Editorial

# Age reversing modalities: An overview

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Aging is an inevitable biological process and not a disease. The desire to maintain a beautiful, youthful appearance crosses all racial, cultural, and economic barriers, and with the advent of minimally invasive aesthetic procedures that provide more affordable options and require less downtime, these goals can be more readily achieved. A component of beauty may also include a retained youthfulness despite advancing age, by the appearance of smooth, even skin complexion and the absence of rhytides, volume loss, and skin laxity.[1]

Medical and procedural interventions are now available to improve the aging skin. Medical interventions typically refer to topical agents (including natural, organic compounds) to be applied on the skin. The results of these medical treatments, although measurable, can be subtle and occur over fairly long periods of time. Procedural treatments on the other hand lead to more dramatic changes and the effects are noted earlier than with medical therapy alone. However, appropriate identification of individuals to carry out the procedures is of utmost importance.

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## MEDICAL TREATMENTS

### Sunscreens

One of the most important measures to prevent photoaging is through adequate protection against ultraviolet (UV) radiation from sunlight. Sunscreens are broadly defined as the agents that protect the skin against UV damage, sunburn, wrinkles, and pigmentary change. Sunscreens may be physical or chemical. Physical sunscreens act by blocking or reflecting UV light. Examples include zinc oxide and titanium oxide. Advantages of physical sunscreens are: a) block both UVA and UVB, b) are chemically inert i.e., do not cause phototoxic or allergic reactions. But they give chalky opaque white appearance when applied which is cosmetically not acceptable. Recently, nanoparticle technology has been introduced which is non greasy and spreads more evenly without the chalky white appearance.

Chemical sunscreens initially conferred protection against only UVB but the recent generation products protect against both UVA and UVB. Examples of UVA blockers are avobenzone and oxybenzone.

### Antioxidants

N-acetyl cysteine (NAC) is an amino acid derivative that is converted to glutathione, an endogenous antioxidant. Topical NAC 20% when applied under occlusion to human skin increases the quantity of reduced glutathione, the form of glutathione with potent antioxidant potential. It also prevents UV induced extracellular signal-regulated protein kinase (ERK) activation and subsequent up regulation of matrix metalloproteinase (MMP)s which prevent collagen breakdown. Another agent, genistein, an isoflavone and the major active constituent in soybeans has well documented potent antioxidant activity.[2]

Topically applied vitamin C stimulates the collagen producing activity of the dermis and leads to clinical

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improvement in photoaged skin with respect to firmness, smoothness and dryness compared to vehicle.[3] Idebenone, a synthetic analog of coenzyme Q10 with potent antioxidant activity, reduces the skin roughness, increases hydration, reduces fine lines and causes overall improvement in photoaged skin.

### Hormones

Estrogen exerts its actions on skin especially the post menopausal, through estrogen receptors present on both the epidermis and the dermis. In the epidermis, it is associated with increased thickness, hydration and an increase in surface lipid content. In the dermis, it causes increased hydration through an increase in glycosaminoglycan content as well as through increased collagen.[4] Estrogen based treatments are believed to be beneficial for improving the appearance of photoaged skin, but the scientific evidence is scanty. Similarly, testosterone is being tried to improve the appearance of naturally aged skin.

### Vitamin "A" derivatives

Retinol, a vitamin A derivative increases collagen production, glycosaminoglycan expression, procollagen I immunostaining and inhibits UV induction of collagen degrading enzymes in photoaged skin.[5] In addition, it also improves naturally aged skin. Retinol derivatives such as retinyl acetate, retinyl propionate and retinyl palmitate are widely used in over the counter anti aging treatments. Retinyl retinoate has also been associated with upregulation of hyaluronan synthase 2 gene in human keratinocytes.

However, tretinoin and tazarotene are the only two retinoids which are FDA approved as antiaging drugs. Tretinoin induces the synthesis of collagen 1 and decreases the quantity of abnormal elastin. Tazarotene, another retinoid which is metabolized to tazarotenic acid was found to significantly improve mottled hyperpigmentation and fine wrinkles at week 24 in a prospective, multicenter, randomized study. The higher concentration demonstrated the best efficacy, and it was found to be comparable to tretinoin.[6] It should be noted that tazarotene carries a pregnancy category X rating in contrast to tretinoin which is pregnancy category C.

