INTRODUCTION

Aging unavoidable consequences are evident in almost all living beings. Organism aging is generally characterized by a decline in fertility, increased susceptibility to disease and tissue dysfunction and increased risk of mortality.[1-3] Aging is associated with a gradual loss of homeostatic mechanisms that maintain the structure and function of adult tissues. [4] According to the United Nations, the number of people worldwide aged 60 years or older will increase from 1 in 10 currently to 1 in 5 by 2050. By 2050, the ratio of people aged 65 years or older to those aged 15–64 years will double in developed nations and triple in developing nations. This demographic shift compels us to confront the aging associated changes.[5]

Human skin assumes several important physiological functions and is directly exposed to many environmental factors and shows an invariant age-dependent phenotype.[6] Aging is defined by characteristic phenotypic changes, but there appear to be few corresponding changes in the genotype. So, aging represents a fundamental epigenetic phenomenon[7]

Facial remodeling with the skin aging process

Aging produces a number of changes that occur in the skin, soft tissues and bones.[8, 9] In childhood, the face presents a round format, due to the great skin elasticity and distribution pattern of fat, the nose and ear cartilage provide subtle and delicate contours, while the bones are still in development till adolescence where bones and cartilage reach the expected growth and define facial contours.

From the third decade onwards, eyebrows start dropping, causing the eyes to appear smaller. With the progression of aging, in the fourth decade, the eyelids become more flaccid, leading to a pseudo-herniation of the retro-orbital fat and the formation of rhytidosis. The nasolabial groove is more prominent and the eyebrows continue to drop.

In the fifth decade, deep wrinkles appear in the forehead and sagging eyelids result from the excess of skin. The jaws' arch loses regularity and vertical wrinkles form around the perioral region. In the sixth decade, wrinkles become more pronounced and evident, even at rest. The dropping of the nasal tip and mid-face structures is observed, which leads to the growth of the nasogenian groove and loss of the jaw contour. The presence of excess of chin fat and platysmal sagging also contributes to the modification of the jaw.

In the seventh decade, the skin becomes thinner, the eyelid opening gets further reduced and facial fat resorption occurs. In the eighth decade, all prior changes are much more evident. Thinning of skin and fat resorption continue progressing. [10]

Intrinsic aging and photoaging:

Cutaneous aging is a complex biological phenomenon.[11] There are two independent processes affecting the skin simultaneously. The first is the innate or intrinsic aging (chronologic aging),'the biologic clock', that affects the skin in the same manner as it affects the internal organs, i.e.by slow, irreversible or partly reversible tissue degeneration.

The second process is the extrinsic aging, 'photoaging', which is the result of exposure to outdoor elements, primarily UV irradiation.[12] They can be distinguished clinically and histopathologically. Photoaged skin usually shows a variety of clinical manifestations, including coarseness, wrinkling, sallow discoloration, telangiectasia, irregular pigmentation and a variety of benign, premalignant and malignant neoplasms.[13, 14]In contrast, in old photo-protected skin is thin and may have reduced elasticity, increased laxity and fold accentuation, but it is smooth and clearly does not develop the leathery, sagging appearance. In addition, it usually maintains youthful geometric patterns.[15]

Photoaging starts as early as late teens and strongly associated to degree of pigmentation while intrinsic aging starts typically in 50s to 60s and in women earlier than men and only slightly associated to the degree of pigmentation.[16]

The histological differences between the two states are dramatic:

- **Intrinsically aged skin is characterized by:**

1) A flat epidermal–dermal interface with loss of the dermal papillae and epidermis thinning with aging.[17] However, cellular polarity and normal epidermal differentiation appear to be maintained.
2) In the dermis, collagen synthesis is diminished , but mature collagen is more stable in degradation.[18] The elastic tissue shows elastogenesis followed by elastolysis 'moth-eaten fibers.[19, 20]
3) No inflammatory response is seen and microvessels are decreased but not changed[15]

- **While photoaged skin shows the following characteristics:**

1. The epidermis is often thickened in early stages and shows atrophy in later stages.[17] Keratinocytes proliferation rate is higher than normal[21] with loss of polarity and numerous dyskeratotic cells. [19]
2. In the dermis, the mature collagen is decreased, [21] and marked elastogenesisis replacing the collagen follows. [19]
3. Pronounced inflammation and perivenular infiltrate of histiocytes and lymphocytes is seen. Vessels become dilated and deranged. [15]

Photoaging clinical features

Typical features of photoaging are strongly influenced by skin phototype. Skin photoypes I–II usually show proliferative exhaustion, epidermal atrophy, focal depigmentation, pseudoscars, mutation and dysplasia, freckles, nevi, lentigo maligna and actinic keratosis. While skin phototype III–IV shows protective hyperplasia, tanning, lentigines, epidermal thickening and coarse wrinkling[22]

Photoaging clinical assessment

Clinical manifestations of skin ageing are assessed by trained clinical technicians using descriptive grading scales (e.g. Fitzpatrick classification of wrinkles and Glogau's classification) to quantify baseline and post-treatment parameters. Comparison of before and after scores enables the evaluation of the treatment under study.

A comprehensive grading scale designed by Alexiades-Armenakas, [23] (Table 3), separates the individual categories of skin aging and allows for quantitative analysis of changes within each category as well as overall change. This grading scale may be employed in assessing the efficacy of any or all laser resurfacing technologies and cosmetic treatment modalities for their clinical impact on each individual aspect of the aging skin, providing a more quantitative analysis of each category as well as overall improvement.

