A range (700-1400 nm) also induces oxidative damage,[8] and reaches the dermis and subcutaneous layers.[9]

There are increasing reports of larger amounts of UVC (0-290 nm) reaching the atmosphere than was previously appreciated.[10] This is an evolving area, and will need to be considered in future development in the field of photoprotection. Like UVB, UVC directly damages cutaneous DNA.[4]

Specific cosmeceuticals to target photoageing

There is a myriad of cosmeceutical ingredients now at our disposal to prevent and treat the signs of photoageing. They may be used as stand-alone treatments, or in conjunction with prescription field treatments and in-clinic procedures. I have always found *"The Skin Health and Beauty Pyramid"* authored

by Draelos et al. (2014)[11] a highly useful way to approach cosmeceuticals, and to guide an approach to this ever-expanding topic with my patients. With this in mind, I would like to borrow from the approach championed by these authors in discussing ingredients. A daily approach to cosmeceuticals to address photoageing is shown in Table 1.

Table 1.

A daily approach to cosmeceuticals to address photoageing

1. The fundamental pillars	Broad-spectrum sunscreen, DNA repair enzymes, antioxidants
2. The transformers	Alpha-hydroxy acids, polyhydroxy acids, bionic acids, bakuchiol
3. The icing on the cake	Peptides, growth factors, cytokines, stem cell stimulators, circadian rhythm modulators

1) Fundamentals – cosmeceuticals to be used daily to protect and repair the skin

The paramount importance of daily (and reapplied!) broad-spectrum sunscreen use is clearly appreciated by this readership. Benefits of daily sunscreen use include reduced risk of erythema, solar keratoses, skin malignancy and visible signs of photoageing. An in-depth discussion of sunscreen is outside the scope of this article. To protect from the effects of visible light, sunscreens must be tinted with iron oxide. These products are elegant to use and usually readily acceptable to consumers.

While sunscreens are the most important topical measure we can take to protect from UV exposure, they do not offer 100% protection. They are unable to scavenge free radicals or repair DNA damage. To augment this protection, DNA repair enzymes and antioxidants are useful on a daily basis.

Table 2.

Mechanism of action of antioxidants targeting photoageing[11-22]

Photoprotection	Preserve or stimulate collagen/extracellular matrix synthesis	Targets pigmentation	Anti-inflammatory	Inhibits protein glycation
Reduces UV-induced erythema Ascorbic acid Green tea Ferulic acid Tocopherol Melatonin	Ascorbic acid Niacinamide Green tea Astaxanthin Ferulic acid Coenzyme Q10 Coffeeberry Idebenone Turmeric	**Tyrosinase inhibition/ downregulation** Niacinamide Ascorbic acid Aloesin Arbutin Mulberry extract Resveratrol Ferulic acid Tocopherol Liquorice root extract	Astaxanthin Niacinamide Ascorbic acid Liquorice root extract Green tea Resveratrol Ferulic acid Aloesin Arbutin Mulberry extract Soy Coffeeberry Melatonin Feverfew Tumeric	Niacinamide Carnosine Green tea
UV protection via antioxidant effects Green tea Resveratrol Soy Melatonin		**Inhibition of melanosome transfer to keratinocytes** Niacinamide		
Reduces sunburn cell formation Ascorbic acid Green tea Ferulic acid				
Reduces thymidine dimer formation Ascorbic acid Tocopherol Coffeeberry				
Reduces UV-induced immunosuppression Ascorbic acid Niacinamide				
UV absorption Astaxanthin				

Antioxidants

Antioxidants scavenge toxic free radicals generated from environmental oxidative stress including UV exposure. Topical antioxidants are able to supplement our innate cutaneous antioxidant systems when they are overwhelmed by environmental exposures. The benefits for skin are well-documented and include induction of collagen formation, fine line reduction, improvement in unwanted pigmentation, and diminished redness via their anti-inflammatory properties. Table 2 lists some of the known benefits of commonly used ingredients in cosmeceuticals, in addition to their antioxidant actions.

DNA repair enzymes

Niacinamide is known to enhance DNA repair activity.[23] Our skin's endogenous DNA repair enzymes play a crucial step in cellular protection against oxidative stress induced by UV exposure.[11] From the medical literature investigating methods to ameliorate the numbers of non-melanoma skin cancers in patients with xeroderma pigmentosum, the use of topically delivered exogenous DNA repair enzymes was shown to augment our innate DNA repair processes.

Small clinical studies have shown decreased solar elastosis, decreased basal cell carcinomas (30%) and actinic keratoses (68%) in studies lasting approximately 12 months.[24, 25] A 2012 study showed a 93% reduction in cyclobutane pyrimidine dimer lesions in patients using SPF 50 and one photolyase repair enzyme.[26] A year later, a further study reported a 53% reduction in cyclobutane pyrimidine dimer lesions and a 37% reduction in mutant p53 expression after 12 weeks of using SPF 29 and one each of the main DNA repair enzyme groups photolyase, endonuclease and 8oxoG glycosylase.[27] The same article reported decreased solar elastosis in treated skin. Currently available products containing DNA repair enzymes contain between one and three of this group. More comprehensive cover is obtained by using three DNA repair enzymes.

Whilst the use of broad-spectrum sunscreen is still the basis of protection and repair of photoaged skin, topically applied antioxidants and DNA repair enzymes act synergistically and additively to sunscreen.

2) Agents to transform photoaged skin

According to the 2014 paradigm of Draelos et al., the middle of the *"Skin Health and Beauty Pyramid"* is occupied by evidence-based ingredients which should be used in those wishing to "transform" the skin. In their article, retinoids, alpha-hydroxy acids (AHAs) and moisturisers should be used daily to transform ageing skin in terms of fine lines, wrinkling, textural roughness, and dyspigmentation. I would suggest that polyhydroxy acids, bionic acids and bakuchiol also deserve a place in this layer of the pyramid. Table 3 outlines the mechanisms of action of these crucial agents which have an abundance of evidence attesting to their

Table 3.

Agents to "transform" photoaged skin

Cosmeceutical class	Therapeutic agent	Mechanism of action
Retinoids	Retinoic acid (tretinoin) Retinol Retinaldehyde (retinal) Retinol esters	Regulate cell growth and differentiation[28] Thicken epidermis[4] Increase fibroblast numbers and collagen synthesis[29] Decrease collagenase production[29] Normalise melanocyte function[29]
Alpha-hydroxy acids	Lactic acid Glycolic acid Mandelic acid Citric acid	Increased exfoliation and cell turnover Stimulate synthesis of collagen and glycosaminoglycans[30]
Polyhydroxy acids	Gluconalactone	Light exfoliation Antioxidant Protects elastin Supports skin barrier function[30]
Bionic acids	Lactobionic acid Maltobionic acid	Moisturising Antioxidant MMP inhibition to protect dermal matrix Stimulates production of dermal matrix components Decreases pigment production[30]
Meroterpene phenol	Bakuchiol	Antioxidant Upregulation of collagen and extracellular matrix synthesis enzymes[31] Anti-inflammatory Targets pigment[32]

MMP *– matrix metalloproteinases*

efficacy in rejuvenating photoaged skin. Tretinoin and AHAs have by far the most clinical studies documenting their ability to transform the skin. But, polyhydroxy acids, bionic acids, and bakuchiol in particular, are excellent options for those with sensitive skin types, or who do not tolerate AHAs or retinoids. Bakuchiol is a phytochemical from the babchi plant *(Psoralea corylifolia)* and several other plant species.[32] It has shown promising anti-ageing and anti-acne benefits for skin when applied topically. It is a functional analogue of retinoids, stimulating similar cutaneous gene expression, and improving photodamage.[32]

3) "Icing on the cake" ingredients

These are newer ingredients which aim to stimulate "dermal activation and regeneration."[6] These ingredients can be considered as "nice to have" if cost is not an issue, and an individual is already using ingredients from sections 1 and 2 above. These include peptides, growth factors, cytokines, stem cells and circadian rhythm modifiers.[6] These ingredients certainly show some promise in terms of efficacy. However, most of the studies are small, and often industry-sponsored. It is likely that more conclusive evidence will emerge in upcoming years to confirm efficacy of these ingredients.

Peptides are short chains of amino acids, which serve as messengers between the epidermis and dermis. Signal, enzyme-inhibitor, neurotransmitter-inhibitor (neuropeptides) and carrier peptides are the four types of peptides included in cosmeceutical preparations.[33] It is important to remember that most peptides are too large to penetrate the skin and exert an effect in the dermis, and, that most evidence for their effectiveness comes from *in vitro* or small *in vivo* studies.[33] However, some small clinical studies using delivery mechanisms ensuring dermal penetration, do show evidence of increased dermal matrix component synthesis in terms of improvement in fine lines. So, with ever-improving technology in terms of ingredient delivery and penetration, peptides may become more important in the treatment of photoageing.

Cytokines included in cosmeceuticals include tumour necrosis factor-α, and a number of interleukins. Their benefits for photoageing are due to activation of growth factor expression in keratinocytes, macrophages, and fibroblasts. Increased epidermal thickness, and a decrease in wrinkles and fine lines has been demonstrated in small studies.[34]

Growth factors are crucial in normal skin for wound healing and tissue repair. Epidermal growth factor (EGF), fibroblast growth factor (FGF-2), transforming growth factor-ß (TGF-ß), and platelet-derived growth factor (PDGF-ß) may be used singly or in combination in cosmeceutical preparations. Growth factors may be obtained via recombinant or non-recombinant DNA technology. In small, controlled studies, improvements in wrinkles, dyspigmentation and skin roughness have been reported.[34]

Live stem cells cannot survive in a skincare formulation. Likewise, stem cells derived from plants cannot interact with human skin cells.[34] However, extracts of stem cells from the eggs of the snail *Crytomphalus aspersa* have been shown to stimulate improved extracellular matrix formation, as well as migration of keratinocytes and fibroblasts.[35]

Maximal cell proliferation, DNA repair, blood flow, skin permeability and skin penetration occur in human skin at night.[36] This has led to interest in developing skincare products to address diurnal variation in the skin's needs. This is a "watch this space" and evolving area in cosmeceuticals.

Conclusion

To conclude, to optimise the use of cosmeceuticals to improve photoaged skin, sunscreen, DNA repair enzymes and antioxidants should be used daily to protect and repair the skin. A single agent, or alternating ingredient approach to AHAs/polyhydroxy acids/bionic acids, bakuchiol and retinoids will be efficacious in improving the common signs of photodamage including fine lines, textural change, loss of skin plumpness and dyspigmentation. Finally, peptides, growth factors, cytokines and stem cell stimulators, are options that fall into the "nice to have"[11] arena in combating photoageing. Future studies may provide further impetus to recommend these expensive and evolving ingredients into our patients' daily skincare routines.

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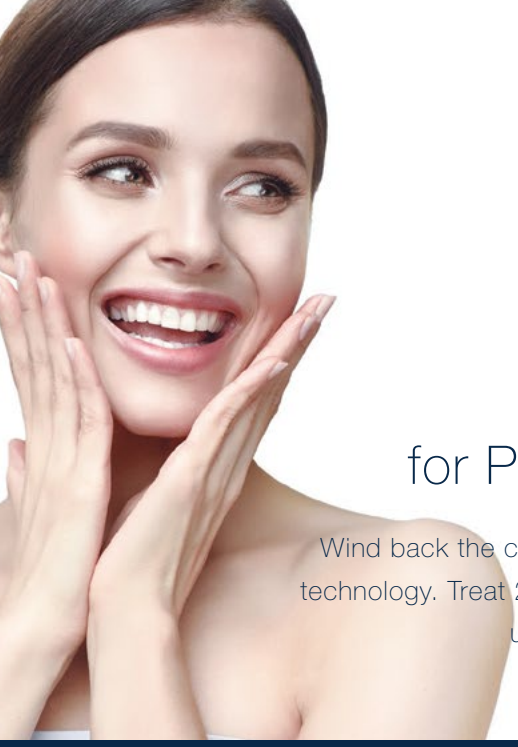

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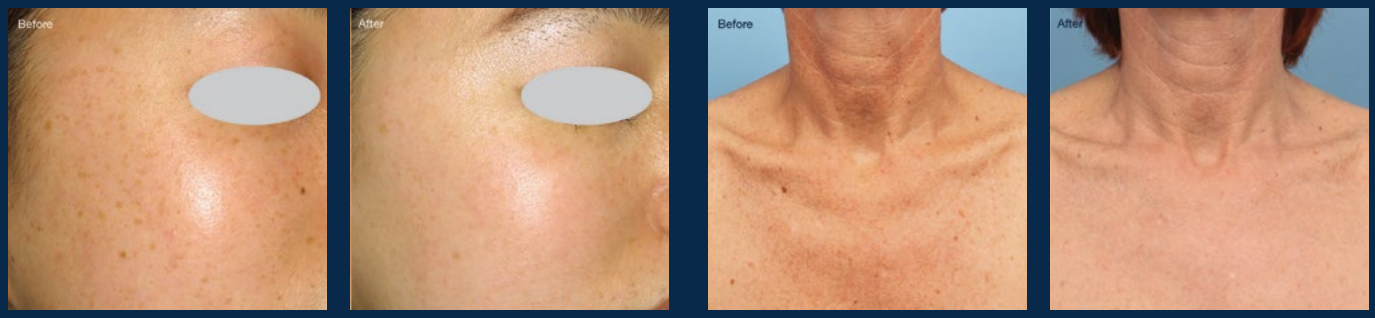

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The role of nicotinamide in skin cancer chemoprevention: a review of the literature

Cong Sun[1], Devita Surjana[2], Davin Lim[2]
1. Princess Alexandra Hospital, Woolloongabba, Queensland, Australia
2. Cutis Clinic, Indooroopilly, Queensland, Australia

Correspondence: Cong Sun tom.cong.sun@gmail.com

Disclosures: *none*

OUTLINE: The incidence of non-melanoma skin cancers (NMSCs), the most common type of cutaneous malignancy, has been increasing, thus placing significant burdens on the healthcare system. Nicotinamide is an isotype of vitamin B3 and is already used in several inflammatory dermatological conditions including acne and rosacea, and autoimmune blistering disorders, including bullous pemphigoid. In recent times, oral nicotinamide has shown promising results as a chemoprophylactic agent in reducing the number of NMSCs in immunocompetent individuals. The evidence for nicotinamide as a prophylactic agent in those who are immunosuppressed, for example solid organ transplant recipients, remains conflicted.

The mechanisms through which nicotinamide acts against the develop of new NMSCs include repleting cellular energy reserve, enhancing DNA repair, and down-regulating ultraviolet (UV)-mediated immunosuppression of the skin. While experimentally, nicotinamide has demonstrated enhanced repair of UV-damaged melanocytes, there are currently no human *in vivo* trials exploring the possible chemopreventive properties of nicotinamide against melanoma.

Overall, nicotinamide has a favourable safety profile with good tolerability even at high doses; there are very few drug interactions. Gastrointestinal disturbance remains the most common side effect for this medication. Rare cases of transient thrombocytopaenia which resolves after cessation of medication and liver toxicity have also been reported in renal and psychiatric patients receiving nicotinamide.

KEYWORDS: nicotinamide, non-melanoma skin cancers, cutaneous malignancies, vitamin B3

Sun C, Surjana D, Lim D. The role of nicotinamide in skin cancer chemoprevention: a review of the literature. Opin Prog Cosmet Dermatol 2022;2(1):14-19.

Introduction

The incidence of non-melanoma skin cancers (NMSCs), consisting mostly of basal cell and squamous cell carcinoma, has increased over the past decade and contributes significantly to healthcare spending.[1] Despite the implementation of public health campaigns, NMSCs remain the most common type of cutaneous malignancy in the light-skinned population.[1, 2]

A variety of therapeutic agents have been assessed for their photoprotective properties over the years. Of these, various retinoids and nicotinamide have garnered the most robust evidence as chemopreventive agents against NMSCs.[3] While oral retinoids such as acitretin can help in reducing the incidence of NMSCs, the potential for liver toxicity and lipid abnormalities can be an impeding factor.[3]

Nicotinamide in dermatology

Nicotinamide is a water-soluble amide isotype of vitamin B3 niacin.[2, 4-6] Nicotinamide is mostly sourced from dietary sources including meats, liver, yeast, legumes, beans, nuts, seeds, green leafy vegetables, and cereals.[1-3] *De novo* synthesis can also occur in the human body through the tryptophan pathway. Nicotinamide is the precursor for nicotinamide adenine dinucleotide (NAD+), the essential factor for adenosine triphosphate (ATP) production.[2] The vital role of nicotinamide in cellular energy production is reflected by the fact that the lack of this vitamin results in malfunction of the gastrointestinal, neurological, and cutaneous systems, which all have high energy consumption.[1-3]

Nicotinamide has been shown to have promising effects in the treatment of several inflammatory dermatoses including acne and rosacea. Nicotinamide has the ability to inhibit the proinflammatory cytokine pathway

and has been demonstrated to have beneficial effects in blistering disorders. The most robust evidence to date is the trial by Fivenson et al., which demonstrated comparable efficacy between the combination of tetracycline 500 mg 4 times per day and nicotinamide 500 mg 3 times per day versus prednisolone monotherapy.[4, 5] Both topical and oral nicotinamide have been shown to decrease transepidermal water loss in impaired skin barriers, which is the likely mechanism behind its efficacy in rosacea and atopic dermatitis.[6]

Additionally, nicotinamide has been shown to be beneficial in treating pigmentation disorders including melasma.[1] The mechanism of action is postulated to be secondary to decreased melanosome transfer within melanocytes and keratinocytes.[1]

Nicotinamide and cellular biology

The role of nicotinamide as a chemopreventive agent against NMSCs has been investigated in several trials with promising results. The mechanism behind which nicotinamide acts as a chemopreventive agent includes replenishing cellular energy, enhancing cellular DNA repair, and reducing immunosuppression associated with ultraviolet radiation.[1-3]

Cellular energy and nicotinamide

Nicotinamide is converted to NAD+ through a two-step salvage pathway, which is a major route of NAD+ biosynthesis in mammals.[3] NAD+ is a co-enzyme in several important redox reactions, which release energy from nutrients. Ultraviolet (UV) radiation has been demonstrated in *ex vivo* skin to reduce the production of ATP through blockade of the glycolysis pathway, leading to depletion in cellular energy reserve.[7] A reduction of 60% in cellular ATP can be induced via high-dose UV exposure (20J per cm^{-2}), but also to a lesser degree in medium and even suberythemal doses of UV radiation.[7] The reduction in cellular ATP production is not present in skin samples treated with low-dose nicotinamide, which is suggestive of the potential of nicotinamide to unblock the glycolysis pathway impeded by UV radiation.[7]

DNA repair and nicotinamide

Both UVA and UVB are implicated in the formation of cutaneous malignancies.[7-9] The formation of cyclobutene pyrimidine dimers (CPDs) which give rise to signature C to T and CC to TT mutations is the main mechanism behind DNA damage through UVB (290-320 nm).[10] UVA (320-400 nm) also can give rise to CPDs as well as 8-oxo7,8-dihydro-2-deoxyguaosine (8oxoG) which is a single DNA photolesion.[10]

Nicotinamide does not change the production of CPDs or 8oxoG in radiated *ex vivo* skin, suggesting that it does not prevent the formation of UV-induced DNA damage.[10] However, nicotinamide has been shown to increase the rate of unscheduled DNA synthesis, a surrogate marker for DNA excision repair in the setting of DNA damage, in *ex vivo* human skin.[10] The exact mechanism behind which nicotinamide stimulates DNA repair in the setting of UV radiation is unclear. Nevertheless, DNA repair is a heavily energy-dependent process and nicotinamide serves as a precursor in the synthesis of NAD which plays an important role in the cellular metabolism and the production of ATP.[3, 7, 10] Given that UV radiation inhibits the synthesis of cellular ATP, nicotinamide likely stimulates the repair of UV-mediated DNA damage through increasing cellular energy production.