### Peptides

Peptides, which age fragments of aminoacid chains, stimulate collagen synthesis and thus are used as one of the antiaging medications. Examples are Pal-KTTS and tripeptide copper complex-GHK-copper peptide. However, none of the peptides have been evaluated by double blinded, vehicle controlled studies for their effects on aging skin.[7]

### 5-flourouracil

5- flourouracil (5-FU) when applied topically is shown to increase the levels of type1 procollagen mRNA and protein, thus increasing the collagen synthesis. For patients unwilling to undergo costly laser resurfacing procedures and for those with actinic keratoses, topical 5-FU can be considered part of the antiaging armamentarium.[8]

### Imiquimod

A few studies have examined the antiaging effects of imiquimod. Topical application of 5% imiquimod, an immune modulator led to wrinkle reduction and improvement in dyspigmentation. The epidermal changes characteristic of aging skin like atrophy and atypia were diminished after therapy, however dermal changes were not noticed.[9]

### Organic, natural compounds

In addition to the above mentioned drugs, there are many natural organic compounds which are being used as a medium to combat aging process. Most commonly used compounds with their mode of action is mentioned below:[10,11]

1. Tea plant camellia sinensis, grape seed extract – polyphenolic compounds – antioxidant, and anti inflammatory action
2. Lemon oil and lavender oil – increase resistance to oxidative stress
3. Rosemary phenolic extract, N-furfuryladenine (plant cytokin) – anti oxidant
4. Chlorella, an aquatic plant extract- regulates vascular endothelial growth factor/ thrombospondin levels.
5. Gingko biloba, aloe vera, cucumber extract, whitch hazel, wheat protein, and algae extract are among the home made remedies used for improving the cosmetic appearance.

## PROCEDURAL TREATMENTS

### Endermalogie

Endermalogie is a noninvasive, mechanical procedure in which the skin with excess and abnormal fat deposition or the cellulite is sucked in between the rollers and held

in position for about 30–45 minutes.[10] This leads to flattening of the affected area but the effect is temporary.

## Chemical peels

Chemical peeling, if used properly, can be an effective means of treating the signs of skin aging, particularly photodamage in lighter-skinned individuals. Deep chemical peels should generally be avoided in darker skin types because of the risk of postpeel complications such as dyspigmentation, keloid formation, and hypertrophic scarring.[1] Peeling agents, when applied to the skin create a superficial wound by exfoliating the epidermis or dermis, which subsequently re-epithelizes along with remodelling of underlying collagen leading to improvement in dyschromia, photodamage, and rhytides.

Different agents used as peeling agents are: a) superficial peels – alpha hydroxy acids (glycolic acid, lactic acid, pyruvic acid), beta hydroxy acid (salicylic acid, lipo hydroxyl acid) b) medium depth peels - trichloroacetic acid 35%, Jessners solution c) deep peels – trichloroacetic acid >50%, phenol.[10]

Common side effects include dyspigmentation, erythema, burning sensation, reactivation of herpes simplex virus, superficial desquamation, vesiculation, hypertrophic scarring and keloid formation. Postpeel erythema is almost always transient but may require treatment with topical corticosteroids to minimize the development of post inflammatory hyperpigmentation (PIH). PIH can be prevented by using topical depigmenting agents such as hydroquinone as part of the prepeel regimens. It can also be prevented by starting at lower peel concentrations and titrating up, or by less-frequent intervals between peels (2–4 weeks).

## Microdermabrasion

Microdermabrasion (MDA) also called "body polishing" is a noninvasive, nonsurgical procedure for revitalizing and rejuvenating the skin.[12] It is a closed-loop process, which uses the abrasive qualities of chemically inert crystals, most common being aluminium oxide to achieve partial skin ablation. It is mainly used to improve or correct photodamage, hyperpigmentation, superficial rhytides, stretch marks, tattoo removal, scar revision, and acne scarring.[13]

In MDA, a flow of inert crystals is projected onto the skin through a controlled graduated vacuum pump or a compressed air source. The crystals transfer their kinetic energy to the cells of the top layers of epidermis, leading to detachment of sebum concretions and corneocytes. A variable depth of ablation can be achieved by altering vacuum pressure, speed of crystals, particle size.[13] It may be performed on all skin types including Fitzpatrick type IV-VI where the usefulness of chemical peels, laser resurfacing, and dermabrasion is limited. Sodium chloride crystals, diamond tipped devices can also be used in the place of aluminium oxide.

### *Contraindications*

MDA is not recommended for those who have rosacea, fragile capillaries, vascular lesions, warts, erosions, and ulcers.[12] It should not be used in patients who have taken isotretinon in the past 6 months because of the associated dryness of the skin and the possibility of scarring.