Table (1): Classification of wrinkles according to the Fitzpatrick score[24]

Fitzpatrick wrinkle score			
Class	**Score**	**Wrinkling**	**Degree of elastosis**
I	**1–3**	Fine wrinkles	Mild (fine textural changes with subtly accentuated skin lines)
II	**4–6**	Fine to moderate depth wrinkles, moderate number of wrinkles	Moderate (distinct elastosis, with yellow translucency under direct light)
III	**7–9**	Fine to deep wrinkles, numerous lines, with or without redundant skin folds	Severe [multipapular and confluent elastosis (thickened yellow and pallid) approaching or consistent with cutis rhomboidalis]

Table (2): Glogau's photoaging classification[25, 26]

Type Characteristics
1: **No wrinkles** Typical age 20s to 30s
Early photoaging Mild pigmentary changes No keratosis No or minimal wrinkles
2: **Wrinkles in motion** Typical ages late 30s to 40s
Early to moderate photoaging Early senile lentigines Palpable but not visible keratoses Parallel smile lines beginning to appear laterally to mouth
3: **Wrinkles at rest** Typical age 50 or older
Advanced photoaging Obvious dyschromias, telangiectasias Visible keratosis
4: **Only wrinkles** Typical age 60 or older
Severe photoaging Yellow-gray skin Precancerous lesions No normal skin

Table (3): Comprehensive grading scale of rhytides,laxity and photodamage[23]

		Categories of Skin Aging and Photodamage								
Grading **Scale**	**Descriptive Parameter**	**Rhytides**	**Laxity**	**Elastosis**	**Dyschromia**	**Erythema-Telangiectasia (E-T)**	**Keratoses**	**Texture**	**Overall Score**	**Patient satisfaction (Y-N)**
0	none	none	none	none	none	none	none	none		
1	mild	wrinkles in motion, few, superficial	localized to nasolabial (nl) folds	early, minimal yellow hue	few (1-3) discrete small (<5 mm) lentigines	pink E or few T, localized to single site	few	Subtle irregularity		
1.5	mild	wrinkles in motion, multiple, superficial	localized, nl and early melolabial 1,(ml) folds	yellow hue or early, localized periorbital (po) elastotic beads (eb)	several (3-6),discrete small lentigines	pink E or several T localized 2 sites	several	Mild irregularity in few areas		
2	Moderate	wrinkles at rest, few, localized, superficial	localized, nl/ml folds, early jowels, early submental/submandibular (sm)	yellow hue, localized po eb	multiple (7-10), small lentigines	red E or multiple T localized to 2 sites	multiple, small	rough in few, localized sites		
2.5	Moderate	wrinkles at rest, multiple, localized, superficial	localized, prominent nl/ml folds, jowels and sm prominent nl/ml folds, jowels and sm, early neck strands	yellow hue, po and malar eb	multiple, small and few large lentigines	red E or multiple T, localized to 3 sites	multiple, large	Rough in several, localized areas		
3	**advanced**	wrinkles at rest, multiple, forehead, periorbital and perioral sites, superficial	Prominent nl/ml folds, jowels and sm, early neck strands	yellow hue, eb involving po, malar and other sites	many (10-20) small and large lentigines	violaceous E or many T,multiple sites	many	rough in multiple, localized sites		
3.5	**advanced**	wrinkles at rest, multiple, generalized, superficial; few, deep	deep nl/ml folds, prominent jowels and sm, prominent neck strands	deep yellow hue, extensive eb with little uninvolved skin	Numerous (>20) or multiple large with little uninvolved skin	Violaceous E, numerous T little uninvolved skin	Little uninvolved skin	Mostly rough little uninvolved skin		

4	**severe**	wrinkles throughout, numerous, extensively distributed, deep	Marked nl/ml folds, jowels and sm, neck redundancy and strands	deep yellow hue, eb throughout, comedones	numerous, extensive, no uninvolved skin	deep, violaceous E, numerous T throughout	No uninvolved skin	Rough through out		

Pathophysiology

Epidermal photoaging:

Little is known about the mechanisms of epidermal photoaging. Epidermal atrophy, slow wound healing and depigmented pseudoscars may be due to UV-induced apoptosis of stem cells in the basal layer and hair bulge, whereas the ‘‘bronzing’’, the permanent ‘‘tan’’ observed in photoaged skin of some darker-skinned individuals, may be caused by the greater melanin production observed in senescent melanocytes.[27] However, the molecular events leading to freckling, lentigines and other pigmentary changes characteristic of photoaged skin are unknown.

Dermal photoaging:

Changes in the dermal extracellular components account for the major visible changes associated with UV-induced extrinsic damage.[28]

Dermal elastosis is the histological hallmark of photoaging. It consists of thickened, tangled and ultimately granular amorphous elastic structures.[29]It is postulated to result directly from dermal fibroblasts damage by ultraviolet irradiation which then produce abnormal elastin, or it may result from chronic low-grade enzymatic digestion of extracellular matrix by proteases elicited by inflammatory mediators. [30]By using immunostaining and confocal microscopy, the fibrillin seemed significantly truncated and depleted in the upper dermis at the dermoepidermal junction of photoaged skin.[31]

Degeneration of the surrounding collagenous meshwork[32] and loss of mature dermal collagen, with a distinct basophilic appearance of collagen (‘basophilic degeneration’) is also seen.[33] This may be due to prolonged elevation of matrix metalloproteinases (MMP) activity that results from exposure to even intermittent small doses of UVB [32, 34] which secondarily reduces new collagen formation.[35, 36]