UV mediated immunosuppression and nicotinamide

UV radiation-mediated immunosuppression is well-documented; both UVB and UVA are immune suppressive.[9, 11-13] UV radiation induces direct immunosuppression in the skin through depletion of Langerhans cells which are antigen presenting dendritic cells critical for presenting antigens to the immune system.[11] The impact of UV on Langerhans cell population in the skin is apparent even with suberythemal doses. UV radiation can also induce increased production of immunomodulatory cytokines including interleukin (IL)-1, IL-6, and IL-10.[11]

Nicotinamide prevents the immunosuppressive effect of UV radiation in mouse models when administered both topically and systemically. In human studies, both topical and oral nicotinamide was effective in preserving the Mantoux reaction, a recall delayed hypersensitivity reaction against tuberculin antigen in UV radiation human volunteers.[12, 13] Interestingly, nicotinamide did not increase baseline immune response to the Mantoux test in unirradiated controls.

Nicotinamide and non-melanoma skin cancers

The efficacy of nicotinamide as a chemopreventive agent against NMSCs was evaluated in a large phase III trial in Australia.[14] The ONTRAC trial was a randomised, double-blinded, controlled trial involving 386 participants divided equally into two arms, with one arm receiving 500 mg nicotinamide twice daily and the other arm receiving a placebo for a total duration of 12 months. The trial participants included those over the age of 18 with at least two histologically confirmed NMSCs in the preceding 5 years. The exclusion criteria included current immunosuppression, pregnancy or breastfeeding, severe hepatic or renal dysfunction, internal malignancy, or invasive melanoma diagnosis in the previous 5 years. The participants were examined at baseline and then at 3-monthly intervals for 18 months by dermatologists who were blinded to the treatment

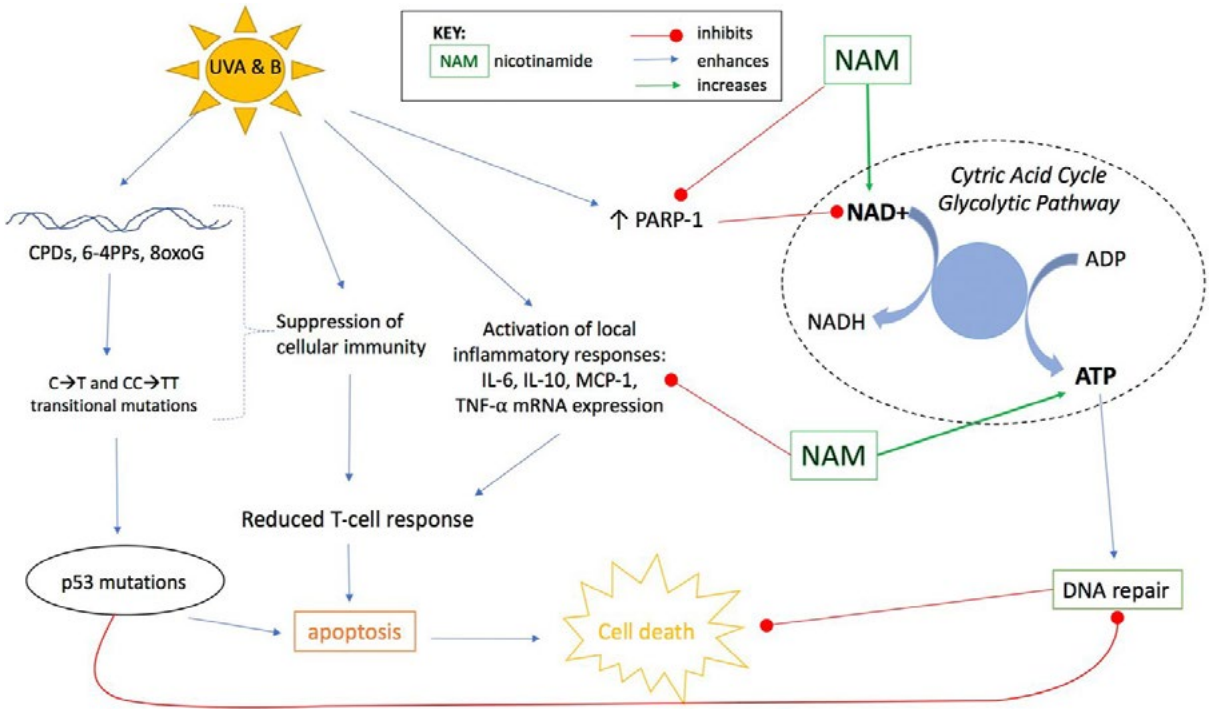

Figure: *Nicotinamide and photoprotection. UVA and UVB within sunlight causes damage in the skin including CPD, 6-4PP and 8oxoG damage to DNA, suppression of cellular immunity and activation of inflammatory responses. Nicotinamide, a precursor to NAD increases ATP production which increases DNA repair, protecting from photodamage.*

allocation. The primary endpoint of the ONTRAC study was the number of new, histologically diagnosed NMSCs through the end of the 12 months period. The secondary endpoints included the number of new basal cell carcinomas, squamous cell carcinomas, actinic keratosis, and any adverse effects or complications of nicotinamide therapy.

The rate of new NMSCs was reduced by 23% (95% CI 4-38; P=0.02) in the nicotinamide group compared to the placebo group.[14] The rate of new basal cell carcinoma (20% lower with nicotinamide; P=0.12) and squamous cell carcinoma (30% lower with nicotinamide; P=0.05) were, however, similar between the nicotinamide and placebo group. The chemopreventive effect of nicotinamide was lost quickly after discontinuation of therapy.[14]

Topical nicotinamide has also been investigated as a potential chemopreventive agent for NMSCs. Moloney et al. assessed the efficacy of topical 1% nicotinamide versus placebo in 26 patients with a history of actinic keratosis on the number of actinic keratoses at 3- and 6-months endpoint.[15] At 3 months, there was a clinically significant reduction in the number of actinic keratoses in the nicotinamide group versus the placebo group (P=0.04). However, this response was not sustained at the 6 months endpoint, possibly suggesting that nicotinamide may have accelerated the natural resolution of actinic keratoses.[15]

Use of nicotinamide in organ transplant recipients

In chronically immunosuppressed solid organ transplant recipients, skin cancer incidence is much greater than that of the immunocompetent population, due to the lack of antitumour immunity which is a vital defence against skin carcinogenesis.[16, 17] In organ transplant recipients, the most common cutaneous malignancy is squamous cell carcinoma which can be up to 65 times higher than that of the general population and often more aggressive and more likely to metastasise.[1] The rate of basal cell carcinoma can be up to 16-fold higher in immunosuppressed organ transplant patients.[18]

The efficacy of nicotinamide as a chemopreventive agent for solid organ transplant recipients has been investigated in two separate trials. Following on with the ONTRAC study, Chen et al. conducted a phase II double-blinded, controlled trial involving 22 renal transplant recipients randomised to the intervention arm receiving 500 mg nicotinamide twice daily and the placebo group.[17] The primary endpoint was new basal cell carcinoma, squamous cell carcinoma, and actinic keratosis up to 6 months of follow-up. The 6-months NMSC rate was not significantly lower for the nicotinamide group compared to the control group (P=0.36); however, the lesion count in the control group was possibly skewed by one patient with 20 new NMSCs over the 6 months trial period.[17] The case-control trial randomised 38 renal

and liver transplant recipients in 1:1 ratio to intervention (500 mg nicotinamide daily) and control groups. Actinic keratoses were identified, photographed, and measured to obtain a single datum in the form of a total "keratotic area" for each individual patient. At 6 months follow-up, the average total keratotic area for the nicotinamide group (0.1+/-0.13) was significantly less than that of the control group (1.01+/- 0.92, P=0.010).[16] Additionally, none of the participants in the nicotinamide group developed new actinic keratoses while 91% of those in the control group developed new actinic keratoses, and 7 had progression of existing actinic keratoses to squamous cell carcinoma.[16]

Nicotinamide and melanoma

Both UVA and UVB are implicated in the carcinogenesis of melanoma by inducing cyclobutane pyrimidine dimers, reactive oxidative species, and increasing the oxidative stress of DNA.[19, 20] In *ex vivo* human skin, UV radiation leads to a significantly increased level of 8oxoG, a marker for cellular DNA oxidative stress. The repair for UV-induced DNA damage in melanocytes is significantly faster in nicotinamide treated cells.[20] Additionally, cells cultured with nicotinamide prior to UV radiation had a lower level of 8oxoG after radiation.[20]

Currently, there is no human *in vivo* trials of nicotinamide as a chemopreventive agent for melanoma in the literature. The ONTRAC trial did not specifically select for melanoma risk. Six *in situ* melanoma and four invasive melanomas developed during the duration of the trial and were evenly distributed between the nicotinamide and placebo groups.[14]

Nicotinamide and side effects

Nicotinamide does not have the vasodilatory effect that niacin has, including skin flushing, headache, and hypotension.[21] Nicotinamide is well tolerated even at high doses with an established safety profile up to 3 g/day.[2] The majority of literature regarding the safety profile and side effects of nicotinamide therapy are from studies involving end-stage renal failure patients on dialysis on treatment with nicotinamide as a phosphate binder to reduced hyperphosphataemia commonly associated with renal disease.

Gastrointestinal disturbance

Diarrhoea has been reported in 7.3% of adult dialysis patients with end-stage renal failure at a mean nicotinamide dose of 1 to 1.5 g.[22, 23] The rate of gastrointestinal side effects in paediatric renal dialysis patients is significantly higher at 30% to 33%.[24]

In the ONTRAC study, 37 patients experienced gastrointestinal events during the study: 9 patients in the nicotinamide arm experienced mild diarrhoea, and 10 patients terminated the trial early in the nicotinamide arm, but no information is available as to the reason behind their termination.[14]

Thrombocytopaenia

The incidence of thrombocytopaenia secondary to nicotinamide has been reported in patients receiving haemodialysis. In the study by Takahashi et al., one patient experienced thrombocytopaenia with subsequent complete resolution two weeks after discontinuing nicotinamide therapy.[22] In another study involving dialysis patients receiving 500 mg to 1500 mg daily nicotinamide, 9 out of 33 patients had some degree of thrombocytopaenia but not clinical complications such as bleeding during the study.[25] A trial reported a statistically significant decrease (P=0.014) in average platelet count in paediatric renal patients receiving nicotinamide between the therapy and control groups.[24] The mechanism behind which nicotinamide causes decreased platelet count is not clearly elucidated but one suggestion is that thrombocytopaenia may result from the low level of thyroxin-binding globulin induced by nicotinamide and its derivatives.[24] The current studies on NMSCs prevention with nicotinamide did not report any cases of thrombocytopaenia as a complication.

Liver toxicity

Hepatic steatosis has been demonstrated in rodents when administered high-dose nicotinamide.[26, 27] Liver toxicity has been documented in psychiatric patients on extended-release nicotinic acid.[28] Biopsy proven hepatic injury in the form of portal fibrosis and cholestasis has been reported in one schizophrenic patient on a daily dose of 9 g of nicotinamide.[29] Reduced DNA methylation and proteins in hepatocytes have been proposed as a potential mechanism for liver steatosis and fibrosis with a dose-dependent relationship being observed in the hepatocytes of rodents on supplementary nicotinamide at the dose of 1 g/kg.[30] Both the ONTRAC study[14] and the study by Drago et al.[16] did not report any cases of liver function derangement in the treatment arms.

Pregnancy/breast feeding

Nicotinamide is able to cross the human placenta with the foetal blood level of nicotinamide greater than the corresponding maternal blood levels.[21] There are no reports of adverse effects due to nicotinamide in human foetus and in the limited trials with pregnant participants, no reports of teratogenicity were reported.

Contraindication and interactions with other medications

There is currently no literature providing sufficient evidence for absolute contraindications to nicotinamide therapy. Liver toxicity is often a worrying prospect of high-dose nicotinamide. While high-dose nicotinamide has been linked to cases of drug-induced

liver injury, studies involving animal models and *ex-vivo* hepatocytes exposed to nicotinamide have demonstrated that nicotinamide ameliorates steatosis and slows progression to fibrosis.[31]

In terms of the potential for insulin resistance, rats treated with cumulative doses of nicotinamide (2 g/kg) demonstrated significantly higher levels of blood glucose and plasma insulin, indicating insulin resistance. However, this has not been replicated in human trials. The existing literature regarding nicotinamide and insulin resistance indicates that nicotinamide is potentially beneficial in decreasing insulin sensitivity in high-risk individuals.[32]

Nicotinamide is a potent hydrophobic agent that can be used to increase the solubility of many drugs in the experimental setting. Despite this, nicotinamide has few known interactions with other medications.[33] Caution should be taken when using nicotinamide concurrently with anti-epileptic medications as nicotinamide has been reported to increase serum levels of carbamazepine.[34]

Conclusion

Nicotinamide is an inexpensive medication with a diverse role in dermatology with an excellent safety profile. It has a demonstrated role in NMSC prophylaxis in high-risk populations and conflicting evidence as a chemopreventive agent in solid organ transplant recipients which is worth exploring further.

Summary and recommendations

Given the clinical efficacy and the low adverse effect profile, nicotinamide supplementation can be beneficial in reducing the incidence of NMSC.

Patients at high risk of NMSC, including organ transplant patients, may derive a greater benefit from oral nicotinamide.

The efficacy of nicotinamide in reducing melanoma is not yet proven.

Recommended dose of nicotinamide is 500 mg twice a day.

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Chemical peels

Michelle K Y Chen[1, 2], Alicia O'Connor[1, 3], Shawn Richards[4], Deshan Frank Sebaratnam[1, 2]

1. South West Sydney Clinical Campuses, University of New South Wales, Sydney, NSW, Australia
2. Department of Dermatology, Liverpool Hospital, Sydney, NSW, Australia
3. Department of Dermatology, Prince of Wales Hospital, Sydney, NSW, Australia
4. Inner Sydney Dermatology, Rhodes Waterside, Sydney, NSW, Australia

Correspondence: Michelle K Y Chen michelle.k.chen@student.unsw.edu.au

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OUTLINE: Photodamage and skin ageing often pose a substantial psychosocial concern, leading to an increased demand for skin rejuvenation procedures. Chemical peeling is one such procedure. Chemical peeling involves the topical application of caustic agents to induce rapid, controlled and uniform injury to part or all of the epidermis, and on occasions, a proportion of the dermis. Their purpose is to promote regeneration and remodelling of the injured layers, ultimately resulting in medical and aesthetic improvement for a variety of cutaneous conditions including photoageing, pigmentary disorders and scarring.

Chemical peels are traditionally classified into three categories based on the depth of injury: superficial, medium-depth and deep. Selecting the chemical peel and peeling agent that will yield the most ideal outcome is dependent on numerous factors, including indication, severity of the condition, patient expectations, available downtime and clinical judgement. To optimise results and minimise the risk of adverse events, an appropriate peel must be accompanied by careful patient selection via a thorough medical history and examination. The procedure also necessitates adequate analgesia, correct application technique, and establishment of a tailored pre- and post-treatment regimen for each individual. When applied to an eligible patient for a suitable indication, chemical peels have demonstrated excellent efficacy at an affordable cost but remain an underutilised therapeutic option.

This review provides a guide for current practice and discusses the different types of peeling agents, their appropriate indications and potential complications.

KEYWORDS: chemexfoliation, chemical face peeling, rejuvenation, photoageing, pigmentary disorders

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Introduction

Photodamage and skin ageing often pose a substantial psychosocial concern, leading to an increased demand for skin rejuvenation procedures.[1] Chemical peeling is one such procedure. The emergence of numerous therapeutic modalities for skin rejuvenation has rendered chemical peeling an underutilised technique despite its favourable safety profile, ease of application, and low cost.[2]

Chemical peeling involves the topical application of caustic agents to induce controlled coagulation and protein denaturation in part or all of the epidermis, and on occasions, a proportion of the dermis.[3] The ensuing skin injury promotes regeneration and remodelling of the affected layers, ultimately resulting in medical and aesthetic improvement of photodamaged and ageing skin.

Chemical peeling is indicated for a range of cutaneous conditions including melasma, ephelides, lentigines, actinic keratoses, rhytides and scarring.[3-5] Chemical peels are traditionally classified into three categories based on the depth of injury: superficial, medium-depth and deep peels. Selecting the chemical peel and peeling agent that will yield the most ideal outcome is dependent on numerous factors including the indication, severity of the condition, patient expectations, available downtime and clinical judgement.

Superficial peels

Superficial peels penetrate variably from the stratum corneum to the basal layer of the epidermis, inducing protein precipitation, epidermolysis and decreased corneocyte adhesion.[1, 6] Following the peel, there is

thinning and compaction of the stratum corneum, and evened melanin distribution.[6, 7] Owing to their depth of penetration, superficial peels are only indicated for superficial pathology including comedonal acne, melasma, dyschromia and mild photodamage.[1, 8] A series of treatments on a weekly to monthly basis is often required for the full benefit of superficial peels.[9] Superficial peels primarily employ alpha-hydroxy acids (AHAs), beta-hydroxy acids (BHAs) or Jessner solution, and are frequently combined with adjunctive topical therapy (e.g. topical retinoids) for optimal efficacy.