### *Histological changes*

Acute changes include stratum corneum thinning and homogenization, while the chronic changes demonstrate an increase in epidermal thickness, flattening of rete pegs, improvement in loss of polarity, liquefaction of basal cells, and hyalinization of papillary dermis.[12]

MDA is seen to stimulate fibroblastic activity along with a new dermal collagen deposition. This increase in collagen synthesis may be further enhanced by the physical sucking action of the MDA.

### *Side effects*

MDA is a safe procedure without many side effects. Aluminium oxide dust is too insignificant to be a health hazard to patients or operators because of the smaller size of crystals used in MDA. However, ocular complications like eye irritation and adherence of aluminium oxide crystals to the cornea are a potential hazard if safety goggles are not used to protect the eyes of both the patient and the operator.[13] Petechiae or purpura may occur especially when the ablation is slow or more vacuum pressure is used, but they usually resolve in one to three days. Rarely, acne or recurrent herpes simplex may occur following MDA. Postinflammatory hyperpigmentation and foreign body granuloma formation are other adverse effects commonly noticed with MDA.

### Ablative laser resurfacing

Ablative laser resurfacing refers to removal of skin in a controlled manner, leading to better wound healing and re-epithelisation and thus, a subsequent improved appearance of the skin. The continuous wave carbon dioxide laser was the first ablative resurfacing device and continues to be the gold standard. The $CO_2$ laser emits a 10,500nm wavelength whose chromophore is water. It generates heat which results in immediate tightening of the skin due to shrinkage and denaturation of type I collagen.[14]

$CO_2$ laser is also known to increase the levels of interleukin 1 (IL-1), tumor necrosis factor alpha (TNFα) and transforming growth factor beta (TGFβ), along with an increase in type I and III procollagen mRNA and this effect was seen to last for at least six months.[15] In addition, enzymes associated with breakdown of fragmented collagen known as matrix metalloproteinases (MMPs) were noted to be elevated when mRNAs levels were measured.

Ablative lasers such as the erbium-doped yttrium aluminum garnet (Er: YAG) and carbon dioxide ($CO_2$) lasers have been the mainstay of treatment for photodamage specially fine facial rhytides in peri oral and peri ocular region, in lighter skin phototypes.[1] These lasers are not commonly used in dark skin color because of the greater risk of complications such as dyschromia and scarring. Other side effects include erythema, reactivation of herpes virus and other bacteria.

### Non ablative lasers

Nonablative lasers induce dermal neocollagenesis without epidermal disruption, thereby limiting adverse effects and virtually eliminating down-time. However, the results are less dramatic when compared to ablative modalities. Most nonablative laser systems emit light within the infrared portion of the electromagnetic spectrum (1000–1500nm). At these wavelengths, absorption by superficial water containing tissue is relatively weak, thereby allowing deeper tissue penetration.[16]

Nonablative skin resurfacing is ideally used for the patient with mild-to-moderate photodamage and signs of skin ageing including lentigenes, mild rhytides and mild to moderate poikiloderma.[16] Nonablative skin resurfacing technology can be categorized into five different general modalities: Radiofrequency systems, mid-infrared lasers which include 1320 nm Nd:YAG, 1450 nm diode, 1540 nm Er:glass lasers, intense pulsed light systems (IPL), vascular lasers (585 nm pulsed dye laser), and light emitting diodes (LED).

Radiofrequency energy is conducted electrically to dermal tissue and the generated heat produces subtle damage to collagen, which along with the subsequent inflammatory cascade induced by heating, produces the tightening effect.[16]

Pulsed dye laser targets the chromophore oxyhemoglobin to create a thermal insult to the dermal microvasculature, thereby inducing production of inflammatory cytokines, which in turn stimulate fibroblast activity leading to dermal collagen production.[15]

1550 nm erbium doped fiber laser is a non ablative fractional laser (NAFL) which emits a mid-infrared wavelength, which creates non-contiguous columns of microscopic thermal zones (MTZ) in the dermis.[17] These MTZs produce localized epidermal necrosis and collagen denaturation and the surrounding normal epidermal and dermal cells migrate into the zone of damage to produce rapid healing.

### Lipotransfer

Recently the lipotransfer technique has been studied extensively regarding the mode of fat harvest, preparation, storage, and use in facial contouring. It was shown that lipotransfer covers not only mature adipocytes but adipose-derived stromal cells (ASC) and preadipocytes. Excisional harvest is better than blunt or needle harvest. Anesthesia of the donor site is considered as a negative factor for fat cell survival.