Other photoaging contributors:

The resident fibroblasts of the dermis adopt a stellate phenotype and at the ultrastrucutural level reveal a highly activated rough endoplasmic reticulum indicating an increased biosynthetic activity. [37]

The common deletion (a 4,977 base pair deletion) [38] within the mitochondria caused by reactive oxygen species (ROS) is up to 10-fold more prevalent in photoaged than in sun-protected skin. The resulting compromise of energy production in mitochondria is postulated to contribute to clinical signs of photoaging, whereas leakage of ROS from mitochondria into the cytoplasm and extracellular space damages many critical molecules, further compromising tissue function.[39]

Progerin is a nonfunctional truncated protein produced in Hutchinson Gifford progeria (HGP). A study showed that progerin is produced also by cells of normal elderly individuals,[40]suggesting a role for compromised nuclear envelope function in normal aging. Another study showed that repeated UVA irradiation of cultured dermal fibroblasts led to progerin production and changes in nuclear morphology, just as observed in fibroblasts from HGP patients and old donors. [41]

Furthermore, an increase in mast cells and neutrophils has been reported in photoaged skin.[30, 42]

Photoaging action spectrum

Photoaging develops gradually over decades so experimental determination of the relative contribution of different wavelengths is impossible in human skin.[43]

UVB, (290–315nm) are far more energetic than (UVA (315– 400nm).DNA damage implicated in both aging and photoaging is predominantly attributable to UVB. Epidermal features of photoaging are largely a consequence of UVB irradiation. However, UVA penetrates deeper into the dermis in a fair- skinned individual. Unlike UVB, UVA is also transmitted through glass, allowing exposure while driving or while indoors near windows. In combination, these considerations have led to the suggestion that UVA has a far larger role in photoaging than in acute effects of UVB or in photo-carcinogenesis and that both; UVB and UVA contribute to specific features of photoaging [22]

Photoaging exacerbating Agents

In addition to UV exposure, several other factors may contribute to skin aging, these include; cigarette smoking [44, 45] air pollution,[46] Infrared (IR),[47] Near-infrared (NIR) radiation(between 1100-1800nm) [48] and exposure to heat [47]

Therefore, novel strategies to block IR and heat induced skin aging need to be developed to minimize their damaging effect on the skin.

Natural photoprotection

Photoprotection of the skin is directly related to the thickness of stratum corneum[49] and the degree of pigmentation.

The protection afforded by stratum corneum may be increased when stratum corneum is thickened by ultraviolet exposure.[50]

Pigmentation of a person may vary considerably from white to black. A very black person may tolerate 20 times as much as a completely white one. [50]

The UV-dose to erythema -independent of pigmentation- is constant in different age groups.[51] The constitutive pigmentation in unexposed buttocks does not change with age[51] while pigmentation increases in sun exposed areas (facultative pigmentation) proportional to sun exposure.[52]

Those two means of natural photoprotection decrease the UV-dose reaching epidermal and dermal structures, thereby protecting these structures. However, with age the melanin distribution becomes patchy with areas with no or little melanin, which may thus be exposed to increased UVR.

Other mechanisms of protection involve repair, apoptosis and adaptive processes that may be provoked by exposure to small repeated UV-doses.[53]

Natural ingredients used in management of photoaging

Phenolic compounds, Flavonoids and Proanthocyanidins from plants are responsible for antioxidative activities of herbal products. This is explained by their chemical structure and their ability to donate free electron and hydrogen. [54, 55]

The extracts of the tropical Cabbage palm fern (Polypodium leucotomos) [56] and Green tea (Camellia sinensis)have strong photoprotective properties.[57]

A great number of plant extracts can diminish UVB-induced photodamage by decreasing activity of enzymes involved in tissue degradation (i.e., Ixora parviflora, Coffea arabica), [58, 59] or by increasing of synthesis tissue constituents (i.e., Labisia pumila). [60]

Numerous plants and plants extracts can attenuate degradation of skin matrix. Arctium lappa [61], Areca catechu [62], Dioscorea villosa [63], Curcuma xanthorrhiza [64] and Styrax japonica [65] are examples of plants that can inhibit Hyalorunidase, Elastase, Colagenase and MMP.

Some plants have the ability to promote synthesis of collagen, that is, Emblica officinalis [66], Centella asiatica [67], Panax ginseng [68] and Cinnamon zeylanicum.[69]

Plants and plant extracts with depigmentation properties act through various mechanisms: inhibition of melanogenesis [70], dispersion of melanocytes [55], inhibition of Tyrosianase [70, 71], decline in activity of cellular DOPA oxidase [72] and downregulation of the gene and protein expression of the Microphthalmia-associated transcription factor (MITF). [72]

Some plants can improve skin firmness and elasticity,mainly due to phytoestrogens and saponosides.[73]

Plant extracts are often considered safe by lay people [74], because of the simple fact that they come from nature.[75] On the other hand, irritation, contact allergic dermatitis and other adverse reactions to natural products have been documented. [73, 76]

Over the past decade, a great number of plant extracts have been studied, though there is a constant need for more evaluation and more clinical studies to evaluate these products. These compounds appear to have some efficacy in at least reducing some of the biochemical manifestations of photodamage.[39]

Management strategies to combat aging:

Familiarity with Fitzpatrick phototype classification of skin types is imperative when evaluating an aging face since the risks as well as the outcomes of treatment procedures correlate with the skin phototype.