Alpha-hydroxy acids

AHAs are carboxylic acids with a hydroxyl group attached at the alpha position of the carboxyl group.[8] Glycolic acid, an AHA with high bioavailability, is commonly employed at concentrations of 20-70% as a superficial peeling agent.[9] When employed in conjunction with 5-fluorouracil, glycolic acid may be helpful for the treatment of premalignant changes including actinic keratosis and actinic cheilitis.[9]

Lactic acid has an identical molecular structure to glycolic acid except for an additional methyl group at the beta-carbon end.[8] Lactic acid decreases melanin synthesis through inhibiting tyrosinase activity, making it an effective treatment for post-inflammatory hyperpigmentation, melasma and solar lentigines.[8]

Mandelic acid is the safest agent among the AHAs, as its large molecular structure enables slow and uniform penetration.[10, 11] Mandelic acid has been used at concentrations of 20-50% for skin rejuvenation and lightening.[12] When used in combination with 20% salicylic acid, 10% mandelic acid has demonstrated clinical efficacy for patients with acne vulgaris and post-acne hyperpigmentation.[13]

To terminate its action, AHAs require neutralisation with water or alkaline solutions including sodium bicarbonate, sodium hydroxide or ammonium salt solutions.[6] The anticipated endpoint of an AHA peel is usually erythema or approximately 5 minutes if erythema is absent.[4, 5] Given lysis is the dominant mechanism of action, AHAs do not cause frosting.

Frosting refers to the whitening of the skin due to protein coagulation where the degree of frosting is directly proportional to the depth of penetration.[6, 14] Three levels of frosting are commonly described: level I frosting pattern corresponds to superficial peel depth and is a light reticular frost with background erythema. A level II frosting pattern corresponds to a medium peel depth and is a confluent light-white frost with background erythema. A level III frosting pattern corresponds to a deep peel depth and refers to solid white frosting in the absence of erythema (Figure 1).

Beta-hydroxy acids

BHAs are carboxylic acids with a hydroxyl group at the beta position of the carboxyl group.[8] The most common BHA used in chemical peels is salicylic acid, a phenolic compound with anti-inflammatory, antimicrobial and depigmenting properties.[4] For superficial chemical peeling, 10-30% salicylic acid in hydroethanolic or polyethylene glycol base is commonly used.[6]

The highly lipophilic nature, high acid strength and small molecular size of salicylic acid allow for rapid and deep penetration of lipid barriers.[3] For this reason, it demonstrates particular efficacy for dermatological conditions such as acne.[1, 11] Salicylic acid has also demonstrated use for photorejuvenation and hyperpigmentation but is less commonly employed for these indications.[3] It is considered a safe agent for individuals prone to post-inflammatory hyperpigmentation; its exfoliative activity on the epidermis is associated with minimal inflammation and thereby lessens the risk of post-inflammatory pigment alteration.[1, 14] Salicylic acid peels are typically applied for 3-5 minutes, resulting in a transient mild-moderate burning sensation.[8] The acid is self-neutralising and does not induce frosting patterns. It does however, form a layer of pseudo frost owing to the evaporation of the hydroethanolic base leaving behind a white crystalline deposit.[4]

Jessner solution

Jessner solution is a superficial chemical peel consisting of resorcinol (14 g), salicylic acid (14 g), 85% lactic acid (14 mL) in ethanol constituted to 100 mL. Modified Jessner solutions replace resorcinol with 8% citric

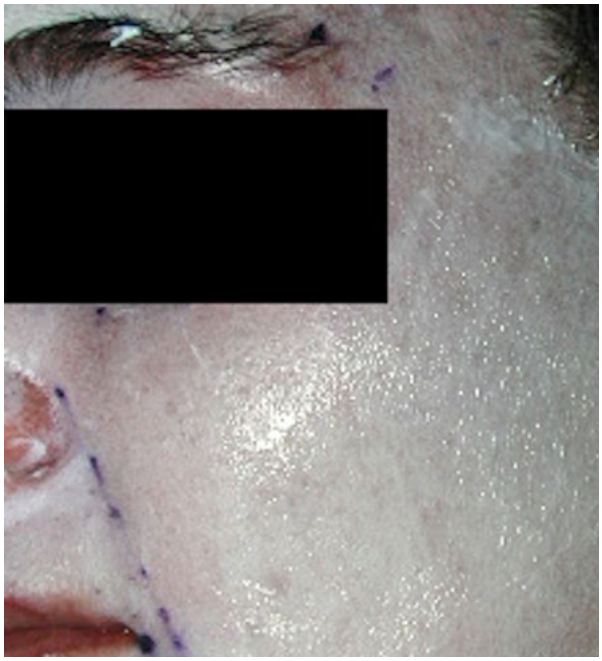

Figure 1: *Level III frosting*

acid and an increased concentration of both salicylic and lactic acids (17 g each). The modification reduces the side effects of resorcinol, which may include contact dermatitis and thyroid dysfunction.[8, 15] Both solutions are commonly used for acne, acne scarring and hyperkeratotic skin diseases.[5, 9, 12] Jessner solutions do not require neutralisation and are generally applied in two to three coats until mild erythema and delicate, patchy frosting develops.[6]

Medium-depth peels

Medium-depth peels cause coagulative necrosis throughout the epidermis and a variable portion of the papillary and upper reticular dermis.[16] Medium-depth peels can be further divided based on the depth of dermal involvement, with the required time for recuperation increasing significantly with deeper penetration of the papillary dermis. Peeling after treatment is usually complete within 7-10 days and is followed by deposition of collagen and elastin fibres over the ensuing three months.[1, 9] Medium-depth peels

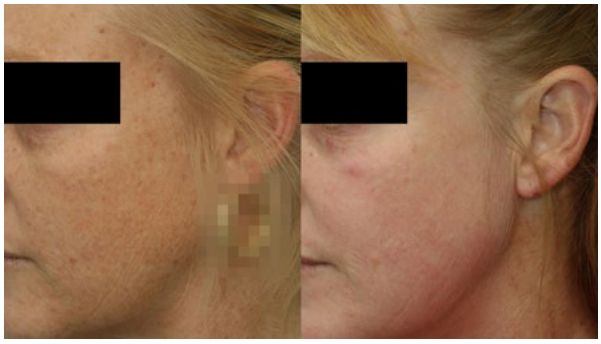

Figure 2: *Before (left) and 1 week after (right) treatment of superficial hyperpigmentation with 35% TCA peel, showing improvement in lentiginous photodamage.*

are recommended for the treatment of fine rhytides, seborrhoeic keratosis, superficial hyperpigmentation (Figure 2), mild-to-moderate photodamage, and field treatment of actinic dysplasia.[7] Due to the increased risk of scarring in low appendageal areas, medium-depth peels are often restricted to the face or the scalp.[4]

The most commonly employed medium-depth peeling agent is 35-40% trichloroacetic acid (TCA), a hydrophilic structural analogue of acetic acid. At concentrations of 35% or above, single-agent TCA peels are only used for the focal treatment of individual lesions due to the considerable risk of scarring and dyspigmentation.[1, 4, 9] For example, 65-100% TCA is delivered to focal areas using various applicators in TCA-CROSS (Chemical Reconstruction of Skin Scars) for the treatment of enlarged pores as well as deep boxcar, ice-pick and fibrotic acne scars.[9, 17] Multiple sessions of TCA-CROSS, repeated at 4-6 week intervals, are often needed to obtain a desired clinical endpoint.[9]

More commonly, 35% TCA is preceded by another agent to form a combination medium-depth peel. Combination peels include solid CO_2 and 35% TCA (Brody peel), Jessner solution and 35% TCA (Monheit peel), or 70% glycolic acid and 35% TCA (Coleman peel).[6] The synergistic action between the active ingredients in combination treatments may enable a slower upward titration, facilitating more controlled and safer peeling compared to the single-agent peels.[2, 10]

The use of TCA peels requires close observation of the frosting pattern to determine the endpoint of the peel.[4] White frost with background erythema (level II frost) is often indicative of an adequate depth of reaction for superficial rhytides, whereas white frost without erythema (level III frost) is usually required for thicker skin or regions with more prominent actinic damage.[3, 15] The presence of a yellow-grey frost indicates injury of the mid-to-deep reticular dermis.[16]

Deep peels

Deep peels denature epidermal keratin and dermal proteins, resulting in coagulation of the entire epidermis and can extend up to the mid-reticular dermis.[16] They are single-session procedures that

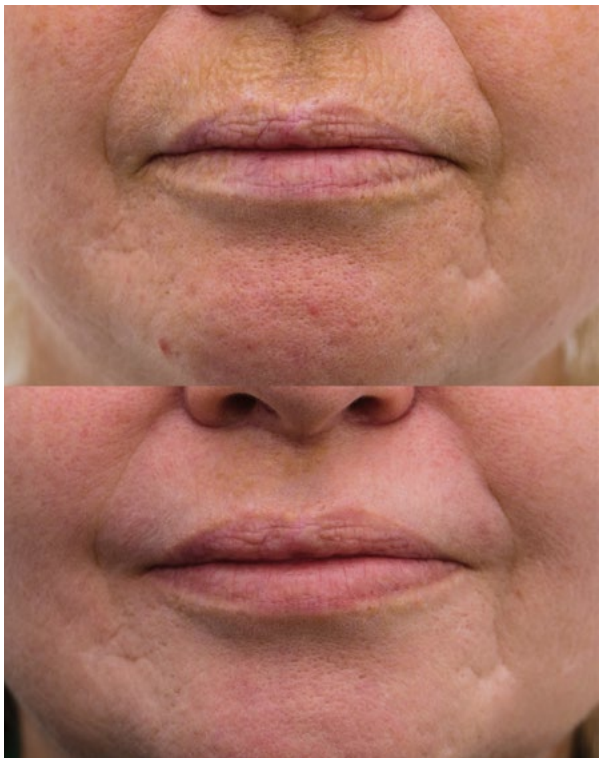

Figure 3: *Before (top) and 3 months after (bottom) a phenol-croton oil peel for the treatment of advanced elastosis and rhytides of the upper lip.*

provide reliable and effective treatment for Fitzpatrick type I and II patients with deep acne scars, severely photodamaged skin, or deep furrowed rhytides in areas such as the lateral canthal and perioral regions (Figure 3).[3] Due to their greater depth of penetration, deep peels achieve more marked improvements in skin tone and texture but require a longer recovery, and carry higher risks of scarring and dyschromia.[9] Re-epithelisation typically commences on day 3 or 4 post-procedure with most patients healed by day 9. Fibroplasia, neoangiogenesis and neocollagen formation is expected to continue beyond six months after the procedure.[3]

Traditionally, 50% TCA formulations were used for deep peels. Phenol-croton oil formulas are now more commonly employed. Phenol is a strongly caustic aromatic hydrocarbon derived from coal tar. At concentrations of >80%, phenol rapidly coagulates epidermal and superficial dermal proteins, resulting in increased dermal collagen and elastin fibres.[6] Phenol was thought to be the active ingredient in these peels, until a series of investigations in the 1990s by Hetter showed that contrary to previous belief, croton oil is the primary active agent and phenol is best regarded as the carrier.[18] Croton oil is a vesicant obtained from the seeds of *Croton tiglium*, the concentration of which is directly proportional to the depth of penetration.[19]

Phenol-croton oil peels were conventionally prepared using the Baker-Gordon formula: this comprises 88% phenol (3 mL), hexachlorophene (8 drops), croton oil (3 drops) and distilled water (2 mL).[19] Use of the Baker-Gordon formula is limited by its high concentration of croton oil (2.1%) which makes it an aggressive and deeply penetrating peel. The deep penetration increases the risk of scarring, persistent hypopigmentation and systemic adverse events associated with phenol.[9, 19]

Variation in croton oil concentration and reduction of phenol concentration to 35% has made phenol-croton oil peels safer and more versatile.[18] Indications for phenol-croton oil peels have broadened to include xanthelasma, actinic keratoses and actinic cheilitis amongst others.[19] The concentration of croton oil is selected according to the area and desired depth of injury. Thicker skin and deeper rhytides found in the glabella and perioral regions often demand higher concentrations whereas moderate damage is treated with lower concentrations.[5]

Hexachlorophene was a widely used surfactant which enhanced penetration of phenol and croton oil, but has been discontinued after neurotoxic effects were demonstrated with its use.[20] Newer surfactants replacing hexachlorophene have produced more stable emulsions.[21]

Patient selection

Pre-procedural consultation is crucial to determine appropriate candidates. The initial consult should begin with a general medical history to identify conditions amenable to chemical peels. Caution should be exercised for patients with risk factors including history of herpes simplex virus infection, connective tissue diseases, atypical scarring as well as causes of delayed wound healing and increased infection risk such as diabetes and immunosuppression should be elicited.[1, 6] Non-urgent aesthetic procedures should be deferred as per any relevant, current public health guidelines including for COVID-19.[22, 23] Open wounds or excoriations are reasons to postpone treatment until their resolution.[1, 24]

Previous COVID-19 infection should not preclude individuals from receiving chemical peels. Patients who have recently recovered from COVID-19 are not expected to pose a greater risk to other patients or healthcare workers compared to healthy individuals.[24] Recent resurfacing procedures, radiation therapy, surgeries and their outcomes must also be elicited during the consultation as these procedures increase the risk of post-peel complications.[6] Previous history of cardiac arrhythmias, hepatic dysfunction or renal impairment are contraindications to deep peels due to the highly arrhythmogenic nature of phenol.[3]

A thorough medication review is also required for risk evaluation. In particular, the use of isotretinoin within the last 6-12 months may delay re-epithelialisation and increase the probability of scarring with medium-depth and deep chemical peels.[1, 6] For superficial peels, international consensus guidelines indicate that isotretinoin is not a contraindication to treatment.[25, 26] Use of photosensitising drugs, hormonal agents and oral contraceptives should also be documented as these medications engender higher risks of post-inflammatory hyperpigmentation.[6, 9] It is also important to assess the patient's motivation for chemical peeling as well as their expectations.[1, 6] A patient who can endure a long-healing period and adhere to pre- and post-procedure regimens is necessary for deep peels.[19]

The Fitzpatrick skin phototype scale should also be employed for the assessment of skin colour, as post-inflammatory hyperpigmentation occurs more frequently amongst patients with darker skin.[10] Superficial peels are applicable to all Fitzpatrick skin types while medium-depth and deep chemical peels are typically reserved for patients with Fitzpatrick scale skin phototype of I to III.[19] Proper selection of peeling agents also requires evaluation of the degree of photoageing, often with the Glogau classification system.[15] Baseline photographic documentation is highly recommended to guide peel selection and to monitor treatment outcomes.[6]

Procedures

Pre-treatment

Pre-treatment preparation allows for the exfoliation of the stratum corneum to allow uniform penetration of the peeling agent, expedited healing, early detection of intolerance, and reduced risk of complications.[20, 27] Skin preconditioning ideally begins at least 2-4 weeks prior to the procedure and is usually discontinued 3-5 days before the peel.[6] Topical retinoids (e.g., tretinoin, retinol, etc.) and hydroquinone are amongst the most commonly recommended agents for this purpose.[1]

For skin priming, tretinoin 0.025-0.05% cream nocte for a minimum of 2 weeks is recommended and may be restarted following the completion of healing.[6] Pre-treatment application of tretinoin thins the stratum corneum to enhance penetration, and stimulates keratinocyte proliferation in the stratum basale to aid regeneration.[20] Hydroquinone inhibits the action of tyrosinase to decrease melanin production. Therefore, hydroquinone 2-4% cream is primarily used as a pre-treatment for dyschromia and lentigines, or to reduce post-inflammatory hyperpigmentation for patients with Fitzpatrick skin types III-VI.[5] Other products used in the pre-peel regimen include glycolic acid, salicylic acid, kojic acid, azelaic acid and topical corticosteroids.[6, 9]

Broad-spectrum sunscreens with a sun protection factor of 50+ should also be initiated 3 months before the procedure and continued indefinitely thereafter.[5, 6] For patients with a history of herpes simplex, prophylactic antiviral therapy with valaciclovir 500 mg three times a day, should be started 1-2 days before the procedure and continued until re-epithelialisation is complete.[19, 28] Prophylactic antibiotics (such as flucloxacillin, cephalexin or erythromycin) may also be considered for medium and deep peels but are seldom required for superficial peels. A test spot 4-8 weeks prior to the procedure may be indicated for patients at risk to evaluate their tolerance for chemical peels and the likelihood of an adverse event.[9]

Analgesia

Analgesia and anxiety management are important considerations for the chemical peel patient. Patients should be warned about potential stinging and burning sensations during the chemical peel which usually subside by the end of the procedure.[7] For superficial peels, patient discomfort is often minimal and hence analgesia is usually not required.[1] However, medium-depth and deep peels may necessitate pain relief in the form of physical cooling agents, oral analgesics (e.g., paracetamol and non-steroidal anti-inflammatory agents), regional nerve blocks, intramuscular analgesia, and general anaesthesia.[6, 15]

Comprehensive local anaesthetic blocks to treatment areas can be an important supplement as patients may experience an immediate and protracted burning sensation in regions of inadequate local anaesthesia.[5]

Treatment

Chemical peeling is ideally performed in an adequately ventilated outpatient surgical setting or office surgical suite.[3] Personal protective equipment should be donned according to the current public health guidelines. For a facial peel, appropriate equipment might include a gown with a head cover, N95 mask, face shield and double gloves.[24] Deep peels may also require ventilation protection with plume evacuation systems such as a high-efficiency particulate air filter or ultra-low penetration air filter.[24, 29] Patients should be positioned in a comfortable supine position with their hair secured away from their face and their eyes closed throughout the procedure. Neutralising agents, eye irrigation solutions and sterile cotton-tipped applicators to wipe teardrops must also be readily available.[6]

The peeling procedure begins with skin cleansing. Cleansing is followed by degreasing of the treatment areas with alcohol- or acetone-soaked gauze to remove lipids, scale and make-up for even penetration of the peeling agent.[1] Peeling agents can be applied using a brush, gauze or cotton-tip applicator according to solution and the quantity to be applied.