Pre-adipocytes are an interesting source for adipose tissue regeneration and lipofilling. Some factors have been identified that enhance the adipogenic conversion of pre-adipocytes. Fibrin matrix and basic fibroblast growth factor are effective in that way. In addition, basic fibroblast growth factor enhances neovascularization in the newly formed adipose tissue.[18]

### Botulinum toxin

Dynamic wrinkles resulting from overactive movements of underlying muscles are the main indication for using botulinum toxin A. Two types of botulinum toxin A are approved by FDA:

onabotulinum toxin (botox) and abobotulinum toxin (dysport). The toxin acts on the presynaptic cholinergic nerve terminals, preventing the fusion of vesicles with the membrane and thus the release of neurotransmitter acetylcholine.[7] The injections are used for the dynamic rhytides of glabella (procerus and corrugators), forehead commonly known as frown lines (frontalis), lateral periorbital region commonly known as crow's feet (orbicularis oculi). The effect of the toxin lasts for about 4 months.

The usual dosage is about 20 U Botox or Xeomin or 5 U Dysport. In the aged brow, frontalis hyperactivity may be required to compensate for blepharoptosis that occurs due to tissue laxity. Here, injection of botox immediately superior to the eyebrow is relatively contraindicated because the muscular relaxation it induces may cause brow ptosis.[19] The alternative is minimal botox injection a millimetre inferior to the eyebrows to somewhat weaken the depressor effect of the superior fibres of the orbicularis oculi.

The most significant adverse effect of botulinum toxin when used in brow lifting is lid ptosis with an incidence of up to 1%. This effect is temporary, lasting about 2–3 weeks. It can be treated by apraclonidine eye drops that contract Mueller's muscle to raise the lid about 1 mm. Brow ptosis is commonly seen after overdose of botulinum toxin. Ectropium or diplopia are much less common possible adverse effects and bruising is more common when botulinum is used to correct crow's feet.[20]

### Soft tissue augmentation

Dermal fillers improve the appearance of the skin with respect to wrinkles and certain types of scars by "filling in" areas that have experienced loss of collagen and structure. Typically, they are injected into the lower two thirds of the face, the most common site being nasolabial creases.[21] Other commonly injected sites are infra orbital, zygomatic, chin, "marionette lines" or lines between the angles of mouth. Prejowl sulcus, between the chin and the mandible, is often a site of fat loss which can be corrected by soft tissue fillers.

The procedure of soft tissue augmentation typically involves a topical anesthetic or regional nerve block followed by injection of the agents either in serial puncture technique or linear fanning technique. Dermal fillers can be categorised as temporary, semipermanent, permanent. Temporary fillers include bovine collagen, porcine collagen, human collagen and cross linked hyaluronic acid (HA). Semi permanent fillers include poly L lactic acid and calcium hydroxylapatite[7] Permanent fillers include liquid silicone and polymethylmethacrylate suspended in collagen. Of these, HA fillers are the most popular. They are derived from bacteria and rooster combs and last for 4-5 months. 'NASHA' is a term used to describe the non animal stabilised form of HA.

Each site has different landmarks and proper care is to be taken while administering the filler. For example, to provide lateral correction in periorbital area, the needle should be introduced perpendicular to the skin surface until it touches bone. Small amount of filler should be injected in a fanning manner slowly as the needle is being introduced, just proximal to the orbital rim.[21]

Side effects usually encountered with fillers are edema, ecchymosis, temporary pain, and some tissue soreness in the first few days following injection. Granulomatous reaction pattern to the injected material is another important side effect to be considered, the histological picture of which varies depending upon the chemical used.[22] Patients taking blood thinners may experience more bruising and swelling than usual. Serious adverse events are uncommon.

## CONCLUSION

The persistent desire of human to achieve a more-vibrant, youthful appearance is more easily attainable in the present era as the field of aesthetic dermatology is expanding, with new developments and advances in the safety and efficacy of cosmetic procedures. Procedures such as chemical peeling and laser resurfacing, if in the hands of a experienced dermatologist can be an effective means of treating the signs of skin aging, particularly pigmentary changes. These treatments are particularly effective in the correction of intrinsic features of aging. Injectable products such botulinum toxin and dermal fillers offer patients with dark skin color, fast and effective results with fewer complications and minimal downtime. As with any procedure, there remains a risk of complications, but with the knowledge of how to carry out the procedure properly and the necessary precautionary measures, the risk of complications can be minimized.