Therapies for the treatment of photodamage can be subdivided into primary, secondary and tertiary treatment/prevention. Primary prevention, in the form of photoprotection, will reduce development of extrinsic aging. Secondary treatment/prevention in the form of topical retinoid therapy, aids in attenuating the effects of photoaging. Lastly, tertiary treatment/prevention ameliorates the effects of photoaging as well as intrinsic aging via the use of botulinum toxin, soft tissue fillers and superficial chemical and laser skin resurfacing.[77]

Table (4): Photoaging therapies categorized by type of treatment/prevention strategy and disease severity[78]

Primary	Secondary	Tertiary
Photoprotection	Photoprotection	Chemical peelings
	Retinoic acid	Microdermabrasion/ microcoblation
	Antioxidants	Laser
	Estrogens	Botulinum toxin
	Growth factors/ cytokines	Fillers

1. Primary prevention

A key step is sun protection via sun avoidance, broad spectrum ultraviolet (UV) A and B defense and protective clothing. It is important to note that the sun protection factor (SPF) does not measure protection for UVA defense, which is the portion of the spectrum accountable for photoaging. However, sunscreens with a higher concentration of UVA blocking ingredients, such as dioxybenzone, oxybenzone, titanium dioxide, zinc oxide, do confer protection against photoaging in vivo.[79] Application of sunscreen should be performed at 2 mg/cm2 In addition, patients should be counseled to avoid peak hours of UV exposure from 10 am to 4 pm, wear protective clothing, such as longsleeves, hats, sunglasses and/or UV protective clothing.[77]

2. Secondary treatment/prevention

Retinoids

In the epidermis, retinoids normalize the life cycle of keratinocytes, reduce Keratinocyte atypia and normalize the spread of melanosomes. Dermal changes are represented by an increase of collagen, elastin and glycosaminoglycans.[16, 80, 81]

Retinoic acid (tretinoin) is a powerful compound to treat the signs of aging, including fine lines and stains, but it should be used cautiously to avoid causing undesirable effects, Newer delivery systems may diminish the unwanted effects.[82]

Regarding other forms of retinoids, retinol (vitamin A) exerts topically only a small retinoid-like action when compared to the topical retinaldehyde and retinoic acid.[83] It also has antioxidant action. Retinaldehyde, typically at a dose of 0.05%,[84-86]is clinically effective. Retinyl palmitate has low irritation potential but also weaker efficacy, even with a very high concentration of 2% required to observe an effect.[87]

The main concerns in using retinoids are skin irritation and product instability and teratogenicity. Using formulations to control skin delivery or inclusion of other ingredients such as anti-inflammatory agents can also reduce irritation. Strategies such as retinoid encapsulation and inclusion of stabilizing antioxidants can be used to minimize instability.[88]

Till now, there are no sufficient studies to prove that topical tretinoin is teratogenic. However, it is best to advise young women not to use topical retinoids during pregnancy or when they are trying to become pregnant.[89]

Antioxidants

Antioxidants are responsible for reducing the damage caused by free radicals, thus avoiding damage at the cellular level. They also help to inhibit inflammation and offer protection against photo-damage and skin cancer. They play a major role in the prevention and therapy of UV induced skin aging and are being added to the formulations for sun protection.[90]They include alpha-lipoic acid (ALA),[91] L-ascorbic acid (vitamin C)[92] Vitamin E, [93] niacinamide (B3 vitamin),[94, 95] and ubiquinone. [96]

i. L- Ascorbic acid (Vitamin C)

Vitamin C is used routinely in topical formulations, due to its collagen synthesis stimulating effect and antioxidant property. It inhibits tyrosinase, reducing areas with hyperpigmentation and provides some protection against UV radiation by its antioxidant properties.[92]

ii. Vitamin E

Vitamin E has an antioxidant and moisturizing property. Some studies have demonstrated that it has topical action in the protection against UVB radiation damage.[93] Vitamin C is capable of regenerating oxidized vitamin E so their combination result in synergistic effects.[97]

The application of topical vitamin E has been recognized as a safe substance with adverse reactions generally limited to a slight irritation.[98]

iii. Niacinamide (vitamin B3)

Niacinamide is a powerful and well-tolerated antioxidant. It acts as a melanosome transfer inhibitor, hence improving hyperpigmentation.[94, 95]

The most important challenge of working with niacinamide and nicotinate esters is avoiding hydrolysis to nicotinic acid. Nicotinic acid, even at low doses, can induce an intense skin reddening (flushing response).[99] Formulating in the pH range of 4 to 7 is preferred to avoid hydrolysis.

Moisturizers

Should be used in support of the use of home formulations for skin rejuvenation they are responsible for keeping water in the epidermis; promotes a protective film against water loss and help maintain the barrier.[100]

Hormone replacement therapy

Estrogen replacement, when well prescribed, including hormones in topical formulations, is effective in rehydration, increased collagen and dermal thickness.[85]

3. Tertiary treatment/prevention:

- **Ablative and non ablative rejuvenation**

Numerous lasers are available currently for the treatment of the aging face. Lasers can be used to target telangiectasias, benign lentigos and for textural improvement.

Ablative skin resurfacing is the gold standard for treating photo-aged skin and produces the most dramatic clinical results but it is associated with prolonged recovery times and the risk of severe post-operative consequences.[101] Ablative laser surgery is conducted with either the continuous wave carbon dioxide (CO2) [10,600 nm] or Erbium: Yttrium Aluminum–Garnet Laser (2940 nm) and is a serious commitment by both the physician and the patient.