Peels should be applied with firm even strokes, with care taken to avoid overlap and skipping.[6] In periorbital and perioral regions where rhytides may be deeper, a more uniform application of the peeling agent can be ensured by manual stretching of skin by an assisting professional.[16] Chemical peeling should also ideally move from areas of thicker to thinner skin: forehead to temples first, cheeks, nose and chin after, followed by perioral and periorbital regions.[6, 27] Extra care should be taken when applying peeling solution to the eyelid. A 2-3 mm safety margin is recommended to prevent the peeling solution from entering the eyes.[3]

Prominent lines of demarcation may be avoided by extending the peel into the hairline when treating the forehead and temporal regions, and beyond the vermillion border in the perioral area.[5] Sharp demarcation lines can be further concealed by feathering the solution around the edge of the jaw and brow.[6, 27] Cosmetic outcomes may also be improved by peeling individual facial regions to different depths. Depth of penetration may be altered through variation of the peel type, concentration of the active ingredient and pressure on application.[30]

Systemic toxicity due to absorption of phenol in deep peels is associated with cardiac arrhythmias.[8] Hence, full-face phenol-croton oil peels necessitate electrocardiographic monitoring, intravenous access

and 10-15 minute time-lapse between facial units to allow for phenol clearance.[15] The peel should be immediately paused in the event of a supraventricular arrhythmia, and only resumed when the patient returns to normal sinus rhythm.[5, 19]

Post-treatment

Patients should be provided with a patient information leaflet on what to expect over the entire healing process and written instructions for post-peel care.[6] The importance of adhering to post-operative care for a hastened recovery and prevention of complications should be stressed.

Immediately post-peel, generous use of a water mist spray may alleviate patient discomfort. Once frosting has dissipated and only erythema remains, a thick layer of emollient should be applied to the peeled areas.[3, 5] A generous coat applied over the entire peeled region should be consistently reapplied 3-5 times per day or as needed until new skin is visible and the treated regions are fully peeled.[5, 16] For the first 24 hours, non-steroidal anti-inflammatory drugs, cool compresses with ice packs, and gentle debriding soaks with dilute bleach or vinegar can ameliorate the immediate post-operative swelling, pain and necrotic epidermal debris.[3]

Approximately 1-3 days post-peel, gentle cleansing and direct contact with water during showering may be resumed.[15] Direct, prolonged sun exposure should be avoided for 12 weeks post-peel, with daily sunscreen application resumed as soon as tolerated.[5, 6] Oral contraceptive pills and hormonal replacement therapy should be avoided where possible as increased levels of oestrogens can cause hyperpigmentation.[31]

Adverse events

Chemical peels are relatively safe provided that the appropriate peel is used for the indication and the patient, and that it is performed under the supervision of an experienced clinician.[6] Complications are often minor, more common in darker-skinned individuals and following medium-depth or deep peels. Minor adverse events including skin irritation, erythema, pruritus, oedema and blistering, may become evident within minutes to hours of the procedure.[6, 31] They are more frequently encountered in those with sensitive skin and may persist until the completion of re-epithelialisation. Application of ice, topical corticosteroids and emollients may be used for symptomatic relief until resolution.[31]

The length of post-peel erythema should be expected to last proportional to the depth of penetration.[19] Persistence of erythema, especially if erythema is localised, irregular or progressive, is predictive of potential scarring or hyperpigmentation.[20] Hydrocortisone 1% ointment, pulsed dye laser and frequent application of a broad-spectrum sunscreen may be employed to accelerate the resolution of prolonged erythema.[5, 10, 28]

Complications may also arise days to weeks following the procedure. Post-inflammatory hyperpigmentation is a comparatively common complication of chemical peels. Post-inflammatory hyperpigmentation usually lasts less than six months and is especially prevalent amongst patients with Fitzpatrick skin types III to VI, excessive post-peel sun exposure, underlying pigmentary disorders and use of photosensitising medications.[5, 10] Post-inflammatory hyperpigmentation can be managed with a combination of broad-spectrum sunscreens, tretinoin 0.05% cream, hydrocortisone 1% cream, and hydroquinone 4% cream.[5, 27]

Post-inflammatory hyperpigmentation may be followed by a period of pseudo hypopigmentation where the colour of the treated areas appears hypopigmented relative to the untreated, photo-damaged skin.[19] True hypopigmentation is rare but often permanent; it was more frequently observed when deep chemical peels were commonplace, likely due to the depth of injury and the use of phenol which is melanotoxic.[31] Risk of depigmentation may be reduced by using bismuth subgallate as a post-phenol peel mask.[20]

Damage to the skin barrier exposes the individual to an increased risk of infections, often by *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and herpes simplex.[1] Lesions should be swabbed for microscopy, culture and sensitivity. A course of antibiotics, antiviral or antifungal medication may be considered to minimise the risk of delayed healing and scarring.[5]

The risk of scarring increases with increasing peel depth, inappropriate patient selection and inattentive post-operative care. The most susceptible areas are in the upper lip or skin overlying bony prominences such as the zygomatic arch and mandible.[3] Hypertrophic scarring may be managed with silicon coverings, and intralesional corticosteroid injections or 5-fluorouracil injections.[5, 6] Multiple sessions with flash-lamp pulsed dye laser and intense pulsed light are also useful for erythematous scars.[5] Atrophic scars may benefit from fractional laser.[17]

Conclusion

In recent years, light-based resurfacing modalities including non-ablative, fractional and ablative lasers have largely superseded chemical peels due to their enhanced depth modulation and relative lack of adverse effects and toxicity. However, the simplicity, availability and cost-effectiveness of chemical peels allow the procedure to retain its clinical utility in the dermatology

armamentarium against photodamaged skin and ageing. Careful patient selection, curation of peeling agents, application technique and post-operative care will optimise results.

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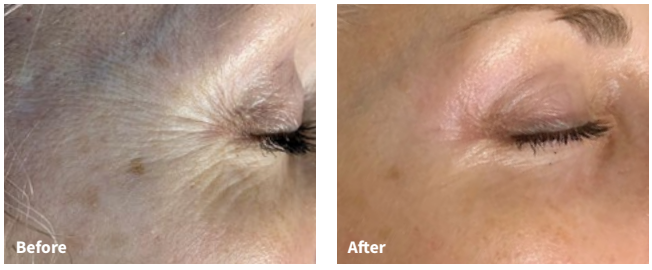

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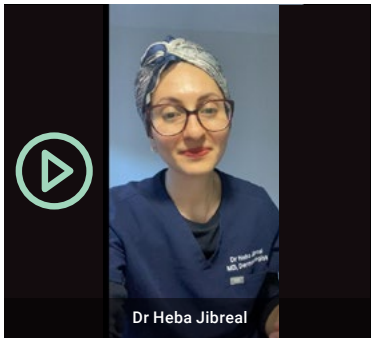
Laser resurfacing and laser-assisted PDT for actinic keratoses: a review



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Alvin Lim[1], Davin Lim[2], Heba Jibreal[2,3]

1. University of Melbourne, Victoria, Australia
2. Cutis Clinic, Queensland, Australia
3. Faculty of Medicine, University of Queensland, Brisbane, Australia

Correspondence: Alvin Lim alvinlimdr@gmail.com

Disclosures: *none*

OUTLINE: Actinic keratosis (AK) is a premalignant lesion arising from chronic ultraviolet exposure. It appears as small erythematous, scaly papules and plaques on sun-exposed areas of fair-skinned individuals. The presence of AK indicates chronic sun damage and increased risk of skin cancer. The estimated risk of malignant transformation to squamous cell carcinoma ranges from 0.1% to 20% per annum, and 1-10% over a 10-year period. It is difficult to reliably determine which individual lesions will become malignant. Therefore, treatment of AK is appropriate to reduce the risk of malignant transformation.

A wide range of treatment modalities are available to treat AK. These include topical treatments (5-fluorouracil, imiquimod, diclofenac, ingenol mebutate), cryotherapy, curettage, surgical excision, chemical peels, photodynamic therapy (PDT), and most recently, laser and energy-based treatments. Treatment choice is guided by disease severity, body site, patient preference, comorbidities, previous treatments, cost and side effects of the treatment.

Laser resurfacing offers significant advantages compared to conventional treatments for AK management. It is useful for treating hyperkeratotic lesions and increasing absorption of topical treatments. Likewise, laser-assisted PDT is promising, with results suggesting it is better at clearing AK and improving photoageing than PDT alone.

In this article, we provide an up-to-date review of the laser and energy-based treatment modalities used to treat AK and actinic cheilitis. We also summarise studies comparing them to PDT, as monotherapy and in combination.

KEYWORDS: actinic keratosis, actinic cheilitis, laser therapy, photodynamic therapy, laser-assisted photodynamic therapy

Lim A, Lim D, Jibreal H. Laser resurfacing and laser-assisted PDT for actinic keratoses: a review. Opin Prog Cosmet Dermatol 2022;2(1):28-37.

Introduction

Actinic keratosis (AK) is a premalignant lesion arising from chronic ultraviolet (UV) exposure. It appears as small erythematous, scaly papules and plaques on sun-exposed areas of fair-skinned individuals. Typical sites include the head and neck, and dorsal aspect of hands and lower extremities. Actinic keratoses can be classified into three Olsen grades (I-III), depending on the lesion's thickness and degree of hyperkeratosis.[1] The presence of AKs indicates chronic sun damage and thereby an increased risk of developing skin cancer. Although some lesions may spontaneously regress (15-63% per year[2]) there is a small proportion which evolve into keratinocyte carcinoma (intraepidermal and squamous cell carcinoma [SCC]). The estimated risk of malignant transformation to SCC ranges from 0.1% to 20% per annum,[2,3] and 1-10% over a 10-year period.[4] It is difficult to reliably determine which individual lesions will become malignant. Therefore, treatment of AKs is appropriate to reduce the risk of malignant transformation.

A wide range of treatment modalities are available to treat AKs. These include topical treatments (5-fluorouracil, imiquimod, diclofenac, ingenol mebutate), cryotherapy, curettage, surgical excision, chemical peels, photodynamic therapy (PDT), and most recently, laser and energy-based treatments. Treatment choice is guided by disease severity, body site, patient preference, comorbidities, previous treatments, cost and side effects of the treatment.[5] Treatments can be

categorized as lesion-directed or field-directed; the distinction depends on the method of application rather than the treatment modality per se. Field treatment follows the principle of field cancerisation, whereby a clinically visible AK lesion contains an adjacent area of subclinical extension that is predisposed to malignant transformation. This is supported by evidence of DNA damage in perilesional skin, including the p53 marker of keratinocyte carcinogenesis.[6]

Overview of PDT

Photodynamic therapy involves directing wavelengths of light onto a specific area pretreated with a photosensitising agent. The origins of modern PDT can be traced back to 1900, when it was discovered that *Paramecium caudatum* incubated with acridine orange dye and subsequently exposed to sunlight caused the organism to die.[7] In 1904, the importance of atmospheric oxygen to this reaction was noted.[8] As systemic porphyrins localised to tumours,[9] they started to be used as a photosensitising agent for PDT. However, early systemic applications for treating cancer were hindered by prolonged generalised photosensitivity. Topical 5-aminolaevulinic acid (ALA) was introduced in the 1980s to treat skin disorders as it demonstrated specificity for dysplastic cells without causing generalised photosensitivity.[10] Once absorbed into skin, ALA is metabolised to protoporphyrin IX (PpIX), which mediates the photochemical reaction. Today, ALA or its methyl ester, methyl-aminolaevulinic acid (MAL) are the most commonly used photosensitisers for treating AKs. The photosensitiser is applied topically and allowed to absorb into the skin. After an incubation period, the activation of the photosensitiser by a light source produces cytotoxic oxygen species which results in apoptosis and necrosis of diseased tissue.

International guidelines recommend PDT as first line therapy for multiple AKs due to its high efficacy, excellent cosmetic outcome and improvement of photoageing.[11, 12] Clearance rates for the face and scalp ranges from 69% to 93%,[5] with 24% recurrence at 12 months.[13] PDT is very effective as field treatment since it can treat large areas with multiple visible and subclinical AKs. It is also a feasible option for AKs on the legs due to lower risk of wound complications.[5] Efficacy is greater for treating AKs on the face and scalp compared to the hands, but there are no studies directly comparing treatment between the two sites.[5] Compared to traditional treatments, PDT has demonstrated similar efficacy to imiquimod,[14, 15] 5-FU[16] and cryotherapy,[17, 18] with the advantages of being a sessional treatment rather than a prolonged course, improved cosmesis and patient satisfaction. Furthermore, PDT may be a better treatment for field cancerisation. MAL penetrates into sebaceous glands, which could destroy atypical keratinocyte deposits that are untreated by cryotherapy and topicals. It was also demonstrated that expression of p53, an early marker of epidermal carcinogenesis, was significantly reduced after PDT, suggesting it can inhibit the process of carginogenesis.[19]

The main disadvantage of PDT is that it is less effective for Grade II to III AKs as it is more difficult for the photosensitiser to penetrate through hyperkeratotic lesions. It is recommended in practice to curette thicker lesions prior to PDT.[5] Furthermore, side effects of pain, erythema and crusting can be significant.[20] Compared to ALA, MAL has greater skin penetration due to increased lipophilicity[21] and greater selectivity for tumour cells.[22] Conventional PDT (cPDT) uses topical ALA or MAL and a light source such as red or blue light, or lasers in the red and blue range. As we will discuss in this review, the use of lasers can increase the efficacy of PDT and reduce the application time of the photosensitiser.

The choice of light source for PDT is determined by two main factors: the absorption spectrum of the photosensitiser and the wavelength and penetration depth of the light.[23] The first photosensitisers used were porphyrins, which have peak absorption in the Soret band corresponding to blue wavelengths of the visible spectrum. The earliest light sources used to activate photosensitsers were broad spectrum light sources. These include the quartz lamp, xenon arc lamp (600-660 nm), slide projectors (400-650 nm), halogen lamps (600-800 nm), and tungsten lamp with red filter (600 nm). However, they had pronounced side effects of discomfort, erythema and localised phototoxic reactions.

Longer wavelengths of light have greater penetration depth into the skin. Thus, red light was adopted for use in PDT, which is less well absorbed by porphyrins but has deeper penetration. In 1990, skin cancer and AKs were successfully treated with topical ALA and a tungsten slide projector with a red filter (600 nm).[10] Since then, topical ALA and light sources with red filters became common practice. Topical ALA is converted to protoporphyrin IX (PPIX) in target cells and has peak absorption of blue light at 417 nm wavelength and a second peak absorption of red light at 650 nm. In the late 1990s, blue light became more widely used for the treatment of AKs due to these lesions being predominantly superficial. One of the earliest RCTs showed 89% of patients had greater than 75% clearing of AKs at 12 weeks follow up after one or two sessions of blue light ALA-PDT.[24] Current PDT practice is to use ALA with blue light or MAL with red light.

More recently, daylight PDT (dPDT) was introduced to overcome the side effects from traditional light sources. Daylight PDT involves the application of MAL to the skin without occlusion and subsequent exposure to ambient daylight. A high SPF sunscreen without mineral

filters is applied before the photosensitising cream. Thirty minutes later the patient spends two hours outdoors.[5] Trials from Australia and Northern Europe support the use of dPDT for grade I and II AKs on the face and scalp. Its main advantages are that it is almost painless, well-tolerated and convenient, requiring reduced treatment time per session.[25] Two split-face randomised controlled trials of dPDT and cPDT showed dPDT was non-inferior to cPDT at 12 weeks (complete clearance rate of 89.2% vs 92.8%,[26] and 70% vs 74%,[27] for dPDT and cPDT, respectively). In Rubel's study, 96% of mild lesions maintained complete remission at 24 weeks.[26] Pain scores were significantly lower (nearly painless) and patient satisfaction was higher with dPDT.

Laser-illumination PDT

In recent years, researchers have investigated combining field treatments to increase efficacy. A review of combination therapies found limited data supporting combining laser, cryotherapy, curettage, or topicals (5-FU, ingenol mebutate, tazarotene, calcipotriol) with PDT.[28] Lasers were first used as a light source with PDT in the 1990s.[23] Lasers used with topical ALA were mainly of the red wavelengths, including copper vapor-dye laser (630 nm), nd:YAG laser (630 nm) and argon ion-dye laser (630 nm).[23] The reported clearance of AKs ranged from 80-100% (average 92%) with 3-12 month follow up among various studies.[29] Despite this, most studies reported significant pain and discomfort during treatment, and post-treatment erythema, blistering, crusting, and dyspigmentation. As with laser monotherapy, there is a lack of consensus among guidelines on the use of laser-assisted PDT for AK treatment. A meta-analysis of four RCTs for laser-assisted PDT reported a 33% higher clearance of AKs and no difference in pain than PDT or laser alone, but the quality of evidence was low.[30]

Laser resurfacing as monotherapy

Laser resurfacing allows treatment depth to be controlled, with better lesion- or field-directed tissue destruction.[31] By contrast, conventional field treatments such as cryotherapy, chemical peels and dermabrasion are limited by unreliable penetration depth, which may miss deposits of dysplastic keratinocytes in adnexal structures. A high rate of recurrence is observed with conventional treatment for widespread AKs. Field laser resurfacing destroys not only clinically affected skin, but also adjacent actinic-damaged skin, which may result in fewer recurrences and prevent development of AKs and skin cancer. Resurfacing lasers started as fully ablative devices that removed horizontal layers of skin through vaporisation of water-based tissue. In the mid-2000s, the advent of fractional laser technology led to fractional delivery of laser energy that created micro-columns of tissue injury with preserved intervening skin allowing safer and faster recovery. Nevertheless, guidelines do not currently recommend laser resurfacing as a primary treatment for AKs due a lack of large, placebo-controlled and replicable studies. Canadian and European guidelines suggest resurfacing lasers can be used to treat areas of clustered AKs,[32, 33] while British guidelines ascribe a level B recommendation as an effective AK treatment in principle.[5]

Full ablative laser resurfacing

The most common ablative lasers are the CO_2 and the erbium (Er):YAG lasers, and treatment depth is proportional to energy (fluence) and number of treatment passes. CO_2 laser (10 600 nm) has greater residual thermal heating and correspondingly increased side effects such as oedema, burning, oozing, crusting and erythema, and prolonged downtime of up to two weeks.[34] The Er:YAG laser (2940 nm) produces less coagulation than CO_2 laser, which makes bleeding more likely.

Laser resurfacing has several advantages compared to 5-FU, which is widely used for field treatment[35] and has approximately 80% reduction in lesion count[36] and 52% average complete clearance rate.[37] Treatment course for 5-FU is typically twice daily for 3-4 weeks, but anticipated side effects of erythema, crusting and pain reduce patient tolerance and compliance. Data from RCTs suggest that CO_2 laser monotherapy is equal or better than 5-FU,[35] but not better than ALA-PDT.[36] In one study, Er:YAG laser monotherapy was associated with lower AK recurrence at 12 months compared with 5-FU (laser 40.7% vs 80.8% 5-FU), which also required a treatment period of four weeks and additional healing time.[37] Er:YAG laser required only one treatment session with average recovery time of 7 days. However, the drawback of fully ablative resurfacing lasers for field-treatment of AKs are: lack of lesion-specificity, recovery time, potential short- and medium-term adverse effects, cost and operator dependency.