## REFERENCES


1. Davis EC, Callender VD. Aesthetic dermatology for aging ethnic skin. Dermatol Surg 2011;37:901-17.
2. Kang S, Chung JH, Lee JH, Fisher GJ, Wan YS, Duell EA, *et al*. Topical N acetyl cysteine and genistein prevent ultraviolet-light-induced signaling that leads to photoaging in human skin in vivo. J Invest Dermatol 2003;120:835-41.
3. Farris PK. Topical vitamin C: A useful agent for treating photoaging and other dermatologic conditions. Dermatol Surg 2005;31:814-7.
4. Hall G, Phillips TJ. Estrogen and skin: The effects of estrogen, menopause, and hormone replacement therapy on the skin. J Am Acad Dermatol 2005;53:555-68.
5. Kafi R, Kwak HS, Schumacher NE, Cho S, Hanfit VN, Hamilton TA, *et al*. Improvement of naturally aged skin with vitamin A (Retinol). Arch Dermatol 2007;143:606-12.
6. Kang S, Leyden JJ, Lowe NJ, Ortonne JP, Phillips TJ, Weinstein GD, *et al*. Tazarotene cream for the treatment of facial photodamage: A multicenter, investigator-masked, randomized, vehicle-controlled, parallel comparison of 0.01%, 0.025%, 0.05%, and 0.1% tazarotene creams with 0.05% tretinoin emollient cream applied once daily for 24 weeks. Arch Dermatol 2001;137: 1597-604.
7. Sachs DL, Voorhees JJ. Age-reversing drugs and devices in dermatology. Clin Pharmacol Ther 2011;89:34-43.
8. Sachs DL, Kang S, Hammerberg C, Helfrich Y, Karimipour D, Orringer J, *et al*. Topical fluorouracil for actinic keratoses and photoaging: A clinical and molecular analysis. Arch Dermatol 2009;145:659-66.
9. Metcalf S, Crowson AN, Naylor M, Haque R, Cornelison R. Imiquimod as an antiaging agent. J Am Acad Dermatol 2007;56:422-5.
10. Vedamurthy M. Anti aging therapies. Indian J Dermatol Venereol Leprol 2006;72:183-6.
11. Thappa DM, Pise GA. Anti aging therapies: Other half of the story. Indian J Dermatol Venereol Leprol 2006;72:459-60.
12. Savardekar P. Microdermabrasion. Indian J Dermatol Venereol Leprol 2007;72:272-9
13. Bhalla M, Thami GP. Microdermabrasion: Reappraisal and brief review of literature. Dermatol Surg 2006;32:809-14.
14. Railan D, Kilmer S. Ablative treatment of photoaging. Dermatol Ther 2005;18:227-41.
15. Orringer JS, Kang S, Johnson TM, Karimipoul DJ, Hamilton T, Hammerberg C, *et al*. Connective tissue remodeling induced by carbon dioxide laser resurfacing of photodamaged human skin. Arch Dermatol 2004;140:1326-32.
16. Sachdeva M, Hameed S, Mysore M. Nonablative lasers and nonlaser systems in dermatology: Current status. Indian J Dermatol Venereol Leprol 2011;77:380-8.
17. Alam M, Hsu TS, Dover JS, Wrone DA, Arndt KA. Nonablative laser and light treatments: Histology and tissue effects- a review. Lasers Surg Med 2003,33:30-9.
18. Cho SW, Kim I, Kim SH, Rhie JW, Choi CY, Kim BS. Enhancement of adipose tissue formation by implantation of adipogenic differentiated preadipocytes. Biochem Biophys Res Commun 2006;345:588-94.
19. Wollina U, Payne CR. Aging well – the role of minimally invasive aesthetic dermatological procedures in women over 65. J Cosmet Dermatol 2010;9:50-8.
20. Wollina U, Konrad H. Managing adverse events associated with botulinum toxin A: A focus on cosmetic procedures. Am J Clin Dermatol 2005;6:141-50.
21. Busso M. Soft tissue augmentation: Nonsurgical approaches to treatment of the mid and lower facial regions. Dermatol Nurs 2008;20:211-4,217-9.
22. Requena L, Requena C, Christensen L, Zimmermann US, Kutzner H, Cerroni L. Adverse reactions to injectable soft tissue fillers. J Am Acad Dermatol 2011;64:1-34.