Nonablative rejuvenation was developed to rejuvenate the skin while minimizing the length of recovery and potential side effects of ablation. The term first applied to treatment parameters with the 585-nm pulsed-dye laser,[102]now refers to the series of techniques that were developed to treat aspects of aging without the downtime of ablative resurfacing. Beside lasers, intense pulsed light (IPL) sources, low-intensity light sources (light-emitting diodes) and radiofrequency devices are considered nonablative.[103] Each of these nonablative adjunctive treatments are effective in the elimination of pigment, telangiectasia, sebaceous hyperplasia and/or generalized tissue remodeling, but they do not cause resurfacing in the same way as ablative treatment.

The need for the ablative laser effect with the advantage of nonablative laser led to invention of fractional lasers.

- **Scientific Conception of Fractional photothermolysis (FP)**

Application of microscopic beams of pixilated light, induce small, focal zones (micro thermal zones; MTZ) of tissue injury. Re-epithelialization is significantly fast because treatment spares surrounding normal tissue. The tissue injury created with FP stimulates the process of collagen remodeling and deposition and promotes elastic tissue formation, hence clinical improvements is seen with FP. [104]Repair of the epidermal defect occurs rapidly, within the first 24 hours, through keratinocyte migration and extrusion of damaged epidermal components at the border of the column of thermal damage. Additionally, stationary cuboidal cells in the most inferior aspect of the MTZs are changed to migratory spindle cells shortly after treatment [104] This change in cellular phenotype is postulated to account for the rapid wound healing after FP. Persistent collagen remodeling occur for at least 3 months after treatment. [105]

Nonablative fractional resurfacing was introduced in 2004 with a 1550 nm wavelength laser.[106] It creates dermal injury in columns without injuring the overlying epidermis to improve the aging face. It is the first non-ablative laser technology to result in the extrusion of damaged dermal material through a perforated dermal–epidermal junction with subsequent stimulation of re-epithelialization and repair. [104-107]So, it may provide a unique therapeutic option for a number of diverse clinical indications of epidermal and dermal biology**.**

In contrast, fractional ablative resurfacing was introduced in 2007, with technological advances allowing for fractionation of the CO2 laser beam.[108] It creates

damage in regularly spaced columns to the epidermis and dermis over the treated surface[109]. While neither of these modalities illicit results similar to that of traditional ablative laser surgery, the recovery time and risk profile are much improved and thus, are a favored means of treatment. Fractional laser therapy has been shown to be efficacious for dyschromia, photoaging on the face, chest, neck and hands, telangiectasias and improvement in texture and laxity[110]

- **Non-ablative Laser Technologies & Light Sources**

a. **Potassium Titanyl Phosphate (KTP) Laser 532 nm:** is used to treat unwanted vessels and pigment. At the same time, little textural improvement is also seen.[103]The high absorption of 532 nm KTP by melanin makes it unsuitable for treatment of darker skin types.[111, 112]

b. **Pulsed Dye Laser (PDL):**Despite approval by the US FDA for treating photodamage with the PDL, only modest results have been observed with its use, presumably because of predominantly vascular targeting and superficial penetration to the papillary dermis.[109]

c. **Pigment-specific Laser is** used to treat the pigmentary changes that occur with photodamage, including solar lentigines, ephelides or freckles. These include Q-switched (QS), frequency doubled Nd:YAG (**neodymium-doped yttrium aluminium garnet)** (532 nm), QS ruby (694 nm) and QS alexandrite (755 nm) lasers as well as QS 1064 nm (Infrared spectrum) laser.[113, 114]

d. **Nd: YAG Laser:** The long pulsed Nd: YAG emits energy in infrared spectrum at 1064 nm with extended pulse duration. Severe heating remains localized to hemoglobin and melanin because water weakly absorbs laser energy at this wavelength and is gently heated.[114, 115]Facial telangiectasia (spider veins) and mild photodamaged skin are main clinical indications.[115, 116]

The frequency doubled Nd: YAG laser emits radiation with a wavelength at 532 nm and pulse duration in nanoseconds. At 532 nm, the wavelength is absorbed not only by melanin but also by hemoglobin.[108, 114]

QS 1064 nm Nd: YAG is one of the first lasers used for non-ablative skin rejuvenation. It could be used for treating pigmentary changes beside vascular changes that occur with photodamage, because it highly targets melanin within dermal melanocytes.[108, 114]

Side effects include mild erythema in all patients (lasting from 1 to 2 h), purpura, rarely post-inflammatory hyperpigmentation and temporary hypopigmentation, can be avoided by using lower fluencies.[116, 117]

e. **Nd: YAG 1320 nm Laser.** The 1320 nm laser system was the first available system designed exclusively for selective dermal heating. The primary chromophore is dermal water.[103, 117, 118] It has beneficial effect in reversing the signs of skin aging both clinically and histologically.[119-122]

f. **Diode Laser 1450 nm:** It is used for facial rejuvenation targeting the water in the upper dermis, this laser remodels the skin's underlying collagen and promotes formation of new collagen, improving facial and periorbital rhytides. Patient acceptance of the treatment was high, but most felt that there was little improvement of the treated rhytides.[103, 123] Side effects are usually minimal and can include postoperative erythema, edema and hyperpigmentation in patients with darker skin type.[114, 124]

g. **Erbium: Glass Laser 1540 nm:** It is used in skin rejuvenation, scars and acne scars by stimulating the formation of new collagen.[117, 125] Advantages of therapy include a lack of pain, discomfort or downtime. Disadvantage of therapy is that results are below the patients' expectations and improvement is slow (occurring in months) and mild.[117]