There was no significant difference between CO_2 and Er:YAG laser efficacy for facial AKs in one retrospective study.[38] Seventy-eight percent of patients showed 75-100% improvement in actinic damage in treated areas. Recurrence rate was 56% over an average follow-up of 39 months, and all except one patient had fewer than four recurrent lesions. Similarly, another retrospective analysis of 24 patients reported 87% had full clearance at one year and 58.3% at two years.[39] Overall reduction in AKs was 94%.[39] This was comparable to Er:YAG laser monotherapy in five patients, which found an overall 93% reduction in AKs at three months.[40] For CO_2 laser monotherapy, 31 patients had 58% complete clearance rate after 15-72 months.[31]

Fractional laser resurfacing

Fractional laser resurfacing is effective at clearing AKs but is likely to require either multiple passes or

multiple treatment sessions. A split-face study of nine patients with face or scalp AKs comparing one session of fractional CO_2 ablative laser resurfacing and no treatment found a significant reduction in AKs on the treated side at one month (47% vs 71% non-treated, P=0.01), but this difference was not sustained at three months (49% vs 57%, P=0.47).[41] Notably, most clearance was for Grade I AKs, with thicker AKs unchanged.

It is unclear whether laser resurfacing can help prevent AKs and skin cancer in patients with actinic skin. A report of two patients who had non-melanoma skin cancer (NMSC) treated with facial CO_2 resurfacing had no recurrence after 33 and 52 months respectively, but developed cancer at untreated sites.[42] Similarly, CO_2 laser treatment was associated with lower incidence of NMSC over 5-year follow up compared to control.[43] Fulton et al. concluded that CO_2 laser resurfacing was ineffective against preventing AKs and basal cell carcinoma (BCC), and not better than dermabrasion and chemical peels as prophylaxis. Of 35 patients, 14% developed AKs or BCC within 12 months of laser treatment.[44] In a comparable study, three of 25 patients developed NMSC in treated areas.[38] However, it was argued that the tumours might have been pre-existent, or the patients already had high baseline risk given their history of skin malignancies.[38]

Non-ablative fractional lasers use heat to induce thermal injury columns in the epidermis and dermis without destroying tissue. The stratum corneum remains intact, and active cooling reduces heat transfer to the surrounding tissue. The coagulated tissue stimulates removal of UV-damaged cells and repopulation by healthy follicular-based cells.[45] As a result, non-ablative lasers exhibit reduced downtime compared to ablative lasers. However, their long-term efficacy is uncertain due to limited studies to date. Multiple passes and treatment sessions may be required to improve efficacy.

As reviewed by Dong and Goldenberg,[46] a number of non-ablative fractional lasers have been shown to be effective for treating multiple AKs. All studies reported excellent patient tolerance and reduced downtime, and good cosmetic outcome. Unfortunately, the studies had small sample sizes, short follow-up, and lacked controls.

The 1927 nm fractional thulium laser was used to treat facial AKs on 24 patients with up to four treatment sessions.[45] Patients had a 6-month reduction in absolute AK counts of 86.6%. The 1550 nm erbium-glass fractionated laser was studied in 10 patients who received 5-10 treatments over 4-6 week intervals, with 0.025% tretinoin cream between laser treatments.[34] At 6-month follow up, they reported a 46% mean reduction in AKs.[34] Post-treatment erythema and oedema occurred in all patients for up to 48 hours. In another study, the 1550 nm fractional erbium-doped fibre laser was tested on 14 men who received five treatments over 2-4-week intervals.[47] At 6 months, a 55.6% mean AK reduction was reported. The 1540 nm non-ablative fractional laser was studied on 10 patients who received three treatments at 4-week intervals.[48] At 3-month follow up, the investigators reported a significant reduction in AK count and 79% reduction in severity (P<0.001).[48] In addition to the above, it is worth mentioning one study of a hybrid laser consisting of 1470 nm diode non-ablative/2940 nm Er:YAG ablative fractional laser. In nine patients with AKs at various sites who received one treatment, 92% of lesions resolved after 2-3 months.[49] No adverse events occurred while improvement in skin texture and tone was also observed.

Two studies of the Q-switched 1064 nm Nd:YAG laser reported promising results. After four treatments, five out of six patients in one study had complete clearance at 3-month follow up.[50] After one treatment of combined Q-switch 532 nm KTP and Nd:YAG 1064 nm laser, full clearance of AKs in 10 patients was observed within 20 days.[51]

Laser-assisted drug delivery and PDT

Fractional laser resurfacing can also enhance the skin penetration of topical treatments. The principle of laser-assisted drug delivery is to create microscopic channels within the skin surrounded by a thin coagulation zone to facilitate penetration of topical drugs. The coagulation zone becomes a reservoir for the drug, resulting in gradual release of the drug over a few hours. In this sense, laser treatment has the benefit of reducing the treatment duration of the topical therapy. A case report of two patients with multiple facial AKs who underwent fractional Er:YAG laser ablation followed by 5-FU for six nights showed complete clearance up to 9 months follow up.[52] Another case report demonstrated enhanced response to ingenol mebutate after Er:YAG laser pretreatment.[53] No significant adverse effects were reported from combining both treatments.

Laser-assisted PDT may target the aberrant immune response in AK pathogenesis. Reduced epidermal expression of cancer-associated genes p53 and Ki67 were observed following Er:YAG laser-PDT.[54] Compared with ALA-PDT, Er:YAG laser-PDT treated skin showed significantly lower CD1a+ Langerhans cells at 48 hours, while at three months CD8+ T cells were significantly lower.[54]

A direct comparison between ablative laser-assisted PDT and conventional-PDT demonstrated superior response to the addition of laser. Choi et al. conducted a prospective randomised controlled trial of 88 patients with facial and scalp AKs. All patients received conventional PDT with MAL (MAL-PDT), with some

randomised to receive Er:YAG laser pretreatment.[55] Treatment arms were laser-PDT with 2-hour incubation, laser-PDT with 3-hour incubation and MAL-PDT with 3-hour incubation. At three months post-treatment, complete clearance was higher for 3-hour laser-PDT (91.7%) than for 2-hour laser-PDT (76.8%) and MAL-PDT (65.6%).[55] Differences in efficacy remained significant at 12 months. Recurrence rate was lower for 3-hour laser-PDT (7.5%) than for MAL-PDT (22.1%) at 12 months.[55]

In a split-face study of 15 patients, two symmetrical areas on the face and scalp were randomised to a single treatment of MAL-PDT, or MAL-PDT with CO_2 laser pretreatment. At three months, the laser-PDT side showed higher complete clearance compared with PDT alone for grade I AKs (laser-PDT 100% vs 80% PDT alone), and grade II-III AKs (88% vs 59%).[56] Similarly, two small studies of CO_2 laser pretreatment with MAL-PDT reported 85-100% clearance after 2-3 treatments.[57,58] These studies did not report any serious adverse effects, apart from mild pruritus and erythema.[57] Furthermore, CO_2 laser-PDT was associated with lower recurrence and improved photoageing compared to PDT-alone.[56-58]

Er:YAG laser pretreatment was shown to improve efficacy of daylight PDT. The clearance rate of Er:YAG laser-dPDT was 74% vs 46% for dPDT alone in a study of organ-transplant recipients.[59] Erythema and crusting were more intense after Er:YAG laser-dPDT than dPDT alone. Likewise, Er:YAG laser was found to be superior to microdermabrasion pretreatment for daylight PDT. Er:YAG dPDT showed higher AK clearance (81 vs 60%), lower AK recurrence and better improvement in pigmentation and texture after three months.[60] However, the laser-treated side resulted in more localised skin reactions including erythema, crusting and infection.

On the other hand, fractional 1927 thulium laser combined with PDT (3-hour MAL incubation) was not better than PDT alone. In 12 women who were treated for AKs to the décolletage, thulium laser-PDT showed higher 12-week clearance to MAL-PDT, 100% and 82% respectively, but no statistical significance (P=0.464).[61] There was no difference in efficacy between thulium laser with or without PDT. Patients rated cosmetic improvement with thulium laser to be higher.

A recently developed synergistic irradiation procedure combining the advantages of conventional and daylight PDT (called synergistic PDT) involves 1-hour incubation and 1-hour irradiation time using an artificial light source emitting wavelengths of the daylight spectrum adapted to the PPIX absorption peaks. It was demonstrated to be effective and relatively painless. In a study of 28 patients with AKs on the head who received CO_2 laser pretreatment to 5-ALA synergistic PDT, there was 96.4% reduction in AK severity and 100% reduction in AK count at three months.[62]

Incubation times and laser-assisted PDT

Laser pretreatment can reduce the incubation time for photosensitiser absorption and number of PDT sessions. Larger studies are required to determine the optimal incubation time for laser-PDT. One study compared incubation time of 2-hours for CO_2 laser-PDT with conventional 3-hour MAL-PDT. Each group received two treatments two weeks apart. At 10 weeks post-treatment, there was no significant difference in clearance rate, which was 64.7% for MAL-PDT and 71.4% for laser PDT (P=0.55).[63] In another study, 29 patients pretreated with CO_2 laser to AK lesions underwent ALA- or MAL-PDT with 70-90 minutes incubation time.[64] At eight weeks follow up, 70.6% of lesions were completely cleared within three sessions.[64] Despite lacking a control group, the efficacy was similar to another study which reported 66% clearance rate with 3-4 sessions of conventional PDT.[65]

A randomised split-face study of 19 patients with AKs and/or NMSCs compared a single treatment of CO_2 laser-PDT and ALA-PDT.[66] Incubation time was 1 hour for both sides. After six months follow up, the side treated with CO_2 laser-PDT showed superior clearance of AKs and superficial NMSCs compared to PDT alone. The laser-treated side achieved 74% complete clearance of AKs, of whom 53% had no AK recurrence and 21% had no NMSC recurrence after 6 months. One study explored acoustic pressure wave ultrasound added to CO_2 laser-PDT to shorten the incubation time further. Acoustic pressure wave ultrasound and CO_2 laser ablation followed by 1-hour incubation MAL-PDT had similar efficacy to 3-hour MAL-PDT.[67]

Laser settings and PDT

The optimal laser settings for PDT are unknown, but one study suggests that higher density of the ablative laser channel improves the efficacy of PDT, particularly for hyperkeratotic lesions. In this study, 47 patients were randomly assigned to undergo one of three Er:YAG ablative fractional laser treatments at 5.5%, 11%, and 22% density prior to MAL-PDT.[68] At 3- and 12-months follow up, the 22% density laser-PDT showed significantly higher clearance rate than the 5.5% density group (3 months, 88.7% vs 80.0%; 12 months, 81.1% vs 60.9%) and reduced recurrence.[68] There was no difference in adverse effects or cosmetic outcomes.

Coloured skin and ablative lasers

Er:YAG laser is more appropriate for darker skin types compared to CO_2 laser as it induces less thermal tissue damage resulting in faster wound healing and fewer severe side effects of erythema, swelling and post-inflammatory hyperpigmentation. A study of 45 Korean patients involved one session of MAL-PDT to facial AKs, with half randomised to fractional Er:YAG laser

pretreatment. Patients were followed up to 12 months post-treatment. At 12 weeks, laser-PDT had higher overall clearance than MAL-PDT (86.9% vs 61.2%). At 48 weeks, laser-PDT had lower lesion recurrence than MAL-PDT (9.7% vs 26.6%), and higher histological clearance (78.5% vs 45.0%). Excellent or good cosmetic outcome was reported in >90% cases. Erythema and hyperpigmentation were more common in the laser-PDT group. For grade II and III AKs, the clearance rate at 12 weeks were 93.5% and 69.4%, respectively, following laser-PDT. This was comparable to a study by Togsverd-Bo, in which Caucasian patients treated with CO_2 laser-PDT showed 90% clearance at 12 weeks, which ranged from 90% for grade II and 50% for grade III AKs.[56]

Other light sources and PDT

Long pulsed pulsed-dye laser (PDL, 595 nm) was recently explored as a potential laser as it has a short pulse duration of 10 milliseconds and rapid firing rate of 1Hz, which would reduce the exposure time to the laser and theoretically reduce the side effects. This would be sufficient to activate apoptosis in lesioned tissue but reduce surrounding tissue necrosis. In a study of 41 AK patients, PDL with ALA-PDT achieved approximately 90% lesion clearance at 8 months, which was comparable to 5-FU or blue light PDT.[69] Minimal discomfort and erythema were reported. In another study, PDL-assisted PDT was inferior to conventional PDT in a split-face study of 60 patients with facial AKs randomised to receive either PDL-PDT or conventional PDT. PDL-PDT was found to have significantly lower complete clearance rate versus conventional PDT (10.3% vs 44.9%) at 6 months.[70]

Another study compared light-emitting diode (LED) laser and PDL pretreatment for MAL-PDT. Patients received up to five treatments 1-2 weeks apart. At 3-month follow up, there was no significant difference in histological clearance between the two treatments, but LED laser-PDT was better tolerated.[71]

Intense pulsed light (IPL) laser has gained recent attention for use with PDT, as IPL contains blue and red wavelengths which activates PPIX at its various peaks. So far, its efficacy for treating AKs is uncertain. As reviewed by Alexaides-Armenakas, clearance rates of IPL-PDT for AKs were reported to be 50-87% after 1-2 treatments.[23] Pretreatment for 1 week with 5-FU followed by IPL-PDT was reported to have 90% clearance at 1-year follow up.[72] IPL-PDT appears to be superior to IPL alone at improving photoageing signs of fine rhytides, erythema and dyspigmentation. Importantly, these studies had different incubation times and different IPL devices.

Laser treatment of actinic cheilitis

Actinic cheilitis is considered a premalignant lesion of SCC, with higher likelihood than AKs to progress to SCC. PDT is not as effective for actinic cheilitis than for AKs elsewhere. This might be because of inconsistent light penetration caused by lower lip anatomy, and insufficient uptake of photosensitiser on the lip due to dilution by saliva.[73]

In a study of CO_2 laser monotherapy for actinic cheilitis in 43 patients, three (7.0%) developed recurrence, and two (4.6%) developed SCC over 29 months follow up.[74] Recurrent cases were all cleared with a second CO_2 laser treatment. The authors suggest that for extensive areas of actinic cheilitis or persistent cases, ablative laser presents a better option due to histological clearance, better cosmetic outcome, lower invasiveness and lower side effects compared to vermilionectomy and PDT.[74]

The non-ablative 1927 nm fractional thulium laser offers reduced side effects compared to ablative lasers, while being more effective than nonsurgical treatments for actinic cheilitis. A multicentre study of 15 patients reported 51-100% improvement after 1-2 treatments.[75]

Regarding laser-assisted PDT for actinic cheilitis, one study reported that a single session of Er:YAG laser-PDT was superior to two sessions of MAL-PDT, with higher efficacy, lower recurrence rate and similar cosmetic outcome and side effects. At 3-months follow up, histological clearance for laser-PDT versus MAL-PDT was 92% versus 59%; and at 12 months, 85% versus 29% respectively. Recurrence rate was 42% lower in the laser-PDT group (8%) versus MAL-PDT (50%) at 12 months.[73]

PDL-assisted PDT also shows efficacy for treating actinic cheilitis. A study of 21 patients with refractory actinic cheilitis treated with PDL-assisted ALA-PDT with 2-hour incubation showed complete clearance in 68% after a mean of 1.8 treatments and mean follow up of 4.1 months.[76] Side effects were minimal and resolved by 3 days.

Summary Table: Laser and energy-based field-directed treatment options for actinic keratosis/cheilitis

Treatment	% Cleared at 3-6 months	% Cleared at 12 months	Comments
Fractional CO_2 laser (10 600 nm)	47% at 1 mo[43], 60%[67], 65.3%[77], 85.7%[45], 92%[65]	37%[77], 87%[39]	CT[43,45] RCT[67, 77, 65] Not sustained at 3 months[43] Retrospective review of CO_2 and/or Er:YAG[39]
Fractional Er:YAG laser (2940 nm)	78.3%[37], 81%[62]	74.1%[37], 87%[39]	RCT[37, 62] Retrospective review of CO_2 and/or Er:YAG[39]
Q-switched 1064 nm Nd:YAG	100%[49], 60%[48]	Not available	CT[49, 48] Combined Q-switched KTP 532 nm and Nd:YAG 1064 nm[49] 60% improvement in AKs at 3 months on grading scale[48]
1470 nm diode/2940 nm Er:YAG	92%[52]	Not available	CT[52]
1927 nm thulium laser	87.3% at 3 mo, 86.6% at 6 mo[46], 90%[73]	Not available	CT[46] RCT[73]
1550 nm erbium glass laser	55.6%[50], 54%[31]	Not available	CT[50, 31]
1540 nm erbium glass laser	>50%[79], 45%[51]	Not available	CT[79, 51] 3.4 grade improvement on 4-point grading scale (>50%)[79] reduction in AK count from 31 to 17[51]
CO_2 laser-assisted PDT	100%[60], 85.96%[59], 73%[78], 90%[58], 71.4%[64], 72%[68], 89.78% with 30 min PDT and 86.38% with 15 min PDT at 8 weeks[81] 70.6% at 8 weeks[65], 91.3%[63]	Not available	RCT[78, 58, 64, 68, 81] CT[60, 59, 65, 63]
Er:YAG laser-assisted PDT	88.7%[69], 74%[61], 91.7% 3h-PDT and 76.8% 2h-PDT[57], 92%[75], 86.9%[80]	81.1%[69], 84.8%[57], 85%[75], 78.5%[80]	RCT[69, 61, 57, 75, 80] Actinic cheilitis[75]
PDL-assisted PDT	92%[23], 66.7%[72], 10.3%[71]	Not available	RCT[71] CT[23, 72]
LED-assisted PDT	73.3%[72]	Not available	CT[72]
Fractional 1927 thulium laser combined with PDT	100%[73]	Not available	CT[73]
Intense pulsed light with PDT	87%[82], 78%[83]	90%[74]	CT[82, 74, 83]

CT: *controlled trial,* ***h:*** *hour,* ***min:*** *minutes,* ***mo:*** *months,* ***PDT:*** *photodynamic therapy,* ***RCT:*** *randomised controlled trial*

Conclusion

In selected instances, laser resurfacing may be a reasonable alternative to conventional treatments for AK management. Laser resurfacing is useful for treating hyperkeratotic lesions and in fractional mode, can enhance absorption of topical treatments. However, laser application is operator-dependent and there is considerable heterogeneity across studies in terms of laser treatment protocols, laser settings, study design and clinical evaluation. Fractional laser-assisted PDT is promising, with results suggesting it is better at clearing AKs and improving photoageing than PDT alone, although long-term efficacy data is lacking. Many factors remain unknown regarding the optimal laser wavelength and density, and incubation time for photosensitiser. Larger studies with longer follow up are required to determine the clinical feasibility of laser resurfacing as a primary treatment option for AK treatment and prophylaxis.

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Facial surgery: scar minimisation and management

Marlene Wijaya[1], Gilberto Moreno Bonilla[1]
1. Department of Dermatology, Royal North Shore Hospital, St Leonards, NSW, Australia
Correspondence: Marlene Wijaya marlene.wijaya@sydney.edu.au
Disclosures: *none*

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OUTLINE: Facial surgery is a common procedure in dermatology, particularly in the context of skin cancer treatment. While scar formation is the inevitable consequence of every surgical procedure, there are steps to minimise the risk of undesirable scar formation. This is particularly important in facial surgery, not only from a cosmetic point of view, but also from a functional and psychological perspective. This article will explore measures which may be implemented at the pre-, intra- and post-operative stages to minimise surgical scar formation. Additionally, various treatment options for management of established surgical scars will also be discussed.

KEYWORDS: facial surgery, Mohs micrographic surgery, scars, hypertrophic scars, keloids

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Introduction

Scar formation after facial surgery is an unavoidable consequence of the healing process. Nevertheless, one of the goals in surgery is to achieve scars that are minimally visible and blend well with the surrounding skin. This is particularly important in facial surgery, where patients are often concerned about the potential cosmetic consequences of the procedure. Beyond cosmesis, achieving ideal post-surgical scars is also crucial from a functional and psychological perspective. Disfiguring scars could be highly distressing and may interfere with normal physiological functioning, such as eyelid closure, nasal breathing and oral intake. In this article we discuss measures which may be implemented at the pre-, intra- and post-operative stages to minimise and manage surgical scars on the face.

Wound healing and scar formation

In order to understand how various interventions may be utilised in scar minimisation and management, it is fundamental that we revisit the pathophysiology of wound healing and scar formation. There are four stages involved in wound healing, namely haemostasis, inflammation, proliferation, and remodelling.

Following an injury to the skin, such as surgical incision, vasoconstriction takes place immediately, lasting for approximately five to ten minutes to achieve haemostasis.[1] The next stage of wound healing, the inflammatory phase, starts within 24 hours after surgery. This phase is generally completed within three to five days, but may be prolonged in the presence of infection or other factors impairing wound healing.[1] The last two stages of wound healing, proliferation and remodelling, are where scars are predominantly formed. The proliferation phase lasts five to fifteen days, a process that is characterised by fibroblast migration, angiogenesis, collagen and extracellular matrix synthesis, granulation and epithelialisation.[1] The main product of this phase is granulation tissue. Following this, the remodelling phase takes place, a process which could last up to two years. The events involved in this process are collagen cross-linking, collagen remodelling from type III to type I collagen, wound contraction, and re-pigmentation.[1] The final outcome of this last stage of wound healing is maturation of the granulation tissue into scar.

Any factors which interfere with the normal wound healing process could lead to undesirable scar formation. A few examples are excessive wound contraction resulted from suboptimal surgical techniques, decreased blood supply to the wound site, and surgical site infection.

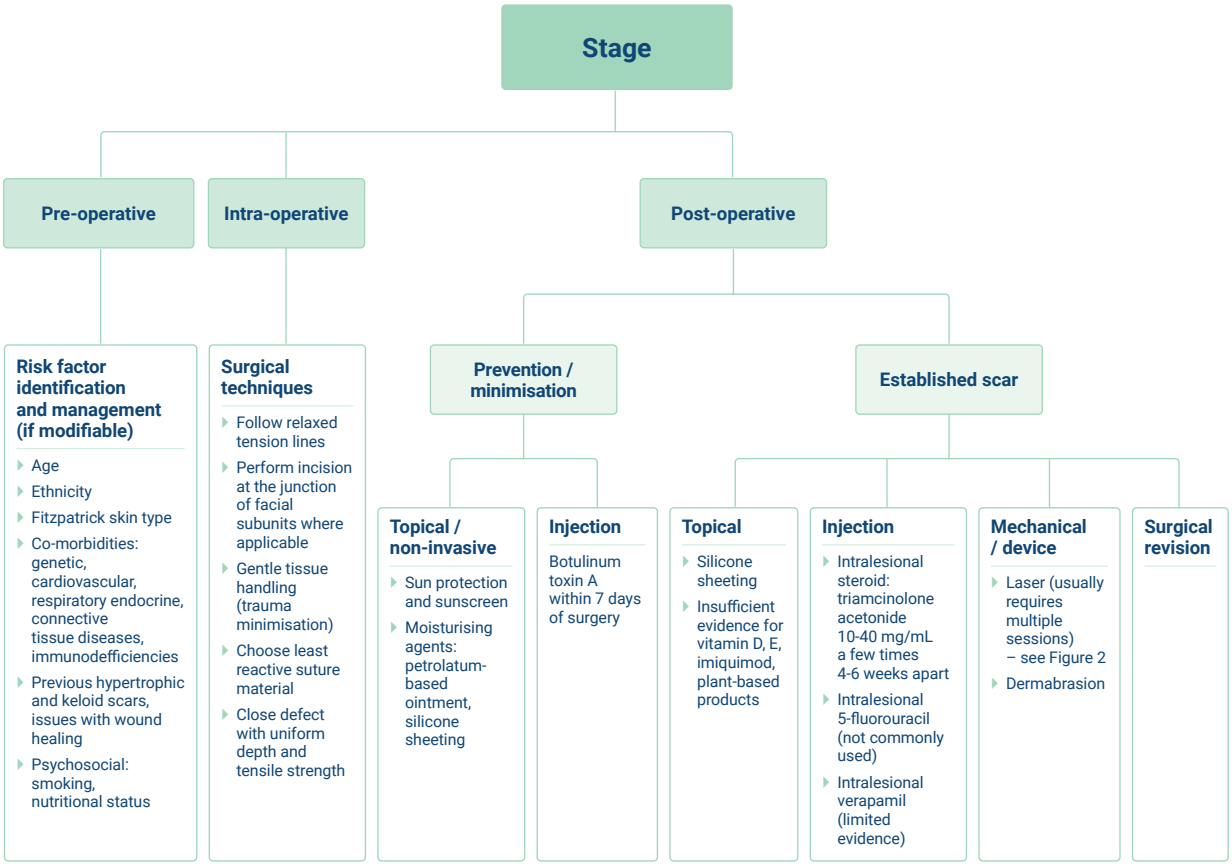

Figure 1: *Summary of recommendation of measures which could be implemented at the pre-, intra- and post-operative stages for minimisation and management of surgical scars on the face*

Scar minimisation and management

There are various measures, which may be implemented at the pre-, intra- and post-operative stages to minimise and manage surgical scar formation on the face (Figure 1). Although there is no gold standard for treatment, the general rule is to start from the least invasive option.

Pre-operative assessment

The goals of the pre-operative assessment are to (1) determine whether a patient is at risk of developing improper wound healing and forming an undesirable post-surgical scar, (2) implement additional precautionary measures for the at-risk group, and (3) maximise the management of modifiable risk factors.

Non-modifiable risk factors include age and ethnicity. Younger patients are at an increased risk of developing hypertrophic scars, likely due to higher skin tension as well as higher proliferative activity during the third stage of wound healing.[2] In a study involving 58 healthy male volunteers aged 18-85 years, two 1 cm incisions were created on the upper arms of all participants and closed using Prolene™ sutures.[3] At 12 months follow up the best scar outcome with the least erythema, projection and visible border was found in the group aged >54 years, while the poorest outcome was found in those younger than 30 years.

Patients with skin of colour are known to be more prone to developing hyperpigmented, hypertrophic and keloid scars compared to fair-skinned individuals.[4, 5]

Medical co-morbidities may or may not be modifiable. It is important that all patients are asked about previous wound healing patterns and scarring history. There are genetic conditions predisposing to keloids and hypertrophic scars, such as Rubinstein-Taybi syndrome and Goeminne syndrome. More common medical conditions impairing wound healing include diabetes, respiratory and cardiovascular disease, connective tissue disorders, and primary and secondary immunodeficiencies.[6]

Pertaining to psychosocial history, two major risk factors impairing wound healing are smoking and poor nutritional status.[6] A discussion about smoking cessation or reduction, and diet modification or nutritional supplementation should be held with the patient where applicable, emphasising their importance in achieving a good surgical outcome.

Intra-operative considerations

The risk of scar formation varies between facial subunits due to variations in dermal thickness. Thicker and more sebaceous areas tend to produce more swelling and therefore heal more slowly. Nevertheless, general surgical technique recommendations for producing an optimal cosmetic outcome apply for all facial subunits. These include choosing a suitable orientation in relation to relaxed tension lines (RTLs), minimising tissue trauma during surgery, selecting suitable suture materials, and closing the defect with uniform depth and tensile strength.[7]

Incisions should follow RTLs to minimise wound contraction and subsequent scarring.[8] Additionally, incisions should be performed at the junction of facial subunits where possible, in order to camouflage scars in within these natural lines.

The choice of appropriate suture materials and employing adequate wound closure techniques is also quite relevant. As a rule, the least reactive suture material should be used to minimise scarring. However, whether absorbable or non-absorbable sutures result in superior outcomes is somewhat controversial. A systematic review and meta-analysis of 11 studies involving 751 patients with facial wounds, showed no difference in cosmetic outcomes between the two groups.[9] Further, and as acknowledged by the article authors, the overall quality of evidence of the studies included was poor with significant variation in assessment methods.

Regarding wound closure techniques, various studies have demonstrated no significant difference in short- or long-term cosmetic outcomes between defects closed with interrupted versus running sutures.[10-12]

Cosmetic results may however vary between different types of running sutures. A split-wound prospective study involving 47 Mohs micrographic surgery patients, whose facial defects were closed with half simple running sutures and half running horizontal mattress sutures, showed that the latter technique produced flatter and narrower scars at 6-months follow-up.[13]

Spacing between sutures does not seem to be of high significance. A randomised controlled trial (RCT) investigated the difference in outcomes between running cuticular sutures spaced 2 mm versus 5 mm apart.[14] They used the split-wound model in 50 patients undergoing head and neck dermatologic surgery, and scars were examined at three months using the Patient and Observer Scar Assessment Scale. The study did not find significant differences in scar outcomes or complication rates, suggesting that wider spacing may be preferable given it is less time-consuming and produces equally good results.

Lastly, it is widely believed that producing eversion of the wound edges is of the highest importance in defect closure, as it counteracts contraction during wound healing and prevents the formation of depressed scars.[7] Interestingly, recent studies have challenged this notion as they demonstrated no association between wound eversion and post-surgical scar formation.[15, 16] Further studies need to be conducted to attest this concept.

Post-operative

Taping

Excessive wound tension could interfere with normal collagen laydown during wound healing, contributing to increased scar formation.[17] A simple and affordable method that may assist in counteracting the tension is taping. Although not tested on facial scars, an RCT involving 70 women post-caesarean section demonstrated that patients who applied Micropore™ tape over the surgical wound for 12 weeks following suture or staple removal were 13.6 times less likely to develop hypertrophic scars compared to controls.[18] Interestingly, while none initially developed hypertrophic scars in the treatment group, following Micropore™ discontinuation hypertrophic and stretched scars developed in one and four patients, respectively. This indicates that long-term taping may be required in order to produce meaningful end results. Further studies need to be conducted to establish the effect of taping on facial surgical scars.

Topical products

Sun protection and sunscreen

All patients should be advised of the importance of sun protection following surgery. Damage from ultraviolet exposure can impair wound healing and increase the risk of scar dyspigmentation.[19, 20]

Moisturising agents

Moisture is not only important in normal functioning of the epidermis, but also in the process of wound healing. A moisture-rich environment has been shown to hasten wound healing by stimulating collagen synthesis, cellular growth, and growth factors activities.[21] Petrolatum-based ointment is preferred over antibiotic ointment. Previous randomised, double-blind trials have shown that petrolatum-based ointment resulted in comparable wound healing outcomes and infection rates, but much less likely to cause contact dermatitis compared to antibiotic ointment.[22, 23]

Silicone is an agent that may help in moisture preservation, thereby preventing and treating established scars. It is available in various forms, such as gel, oil and sheets. A Cochrane review assessing the effectiveness of silicone sheeting for scar prevention and management included 20 trials involving 873 patients.[24] The study showed a significant

reduction in incidence of hypertrophic scars in high-risk individuals compared to no treatment (risk ratio [RR] 0.46, 95% confidence interval [CI] 0.21 to 0.98). However, a similar effect was not found in low-risk individuals. The review also found that for established scars, silicone sheeting significantly reduced scar thickness (mean difference [MD] -2.00, 95% CI -2.14 to -1.85) and hyperpigmentation (RR 3.49, 95% CI 1.97 to 6.15) compared to no treatment.

Other studied and marketed topical products for scar prevention and management, including topical vitamin D, vitamin E, imiquimod, plant-based products such as onion extracts, green tea and aloe vera, have insufficient evidence to support their use.[25-32]

Injections

Botulinum toxin A (BTA) is hypothesised to help minimise scar hyperplasia by reducing wound tension. *In vitro* studies showed that BTA works by inhibiting fibroblast differentiation and TGF-B1 expression, which are important factors contributing to scar hyperplasia.[33, 34] In a systematic review and meta-analysis of 10 RCTs involving 344 patients undergoing facial surgery followed up for at least 6 months, those in the BTA group demonstrated significantly higher Visual Analogue Scale scores, lower Vancouver Scar Scale and Observer Scar Assessment Scale scores, and a smaller scar width (MD = -1.05, 95% CI -1.27 to -0.83, P<0.00001) compared to controls.[35] No difference in complication rates was observed between the treatment and control groups with the majority of patients having BTA injected within 7 days post-surgery.

One of the most widely used treatments due to low cost and high accessibility, is intralesional steroids. They suppress inflammation, fibroblast proliferation, as well as collagen and glycosaminoglycan synthesis. Triamcinolone acetonide at 10 to 40 mg/mL is commonly administered into the scar tissue four to six weeks apart.[36] Unfortunately, the use of intralesional steroids in keloid and hypertrophic scarring is known to result in high recurrence rates like other interventions. The relapse rate for intralesional steroids is high even when combined with surgical revision, which has been shown to be up to 50%.[37] Additionally, an extended duration of administration might be required as demonstrated in a long-term study of 109 keloid scars in 94 Asian patients, where most patients required more than 20 to 30 injections administered over three to five years before reasonable improvement.[38] Only local adverse effects were reported as a result of the treatment, which included atrophy, ulceration, telangiectasias, and dyspigmentation.

5-fluorouracil (5-FU) is a much less used intralesional agent. A systematic review of 18 small trials and case series involving 482 patients with keloid scars found that a combination of 5-FU and intralesional steroids showed 'good' or 'excellent' scar improvement (50-96%) compared to the group utilising intralesional 5-FU alone (45-78%).[39] In studies where patients were followed up for one or more years, the recurrence rate was shown to be 25-47%. Reported adverse effects included purpura, ulceration, and transient hyperpigmentation. Of note, most studies are of poor quality; therefore, further research would be required to establish whether there are significant differences in outcomes between intralesional steroids, intralesional 5-FU and a combination of both agents.

The utility of intralesional verapamil has been investigated in some studies.[40] It has not been superior to intralesional steroids for scar treatment, but has been observed to result in lower rates of atrophy and telangiectasia.[40]

Laser

Laser treatment has gained popularity in the field of scar management in recent years. It can be used alone (Figure 2) or as an adjunct to other treatments (Figure 3). Despite its rising popularity, there is limited evidence to support or discourage the use of laser in surgical scars. Common barriers reported by previous systematic

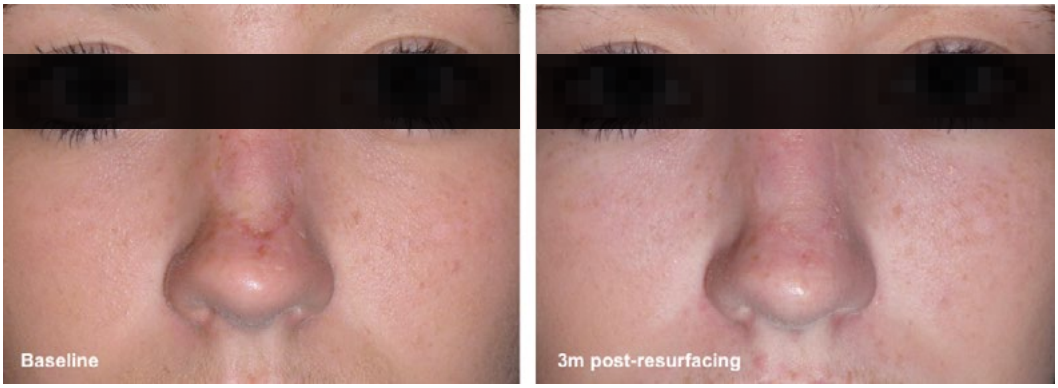

Figure 2: *16-year-old female with a long-standing surgical scar (excision and skin graft of a congenital nevus) on the nose managed with laser therapy alone (full and fractional ablative laser resurfacing)*

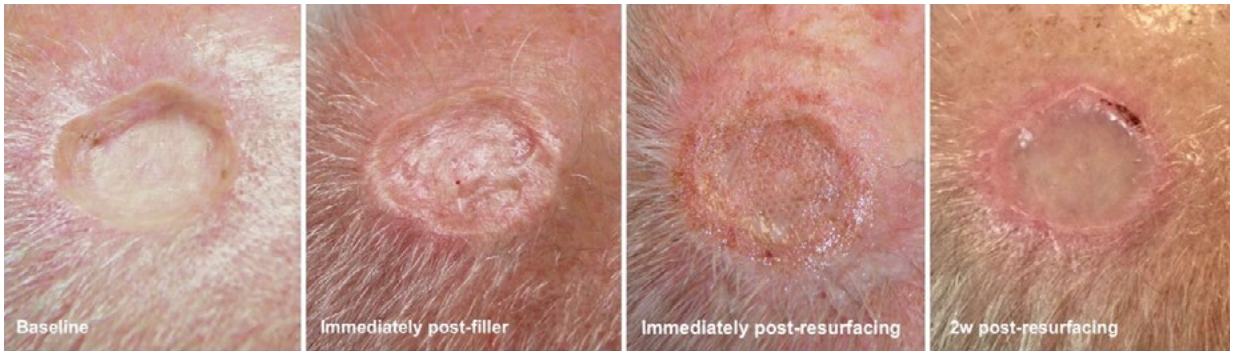

Figure 3: *61-year-old male with a 6-month surgical scar (excision and skin graft of basal cell carcinoma) on the scalp managed with a combination of modalities (calcium hydroxyapatite filler and combination full and fractional ablative laser resurfacing))*

reviews and meta-analysis are the lack of high-quality studies as well as substantial methodological diversity and data heterogeneity across them.[41-44]

Lasers can be divided into ablative and non-ablative. Ablative lasers, such as CO_2 and Er:YAG, reach their target in the dermis by ablating the epidermis. While they are known to yield reasonably good results in treating hypertrophic scars, there are some disadvantages including pain, prolonged downtime, erythema, and risk of hyperpigmentation particularly in darker skin individuals.[45, 46]

Non-ablative lasers are less invasive, targeting the dermis while preserving the epidermal layer. Some examples include pulsed dye laser (PDL) and Nd:YAG.