h. **Erbium: yttrium-aluminum garnet (Er: YAG) 2940 nm Mini-peel.** Although it is utilized primarily for ablative resurfacing, (Er: YAG) laser has been used for non-ablative rejuvenation.[114, 126, 127] Micro-resurfacing is a technique that employs the use of Er:YAG laser system to deliver a single-pass 'mini-peel' by the use of a sequence of short Er:YAG pulses (200–270 ms) below the ablation threshold[128, 129] This causes a noticeable clinical improvement of wrinkles and photoaged skin with the advantage of minimal downtime and side effects.[126, 127]

i. **Intense Pulsed Light (IPL)** is used to rejuvenate aging skin. The device is capable of emitting yellow, red and infrared simultaneously so that multiple components of photoaging can be treated concurrently.[123, 130] IPL is safe effective treatments for redness or flushing of the face, neck and chest and they exert substantial visible improvement with no downtime, bruising or crusting. Disadvantages include large spot sizes and bulky hand pieces and lack of real-time visibility of the treatment area due to the need of contact cooling for epidermal protection.[131, 132]

j. **Light Emitting Diodes** (LED) emits a narrow band of electromagnetic radiation, measured in milli-watts, ranging from the UV to the visible and infrared wavelengths. They can be classified as emitting wavelengths between lasers and broadband light.[133] LED is safe for all skin types and is fast and convenient to use.[117] LED rejuvenation results are not convincing, but the biological effects on skin cells seem to be evident (wound healing, reduction of chronic and acute actinic damage).[108, 115]

k. **Photodynamic Therapy** (PDT) is defined as a photochemical reaction used to selectively destroy tissue. It is considered as a form of photochemotherapy that uses a photosensitizer, light and oxygen.[134] Different studies suggest that PDT may improve the appearance of wrinkles and fine lines, telangiectasias, skin tone and photodamage. In comparison with continual irradiation with red light, PDT with a flash lamp is perceived as less painful. [135, 136]

- **Minimally invasive Non-laser Modalities**

Radiofrequency (RF):Non-ablative RF (monopolar, bipolar, tripolar or multipolar and fractional) is an effective and safe approach for skin rejuvenation.[137, 138] RF was approved by the FDA in 2002 for the non-ablative treatment of wrinkles and skin tightening and for full-face treatment in 2004.[139, 140]

RF does not follow the principles of selective photothermolysis. Heat is generated as a result of tissue resistance to the movement of electrons within the RF field;[141]allowing energy to be delivered to 3D levels of the dermis.[141, 142]

Fractional RF offers controlled dermal heating, allowing for fractional sparing of the epidermis and important adnexal structures.[143, 144]

Ultrasound devices were first approved for eyebrow lifting in the USA in 2009, and have subsequently been used for treatment of skin and tissue laxity.[145] The ultrasonic energy spares superficial dermis so risk of scarring and downtime is decreased and the ultrasound devices can be used in different skin types.[145-148]

Electro-optical Synergy (ELOS) combined electrical and optical energy, is a new technology which is based on the use of the synergistic activity of RF and optical energy from laser or light sources within the same device to be combined in the same pulse profile.[141, 149, 150]

ELOS is an ideal option for darker skin types due to the fact that optical energy has weak absorption of melanin and RF energy does not depend on chromophores for its effects.[118] The bipolar RF component enables the use of lower levels of the optical component, and the optical component is believed to drive the bipolar RF energy to concentrate in a selective chromophore.[150, 151] This technology can be used for skin rejuvenation and improves the clinical and histological signs of aging safely and effectively, and avoids significant downtime.[129]

Patients tolerate the procedure well with minimal discomfort and no need for anesthesia. The most common side effect is transient erythema immediately after the procedure, usually resolving in minutes to hours. Crusting, blisters, pigmentary change and scarring are rare.[151]

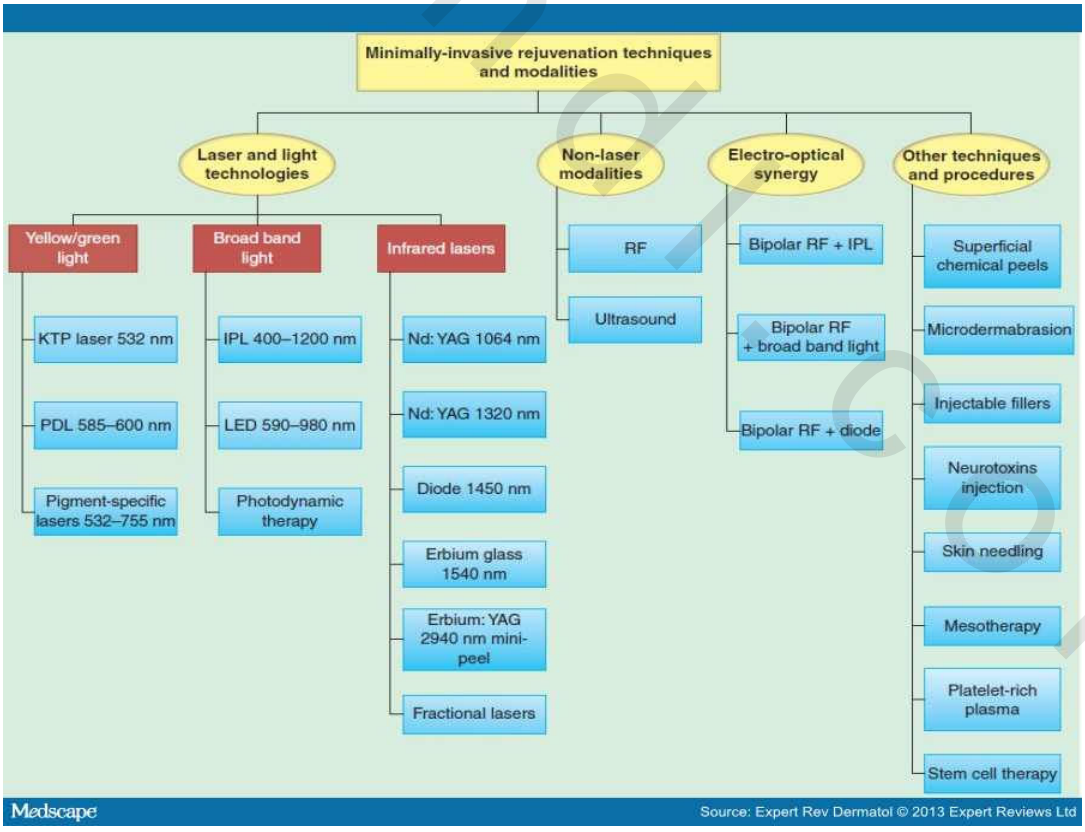

Figure (1): Minimally invasive techniques and modalities for skin rejuvenation.[152]

- **Botulinum toxin**

Botulinum A is the most potent Clostridium botulinum toxin. It inhibits acetylcholine at the neuromuscular junction. The effects of BTX-A typically last 3–6 months, however, some studies report effects lasting up to 12 months duration [153]. BTX-A is contraindicated in pregnancy or lactation, infection at proposed site of injection, history of neuromuscular disorder, or known hypersensitivity to any botulinum toxin preparation or to any of the components of the formulation [154]. Common side effects associated with BTX-A injections include localized ecchymosis, pain and edema at the injection sites, in addition to headache and, rarely, flu-like symptoms [155].

- **Chemical peeling**

Chemical peels of the skin are categorized by the level of injury they produce within the skin into superficial, medium and deep peels.[156] For patients with minimal photodamage, superficial chemical peels, which damage only the epidermis are used.[157] Chemicals used in superficial peeling include trichloroacetic acid (TCA) 10–30%, glycolic acid 20–70% and salicylic acid 20–30%. They are contraindicated in active herpes simplex infection or active inflammation and isotretinoin use within the last 6 months. [158] In contrast, medium (Jessner's-35% TCA) and deep chemical peeling agents (Baker Gordon phenol) produce injury into the papillary dermis and the mid-reticular dermis, respectively, resulting in a higher risk of postoperative complications.[159] Patients with skin types III–VI Fitzpatrick are at greater risk for postinflammatory hypo and hyperpigmentation.[160] Post-peel skin care for all patients includes aggressive photoprotection for all skin types and gentle cleansing and moisturizing during the desquamation and re-epithelialization phases.

- **Microdermabrasion**

Egyptians used sandpaper as early as 1500 BC to smooth scars.[161, 162]Microdermabrasion or particle resurfacing, a minimally invasive procedure that relies on an abrasive component and a vacuum tube, causes mechanical removal of the superficial epidermis and stimulation of new cell growth.[163] It gained popularity because of its ease of use, relatively benign nature and its proposed gross effectiveness

The side effects associated with microdermabrasion are minimal and are usually short-lived, the majority of patients may develop erythema and mild pain, meanwhile minor abrasions and petechiae may occur if aggressive procedure is carried out. [163, 164]Microdermabrasion is considered to be safe in all skin types, and the risk of post-inflammatory pigmentary changes is minimal.[165]

- **Microneedling Therapy**

Microneedling therapy is also known as percutaneous collagen induction (PCI) therapy. The treatment is performed with a dermaroller [166] at 4- to 8-week intervals and multiple sessions are needed to achieve the desired effect on the skin. [167-169]

Microneedling leads to the release of growth factors, which stimulate the formation of new collagen (natural collagen) and elastin in the papillary dermis. [161, 162]

- **Biorejuvenation (Mesotherapy)**

Biorejuvenation, also called biorevitalization, simply describes a method of drug delivery.[170, 171] It is a minimally invasive technique consists of intradermal injection of variable mixtures of pharmaceuticals, in microscopic quantities through multiple dermal punctures.[172] It has been used to rejuvenate (mesoglow) and eventually tone (mesolift) the injected areas of the face and other body areas like neck, low neckline (decoltage), dorsum of hands.[173-175]

- **Platelet-rich Plasma(PRP)**

PRP is an autologous preparation of platelets in concentrated plasma. It has been used clinically in mesotherapy for skin rejuvenation.[176] The α-granules of concentrated platelets secrete a variety of growth factors after being activated by aggregation enhancers.[177, 178]

It is hypothesized that PRP may promote new collagen synthesis as well as other extracellular matrix components through activation of fibroblasts; accordingly it is used to rejuvenate photoaged facial skin.[179, 180]

- **Soft tissue fillers**

In addition to filling static rhytids, fillers act as soft support of the face. They are derived from various compounds and can be categorized as temporary, semipermanent and permanent. Temporary dermal fillers include xenogenic porcine and bovine collagens, bioengineered human collagen and hyaluronic acid (HA) fillers. Calcium hydroxylapatite and poly-l-lactic acid (PLLA) compromise the semipermanent fillers class and polymethylmethacrylate and liquid silicone are permanent fillers.[77]

Side-effects include: pain, ecchymosis and edema at the injection site.[181] In addition, rare cases of necrosis,embolization [182] and nodule formation [182] can occur.