Studies that support the use of laser encourage their early use for more superior outcomes.[42, 43] In a systematic review of 25 studies, the most notable improvement was found where laser was initiated at the inflammatory stage rather than the proliferative and remodelling phases of wound healing.[42] However, the review had major limitations including the heterogeneity in the distribution of studies and the short follow ups with 72% of the studies following patients for less than three months.

Where scars have formed, the choice of laser relies heavily on individual scar characteristics and the concern to be addressed (Figure 4). It is common practice to use a combination of laser therapies to achieve maximum results. Non-ablative lasers such as PDL and Nd:YAG work by targeting oxyhaemoglobin and they are therefore particularly useful in improving erythema.[46]

If scar projection is the concern, the choice would depend on whether the scar is hypertrophic or atrophic. With the former, ablative lasers would provide greater benefits.[46] Fractional CO_2 (fCO_2) has been demonstrated

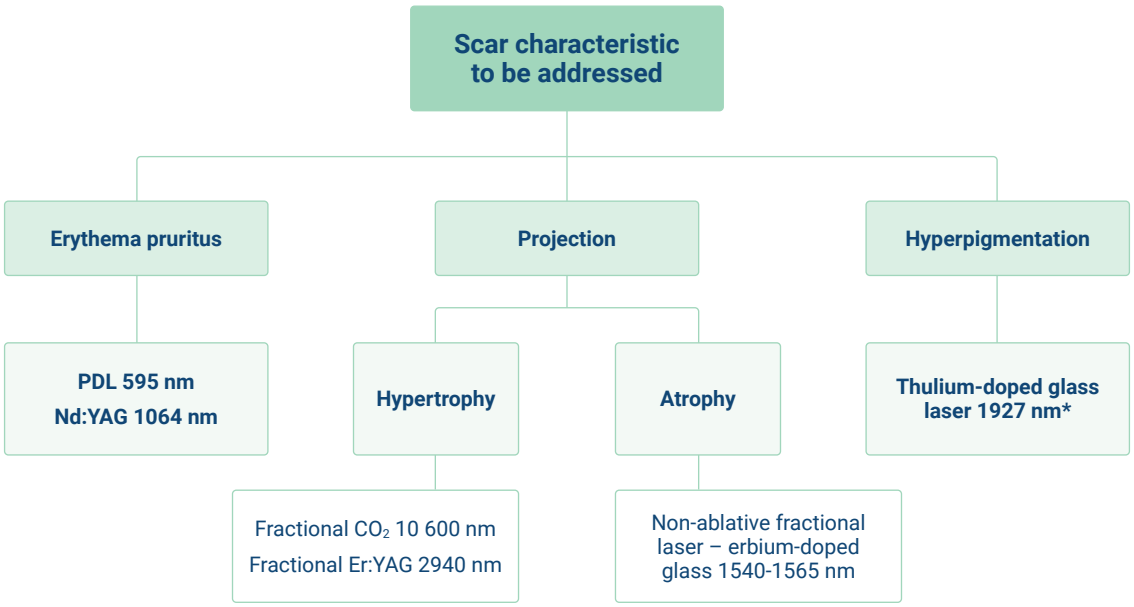

Figure 4: *Laser recommendations based on the scar characteristics*

** Limited evidence – result from one case series*

to be superior to PDL in improving hypertrophic scar volume and pliability.[47] With the latter, the dermis is thin and has lost a significant amount of collagen and elastin, making them more prone to thermal injury and tissue necrosis. Hence, non-ablative fractional laser such as erbium-doped glass 1540-1565 nm is preferred for atrophic scars due to their higher safety profile.[46, 48]

With regards to scar hyperpigmentation as the primary concern, there is only limited evidence available to support the use of laser therapy. One case series reported an improvement in scar hyperpigmentation following a combination of laser treatments, which included 1927 nm thulium-doped glass laser.[49]

It is paramount that extra precautions are taken in choosing laser type and settings in patients with Fitzpatrick skin type III–VI in order to avoid post-procedural hypo- or hyper-pigmentation.[45]

Dermabrasion

Dermabrasion can improve scar appearance by making it look flatter and more blended with the surrounding skin.[50] However, in a split-scar RCT, the fCO_2 laser has been shown to be as efficacious as dermabrasion in improving surgical scars while producing a significantly lower rate of adverse effects.[51] The main advantage of dermabrasion over laser therapy lies in the treatment cost.

Scar revision

Scar revision may be opted should other more conservative treatments have failed. It is important to emphasise to patients that the goal of the procedure is to improve rather than to completely eliminate the scar, so that realistic expectations can be met. There are a wide range of scar revision techniques, such as fusiform scar excision, serial excision, punch excision, and breaking up a scar through Z-plasty, W-plasty or geometric broken line in order to redistribute skin tension.[6] The choice of technique would highly depend on individual scar characteristics, the goal to be achieved, and the facial subunit involved.

Conclusion

Scar minimisation and management will benefit from measures taken pre-, intra- and post-operatively. There are various management modalities for established scars, however a high recurrence rate is still common. Although there is no gold standard of treatment in scar management, the general rule is to start from the least invasive option. A combination of interventions is often used to maximise treatment outcomes. Ultimately, the decision should be made based on each scar characteristics, patient skin type, individual preferences, goals and personal circumstances.

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Mohs surgery as an aid to optimising cosmetic outcomes in facial surgery

Rakesh Anand[1], Emma Craythorne[1]
1. St Johns Institute of Dermatology, Guy's and St Thomas' NHS Trust, London, UK
Correspondence: Rakesh Anand rakesh.anand1@nhs.net
Disclosures: *none*

OUTLINE: Mohs micrographic surgery (MMS) is a specialised technique for the removal of skin tumours. There are four major components to the procedure: surgical excision, histopathological examination, precise mapping, and reconstruction. MMS provides high cure rates with the maximal preservation of unaffected tissue. Once the Mohs procedure has been performed the defect is carefully evaluated and an appropriate reconstruction option selected to optimise the final cosmetic outcome.

Although scarring is an unavoidable consequence of skin surgery, there are a few universally accepted principles of aesthetic surgical design to help optimise scar placement. These principles are: preserving and restoring free margins, preserving and restoring contours, placing scars in subunit junction lines, and placing scars in relaxed skin tension lines.

This article outlines how the principles of Mohs surgery can be brought together with the principles of aesthetic surgical design to help aid better cosmetic outcomes in facial surgery.

KEYWORDS: micrographic, surgery, skin cancer, aesthetic, Mohs, cosmetic

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Introduction

Mohs micrographic surgery (MMS) is a specialised technique for the removal of skin tumours. MMS provides high cure rates with the maximal preservation of unaffected tissue.[1] MMS is time and labour intensive and therefore is often reserved for sites where tissue preservation and cosmetic outcomes are most important, such as the head and neck.

Once the Mohs procedure has been performed, the defect needs to be carefully evaluated and an appropriate reconstruction option selected to optimise the final cosmetic outcome. In this article we will outline the fundamentals of Mohs surgery and how this technique – when used in combination with principles of aesthetic surgery – can aid better cosmetic outcomes in facial surgery.

Mohs surgery

There are four major components to the Mohs procedure: surgical excision, histopathological examination, precise mapping, and reconstruction/management of the surgical defect (Figure 1).

1. Surgery

The whole procedure is generally performed under local anaesthetic. The tumour is removed (debulked) and a bevelled disc of surrounding tissue (layer) is taken. The layer ensures that the entire circumferential margin (peripheral and deep margins) of the tumour are removed and evaluated. The bevelling helps the tissue sample to be flattened so that the bottom and sides can be viewed in a single plane. Before removing the layer, reference nicks are placed extending from the tissue onto the wound edges to maintain precise anatomic orientation. A diagram (Mohs map) of the surgical defect with anatomic landmarks and location of reference nicks is created and the cut edges of the specimen are inked.[2] A dressing is applied to the surgical defect and the patient awaits the margin examination results.

2. Histology

The layer undergoes frozen tissue processing. Thin layers from the bottom of the specimen are removed and stained and mounted onto glass slides so that they can be microscopically examined.[3]

3. Mapping

If any residual tumour is identified on histological examination, it is marked on the Mohs map to guide the

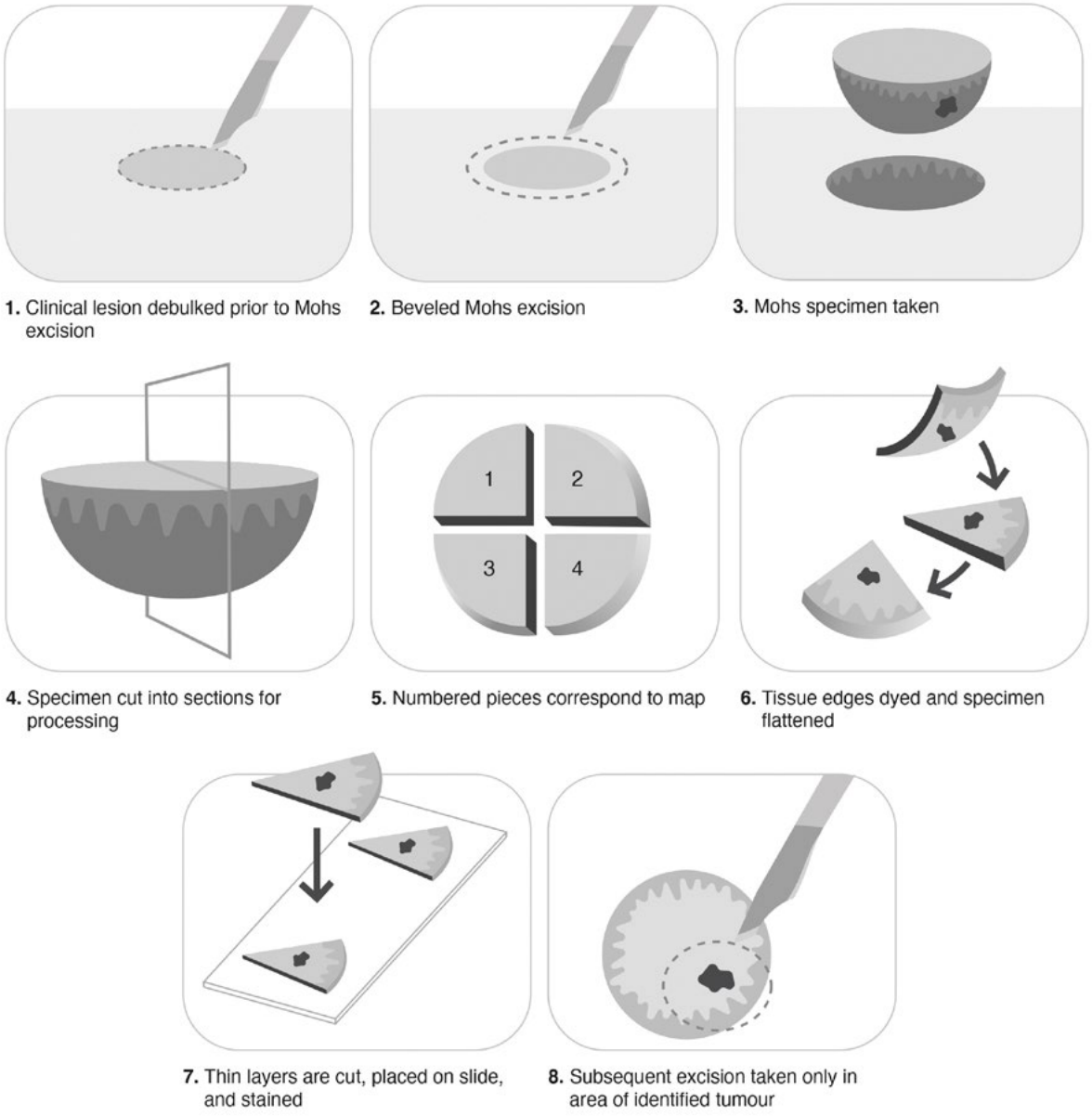

Figure 1. *Components of Mohs surgery.*

removal of residual tumour in the patient. These steps constitute one 'stage' and are repeated until there is complete removal of the tumour. On average this takes two to three stages to remove the whole tumour.

4. Reconstruction (management of the surgical defect)

The tumour-free defect is evaluated and either surgically closed or left to heal by secondary intention. The location and size of the defect and patient comorbidities guide the choice of the repair technique.

MMS offers several advantages over standard surgical excision and pathology processing. The procedure allows for complete removal of the tumour and therefore the highest chance of cure as well as the preservation of as much healthy tissue as possible.

Preserving the maximal amount of healthy tissue is important in helping to maintain normal function and appearance.

Surgical reconstruction

When analysing a defect following Mohs surgery there are some important principles to consider. Preservation of function and appearance is the definitive goal and to achieve this a surgeon requires intimate knowledge of head and neck anatomy. Scarring is an unavoidable consequence of skin surgery regardless of the location, however, there a few universally accepted principles of aesthetic surgical design to help optimise scar placement.[4]

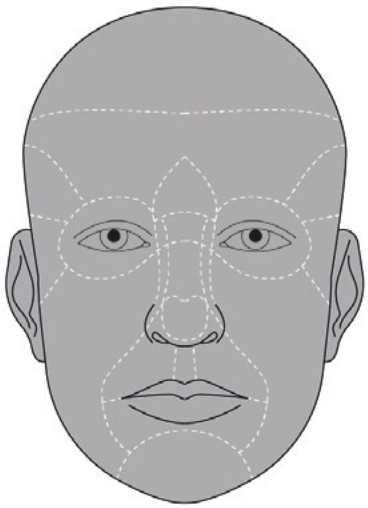

Figure 2. *Aesthetic subunits of the face are primary structural areas of the face that are separated by natural folds and borders such as the eyebrow and hairline. The skin in the subunits tends to have a similar quality, including colour and pore size*

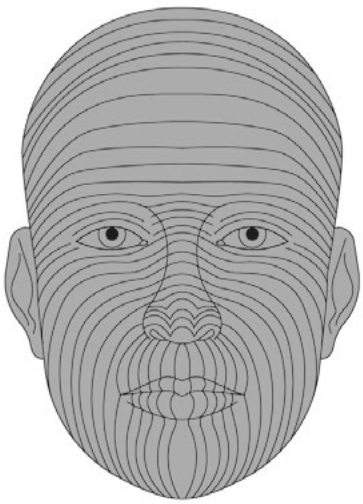

Figure 3. *Relaxed skin tension lines of the face represent a map of the direction in which the tension in the skin is maximal. These show the optimal orientation of wound closure to minimise tension. This leads to optimal scar formation and minimises wound contraction*

Surgical design

1. Preserving and restoring free margins

Delicate facial structures like the eyebrow, hair or beard line, eyelid, lips and nostrils can easily be distorted by excess tension from a wound closure. This can be both cosmetically and functionally problematic for the patient. For example, pulling on the lip, known as eclabion, can cause problems with eating, drinking and speech. Pulling of the lower eyelid, such as an ectropion, can lead to dry or watery eyes and visual disturbance.

2. Preserving and restoring contours

The face has convexities and concavities which need to be carefully considered when planning surgical closures. This is particularly important when considering healing by secondary intention. Defects in concavities such as the medial canthus and the temple can often be left to heal well by secondary intention healing but those in convexities tend to heal poorly by this method.

3. Placing scars in subunit junction lines

The face consists of six major aesthetic units: forehead, eyes, nose, lips, chin, and cheeks. These aesthetic units can be subdivided into additional anatomical subunits (Figure 2). The junction lines are the lines on the face at the borders that separate cosmetic units. Examples include the line between the cheek and the lip, the melolabial fold. The skin within the subunits share similar characteristics such as colour, texture and pore size. Repairing a surgical defect along a junction line provides the best outcome. For large defects that require more complex closures, the best results are often achieved by using tissue from adjacent cosmetic units and placing the suture lines along the boundaries of those units. Light reflections and shadows occur naturally in these areas and therefore surgical scars within these lines tend to be less conspicuous. Scars that cross these junction lines and cosmetic units tend to be more noticeable.

4. Placing lines in relaxed skin tension lines

Skin tension lines are the lines and wrinkles that develop on the face with age and sun exposure (Figure 3). These lines are often the best place for placement of a surgical scar on the face. In older people these lines might be more apparent and therefore surgical scars are easier to place. In younger people, asking them to animate their face, for example asking them to smile or frown, can usually expose these lines. Scars that are not placed within or parallel to the relaxed skin tension lines tend to be more noticeable.

Repair types

The types of repair vary in complexity but are selected based on the principles of aesthetic design and a number of patient factors. This would include patient wishes, if they smoke (as this can impair wound healing), or if they take anticoagulants (which can increase the risk of bleeding).

Primary repair

This is one of the most straightforward ways of repairing a surgical defect. The process converts the opening into a linear scar. The wound is often made longer to allow the edges to come together evenly. Avoiding removing additional skin can cause bunching at the ends of the scar. A longer, smoother scar tends to be less noticeable than a shorter scar with bunched edges. Preservation of free margins, such as the lips and eyebrows, is important,

and this is often why a primary repair is not an appropriate repair option as it distorts these structures.

Healing by secondary intention

Secondary intention healing allows the wound to heal naturally. The wound needs to be cleaned regularly and an ointment such as petroleum jelly, applied to keep it moist and to optimise healing. Secondary intention healing can take weeks or months depending on the size and depth of the defect. Over time the wound will be covered with a new layer of skin. Typically, there is more scar contraction with secondary intention healing and the scars can be lighter in colour or depressed when compared to the surrounding tissues. Sutures can be used to guide the healing in a certain direction and avoid pulling on surrounding structures as the scar contracts during the healing process. Following the principle of restoring contours, secondary intention healing tends to be best for concavities and therefore is not suited to all locations on the face.

Skin grafting

Skin grafting involves removing skin from a different location on the body and using it to repair the defect. This can be taken as a partial thickness (removing the very top layers of skin) or full thickness skin graft. Full thickness skin grafts tend to be used to repair facial defects. A donor site is selected to match the colour, texture and thickness of skin needed. Common sites include the pre- or post-auricular skin or the clavicular region. The donor site is sutured together with a primary repair, and the graft is sutured into the defect. Disadvantages include poor colour, pore size and contour match. Grafts can also fail as they do not develop an adequate blood supply which is related to a number factors including smoking and adequate pressure applied to the graft during the healing process. In this situation the wound will then heal by secondary intention.

Local flap reconstruction

Local flap reconstruction involves using skin adjacent to the defect to cover or drape the wound. There are a number of different types of flap and these are selected based on the location and size of the defect.[5] All flaps involve extending excisions to allow the elevation of the surrounding skin where there may be some laxity. This elevated skin is then advanced over or rotated into the defect. The final scar may have a more irregular shape but if the principles of surgical design are utilised scars can be disguised or at least minimised. Local grafts have the advantage of providing a much better colour, pore size and contour match. As a local flap carries its own blood supply there is also less chance of failure when compared to a skin graft.

Scar revision

All patients who undergo Mohs surgery will be followed up to review the healing following the reconstruction. At this stage additional interventions can be offered to optimise the scar and the outcome. This can include injectable steroids for hypertrophic scars, dermabrasion or laser treatment to improve the colour or contour of a scar, or surgical scar revision.

Discussion

The importance of optimising the placement of surgical scars and the surgical techniques used in procedures cannot be underestimated. Scarring of any type can have a negative impact on a person's psychosocial health and poor surgical reconstruction can be both cosmetically and functionally problematic for the patient. The benefit of Mohs surgery is complete tumour removal while preserving as much healthy tissue as possible, which helps optimise healing and therefore scarring.[1] It also reduces the risk of recurrence and incomplete removal of the tumour, reducing the likelihood of further surgery to the site and additional compromises to aesthetic and functional outcomes. Patients must always be adequately consented, and the risks and benefits of the procedure discussed in full to ensure that there is appropriate management of expectations.

A Mohs surgeon's intimate knowledge of head and neck anatomy and understanding of the structure and the function of skin, combined with the understanding surgical design and repair, best places them for optimising cosmetic outcomes in facial surgery following treatment for skin cancer.

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The great debate: "Injectables versus Lasers" Injectables and sun-damaged skin – a match made in heaven

Stefania Roberts[1]
1. Dermatology Institute of Victoria, Melbourne, Victoria, Australia
Correspondence: Stefania Roberts stefania.roberts@gmail.com

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KEYWORDS: Botulinum neurotoxin A, hyaluronic acid, dermal filler, facial injectables, skin quality, photodamage

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Skin quality, whether assessed by colour, texture or elasticity, is a key factor contributing to facial beauty. Environment, lifestyle, age and genetics may have a positive or negative impact on skin quality. Facial rhytids lead to a perceived negative emotional state of anger, fear, stress, fatigue or hostility. Skin ageing is marked by structural changes in the epidermis and dermis leading to wrinkles, loss of elasticity and textural changes. To address these changes the quest for minimally invasive cosmetic procedures is increasing. Our current armamentarium includes topical skin preparations, chemical peels, microdermabrasion, lasers, light therapies, radiofrequency energy, polydioxanone threads and injectables like botulinum neurotoxin-A (BoNT-A) and a diverse range of hyaluronic acid gels. In the pipeline are injectables ranging from elastin to autologous fibroblast and keratin.[1] Currently, a multi-modal approach is advocated to address the specific needs of the aesthetic patient including skin quality. This paper focusses on the role of injectables, BoNT-A and fillers, to improve sun-damaged skin.

Botulinum neurotoxin-A

Let's start with BoNT-A. Is there any evidence in the literature to support that the most popular non-surgical global cosmetic procedure can address sun-damaged skin? BoNT-A is traditionally injected for aesthetic indications in an intramuscular fashion to denervate muscles of facial expression such as, amongst others, the corrugator supercilii, procerus, depressor supercilii and orbicularis oculi in an attempt to halt the formation of static lines that occur as a result of repeated contraction of these muscles. BoNT-A is also utilised to address the masticatory muscles for facial reshaping.

Several papers support the notion of BoNT-A improving skin quality. A 2017 study reported that patients receiving repeated and regular BoNT-A treatments not only experienced wrinkle reduction but a cumulative and prolonged effect on overall skin quality attributes that in turn lead to a more youthful appearance.[2] In 2001, Wu described the technique of "microbotox" which continues to be utilised in many Asian countries. Microbotox has been advocated for treating forehead and infraorbital rhytides as well as patients with mild neck laxity and crepey skin. This technique involves hundreds of microdroplet intradermal or subdermal injections of diluted onabotulinum toxin targeting sweat and sebaceous glands and the superficial attachment of the muscles of facial expression to the underside of the dermis.[3] This leads to a decrease in the pulling effect of the facial muscles as they insert into the skin resulting in a smoothening effect and tightening of the skin. Wu's concept has been supported by a quantitative evaluation using skin-scanning technology in a pilot study.[4] These authors reported an improvement in skin texture, microroughness and a decrease in pore size in patients treated with microbotox for aesthetic indications of the face leading to high patient and physician satisfaction. Several studies have assessed the impact of BoNT-A on facial erythema.[5] To date the jury is out on the clinical significance of BoNT-A on reducing erythema. Potentially this indication is best left to laser treatments.

Fillers

Let's now shift our attention to fillers. Fillers were initially indicated for the treatment of fine lines and wrinkles. Bovine collagen, in the form of Zyderm, was the first dermal filler approved for cosmetic use in 1981

to treat static lines. Today, the most popular injectable intervention to improve the dermo-aesthetic properties of the skin are hyaluronic acid fillers.[6] The indications for fillers have increased beyond lines and wrinkles with numerous fillers available on the market with differing degrees of cross-linking, gel viscosity, gel hardness, consistency, extrusion force, and total hyaluronic acid concentration that address not only skin quality but volume loss in the ageing face.[7] Skin quality injectable treatments have expanded beyond hyaluronic acids to include biostimulatory agents such as calcium hydroxyapatite (Radiesse) and poly-L-lactic acid (PLLA or Sculptra).

To improve sun-damaged skin, a hyaluronic acid filler with low viscosity and low degrees of cross-linking is ideal. Typically, the hyaluronic acid is injected intra-dermally or sub-dermally via a micro-droplet, serial puncture, linear threading or fanning technique, in the designated treatment area, using either a needle or cannula. The later involves multiple injection points. Areas treated include the face, neck, decolletage and hands. Caution needs to be taken with a meticulous technique to avoid surface irregularities and visible or palpable lumps. Recently a hybrid product consisting of high and low molecular weight hyalurons, not yet available in Australia, has been released in Europe with high biocompatibility and low viscosity favouring tissue diffusion with fewer injection points. The aim of the above hyaluronic acid fillers is to rehydrate the skin via their hydrophilic properties and improve skin texture. A histologic study reported sustained clinical results with hyaluronic acid with an increase in collagen at 3 and 9 months and an increase in elastic fibres after 9 months.[8] They proposed filler longevity was due, not only to hyaluronic acid injected in the dermis, but secondary to dermal remodeling seen on histologic assessment.[8]

Reports of combination treatments with BoNT-A and hyaluronic acid have been published to improve fine wrinkles and skin hydration. Kim published a concoction of microbotox and microhyaluronic acid to improve peri-orbital and forehead aesthetic units.[9] This novel "hydrotoxin" mixture consisted of 2 mL monophasic hyaluronic acid filler mixed with 1 mL of Neuronox 40U. The mix was injected using an automatic injector with nine 31G needles delivering 0.002 mL in 999 sites. The combination treatment was found to have a synergistic action improving skin roughness and hydration.[9] A combination approach published in 2015, claimed to have a "skin booster" effect, combining onabotulinum toxin 10U with 1 mL of uncrosslinked hyaluronic acid (12 mg); the entire face and neck was treated with 50-100 injection points in an attempt to improve skin hydration.[10]

More recently, a study reported a significant improvement in peri-orbital wrinkles, roughness and pore volume using a combination approach with a radiofrequency hydro-injector device that simultaneously delivered an intradermal radiofrequency treatment and hyaluronic acid filler.[11] Bertossi's group reported a multi-modal approach with one session of microbotox combined with a very low G prime hyaluronic acid together with five fractional laser treatments led to a faster and better improvement in skin texture and quality compared to monotherapy.[12]

Conclusion

Injectables in the form of BoNT-A and fillers may be an ideal treatment for beauty seekers requesting an improvement in skin quality that does not interfere with daily work, is minimally invasive, nominal downtime, easy to perform, rapid, safe and convenient. The effects of BoNT-A are short lived necessitating repeated treatment every three to six months versus fillers whose effects are maintained and may require retreatment yearly. For optimal aesthetic outcomes, patient assessment coupled with the patients' expectations and available social downtime, favours a multi-modal approach that may require injectable treatments coupled with light-based devices to improve overall patient satisfaction.

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The great debate: "Injectables versus Lasers" Resurfacing trumps injectables for photoaged skin

Philip S Bekhor[1]
1. Laser Unit, Royal Children's Hospital, Melbourne, Victoria, Australia
Correspondence: Philip S Bekhor philbek@hotmail.com
Disclosures: *none*

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Let us commence this debate by first outlining the characteristics of photoageing – which are in summary, solar dyschromia, dermal injury (solar elastosis and laxity), solar induced epidermal dysplasia and likely seborrhoeic keratoses.[1,2]

A point system (Table 1) has been developed to score the benefit of each modality. A single point will be allocated for definite benefit and half a point for marginal benefit.

The modality of resurfacing will be considered to include superficial, deep, fully, and fractionally ablative systems that use wavelengths targeting tissue water. Injectables will include the pre-packaged agents: botulinum toxin, crosslinked hyaluronic acid fillers, calcium hydroxylapatite, and poly-L-lactic acid but excluding platelet rich plasma, which is not pre-packaged.

Solar dyschromia

There is clearly no way in which injectables can address epidermal dyspigmentation so this will not be discussed further. This contrasts with resurfacing modalities that are highly effective for this indication.[3]

(**Score:** 1 point Resurfacing, 0 points Injectables)

Solar elastosis and laxity

Resurfacing lasers that penetrate the epidermis can destroy solar elastosis resulting in repair mechanisms that replace it with healthy collagen. Even resurfacing techniques that injure but do not destroy the epidermis are able to induce signaling systems that result in collagen remodeling.[4]

Skin laxity is also induced by more deeply penetrating ultraviolet A (UVA) and is also addressed by both fully ablative and to a lesser extent fractional ablative lasers.[4,5]

There is limited evidence that hyaluronic acid fillers may be able to stimulate collagen production but the clinical significance of this remains uncertain. Light weight hyaluronic acid may theoretically be able to mask some of the fine lines. In practical terms the lightweight hyaluronic acid injectables are tedious to inject, require multiple sessions, result in significant bruising-related downtime and have not been widely adopted. It is possible that this may change with newer non crosslinked easily injected hyaluronic acid products but these have not yet been released in Australia so there is no direct independent local experience on which to comment. Some cases have been published regarding the use of hydroxylapatite and poly-L-lactic acid to induce new collagen but again these techniques are more research based and have not translated into treatments used widely in cosmetic practices. They are also irreversible which adds to their risk profile.

Fillers cannot directly address skin laxity but by augmenting fat pads over the malar prominence may induce some lifting of skin, but this is limited by the degree to which an area can be filled before it looks unnatural.

The role of botulinum toxin in the management of movement, as opposed to solar related lines, is incontrovertible. One might suggest that solar damaged dermal tissue is more likely to develop permanent

lines however this is arguable. Some use toxins to treat upper lip fine lines but it is not universally effective or acceptable to patients in terms of unwanted restriction of lip movement. Also, these are movement-based lines not directly attributable to solar elastosis.

(**Score:** 1 point Resurfacing, ½ point Injectables)

Solar induced epidermal dysplasia

Resurfacing is a highly effective treatment for solar keratoses both superficial and deep. There is no plausible expectation that injectables have any role here.[6]

(**Score:** 1 point Resurfacing, 0 points Injectables)

Seborrhoeic keratoses

It is suspected that UV radiation has a role in the induction of seborrhoeic keratoses.[2] Appropriate resurfacing techniques can remove them but there is no role for injectables.

(**Score:** 1 point Resurfacing, 0 points Injectables)

Summary

As of the time of writing, resurfacing is the mainstay of therapy for photoageing while injectables have limited if any role. The proponents of injectables may argue that they have reduced down time and complications, but one would argue that this presents no real advantage if the actual treatment itself is of little benefit. Further to this, modern superficial resurfacing techniques such as fractional 1927 are of significant benefit with very limited downtime and minimal complications.

Table 1.

Efficacy scores for key photoageing indications (resurfacing versus injectables)

Condition	Resurfacing	Injectables
Solar dyschromia	1	0
Solar elastosis	1	½
Solar epidermal dysplasia	1	0
Seborrhoeic keratoses	1	0
Total score	**4**	**½**

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A fair go for authors and reviewers?

Greg J Goodman[1, 2]
1. Monash University, Clayton, Victoria, Australia
2. University College of London, London, UK

Correspondence: Greg Goodman gg@div.net.au

Disclosures: *none*

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As many senior authors and reviewers have experienced over the years, there seems to be a one-way commitment present in the relationship between authors and reviewers and the journals for which they labour.

Authors write their articles with blood, sweat, and tears, producing the literature on which we all depend. Reviewers give their time and effort freely (and I mean freely) to make sure that what is evident in the articles is truly science and worthy of publication.

The issue at hand is the reciprocity from the journals. There seems to be a disconnect of appreciation. Authors are treated with scant regard, often with cumbersome uploading forms, and reviewers who are commonly subjected to an unfulfilling experience with the journal given the long timelines for publication and often with no notification or access to the article they worked to review. It is not uncommon for an author after all the trouble of organising a study, wandering through the submission process of the journal, responding to reviews, and rewriting the article as required, to not see or have access to the final published article or to see it in the journal. It is also not unusual after acceptance for the author to wish that others may view the full text of this article. However, many journals will charge thousands of dollars, euros or pounds for the "permission" for this article to be made Open Access if the author is not linked to a funding university, companies or organisations. Large companies commissioning articles may have the resources to fund these costs, but this is not the case generally for authors writing on their own topics and may lead to a distortion of what becomes freely available in the public domain.

I would suggest that charging authors for using their own work is a most undesirable practice and one that should not continue into the future. Authors should at least be able to view the journal in which their article is published both online and if applicable in hard copy. Personally, I think every author should have access to the journal in which they have gone to all the trouble to publish to view that journal for that issue and probably for an entire year.

I understand that medical journals have their costs but that does not necessarily allow them to conduct themselves in such a fashion. Judging from the seemingly inexhaustible rate of invitations to publish in obscure journals it would appear that the profitability seems to be at least adequate. Publishers must find other ways to turn a profit that does not include taking this from the authors on whom they depend.

Turning my attention to reviewers, it is not uncommon to be asked to do several reviews a month for multiple journals. I do not have a central problem with this concept neither in theory nor in practice. However, the reviewers are treated equally poorly by the journals as the authors described above. Most journals have a very good reviewers' portal, but some go through overly complicated and quite bizarre questionnaires before the review can be laid down. It is almost as though the journal is doing the reviewer a favour rather than the opposite being true. However, that is not the major problem. The major issue with the review system is one's reward for effort. It has been estimated that over a billion US dollars a year of free service is performed for journals by reviewers, and it is further suggested that this is probably an underestimate.[1] With initial and revised iterations of articles over 20 million reviews are suggested to have been required in 2020 requiring over 130 million hours of reviewers' precious time.[1] The reviewer who puts in all the time to review the article, to look up all the literature pertinent to the article, submit on the portal, often multiple times for articles that need revision gets little credit for this effort from the journal involved above a robotised email. Furthermore, there is suggestion that the peer review system may be a significant waste of time and effort and overrated, with no real evidence for its efficacy.[2] It has been suggested

that as reviewers are paid less than children forced to go up chimneys in the 19th century that reviewers should unionise to protest this state of affairs.[2]

Services like Publons, ORCID and ResearchGate have some "feel good" factor in terms of recognition for effort but surely this is only partial acknowledgment for the effort of reviewing and insufficient. Similarly, the rare event of acknowledging reviewers by the occasional journal is nice but again rare and insufficient.[3] The reviewer does not necessarily see the finished article in print or online. The journal makes no attempt to recompense the reviewer in any way. I'm not entirely certain why they feel that this is a fair system. Medicine does require many of its participants to give that time freely in many circumstances and this is justifiable in the same way that other members of the population are asked to do so in volunteer work. However medical journals are a business, and a cost-free or minimal-cost method of compensation could easily be envisaged if the journal involved had an adequate care factor. It has been suggested that reviewers should be paid a fair price for their efforts which may or may not be affordable given the sheer numbers of reviews.[4] Examples that may present some benefit to reviewers and would not increase costs to subscribers or other journal costs in any major way may include allowing sharing the published article with the reviewer once it is in print or allowing subscription to that journal for the relevant issue or free online journal subscription for that calendar year of the review. Surely, it is more likely that the reviewer will be enticed to subscribe to the journal if they see the quality that that journal can bring.

I feel the days of unequal power in this domain need to come to an end and present a better deal for authors and reviewers. The authors and reviewers who keep the journals alive deserve a better deal – a fair deal from the journals they support.

I realise that Opinions and Progress in Cosmetic Dermatology is an Open Access journal and free to all who wish to read it and is free from the criticism directed above. We have managed to keep this journal afloat without taking advantage of authors and reviewers in this fashion. I would like to see larger publishing companies follow suit.

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