Ablative CO_2 laser

The carbon dioxide (CO2) laser (10,600 nm) enjoyed popularity in the 1990s.[183]So, newer CO_2 lasers were able to operate in a pulsed fashion and vaporize superficial layers of skin, reducing collateral damage to the surrounding tissue. [183, 184] These were able to cause excellent long-term correction of photoaging with minimal conduction of heat to the surrounding tissues. [185-187]

Carbon dioxide laser beam

The CO_2laser beam is in the infrared spectrum of 10600 nm. Because this range is invisible, most CO_2 lasers have a second "aiming" laser parallel to the CO_2 laser that allows the laser beam operator to focus the beam properly.

The CO_2 laser is unique in that it can be almost entirely absorbed by water. Because cutaneous tissue is largely composed of water, the CO_2 laser is able to work rapidly, raising the tissue temperature to greater than 100°C and hence vaporizing it.[188]

The laser medium is mixture of carbon dioxide. Nitrogen and helium gases, usually excited by direct current electricity.[189]

The CO_2 laser can be utilized in either continuous or pulsed delivery modes. The use of a continuous wave mode requires more energy and thus often limits the overall available power that a specific laser can produce. Pulsed delivery modes can be used in both continuous and non-continuous wave lasers. The advent of ultrapulsed CO2 lasers has enabled treatment at maximal power with lessened thermal damage.[190, 191]

The first published report of the CO_2 resurfacing was for the treatment of actinic chelitis in 1968. However, it was not until the 1980s that the CO_2 laser was used to treat wrinkles.[192]

The first CO_2 lasers operated on a continuous-wave (CW) mode. This means that, unlike the pulsed lasers, they did not operate on the principle of selective photothermolysis. The CW CO_2 lasers are not as specific in minimizing surrounding tissue damage. As such, they were initially used in an excisional mode for hemostatic capabilities or a vaporization mode to treat seborrheic keratosis, lentigines, actinic chelitis and other epidermal lesions[192]

More recently, superpulsed/ultrapulsed CO_2 lasers have been developed, which follow the principle of selective photothermolysis. It is these new systems that have allowed lasers to be used for resurfacing of rhytids, photodamage and acne scarring.[192]

CO_2 Laser modes

CO_2 laser have several modes so it has numerous dermatological applications

The super pulse mode can be used to treat benign skin appendageal tumours and hyperplasia such as milia, syringomas and sebaceous gland hyperplasia. This allows generation of high peak power in short durations thus causing disruption of the lesion whilst sparing the deeper dermis and surrounding epidermis. [193] This mode can also be used to puncture cysts or steatocystomas to enable evacuation of the contents. [193]

The fully ablative CO2 mode is used for resurfacing and bulk ablation. It can improve the acne scarring and aging rhytides. [194, 195] Warts, granuloma faciale,[194, 195], plaques of Hailey-Hailey and Darier's disease can also be ablated. Recontouring rhinophyma can be for cosmetic purposes.[196] Vulval lymphangiectasia/lymphangioma can be ablated to produce a degree of fibrosis thus preventing the recurrence. Non-infective, pruritic usually red ink tattoo granulomas which have failed to respond to potent topical or intralesional corticosteroids usually respond well when ablated with the CO_2 laser. [193]

Cutting mode rarely used by dermatologist. The continuous beam of the laser can be used to produce a 'dry' incision to excise recurrent sinuses and nodules of hidradenitis. The dumb bell tumours of neurofibromas can also be excised as well.[197]

Fractional CO_2 laser is largely used for cosmetic indications, principally acne scarring and wrinkles. Their use in non-cosmetic dermatology indications has not been fully explored.

Fractional CO_2 laser guidelines

Patient Selection

As with any cosmetic procedure, patient selection is important. Realistic expectations and a thorough understanding of the procedure and especially postoperative care are crucial. Patients should be prepared for the possibility that more than one treatment may be necessary for best results.[198]

Absolute contraindications to treatment include active cutaneous infection within the area to be treated, isotretinoin therapy within the previous six months, ectropion (for infraorbital resurfacing). [199]

Relative contraindications include diseases that inhibit healing, such as scleroderma and a history of any diseases that Koebnerize such as vitiligo and psoriasis, ongoing ultraviolet exposure or a history of radiation at the treatment site. [199]

Patients with previous history of chemical peels and dermabrasion and anatomic sites with decreased dermal thickness such as the neck and eyelid skin should be treated with caution.[200]

Preoperative Assessment

Preoperative questions and preparations focused on the patient's skin type, chief concerns and tolerance for recovery time can help prepare for a successful outcome. For patients with Fitzpatrick skin types III and higher, there is some debate over whether a preoperative regimen of topical hydroquinone is necessary to minimize post-resurfacing hyperpigmentation. Although many doctors pretreat with several weeks of topical hydroquinone, others say that when the epidermal barrier is reformed, it is repopulated with follicular melanocytes, which are not affected by the topical lightening agents. [201] Similarly, pretreatment with tretinoin has the same controversy [202-204]. Yet, the applicability of these data to fractionated procedures is unknown because the studies were carried on using fully ablative laser devices.

Resurfacing on recently sun-exposed/tanned skin should be avoided, as studies have indicated a higher risk of complications with both pre- and postoperative ultraviolet light exposure.[205]

History regarding scarring, vitiligo, koebnerizing conditions, orofacial herpes and other infections can help individualize treatment.[206, 207] Antibiotic/antifungal prophylaxis[208] should be tailored to each case and has been shown to be beneficial.

Furthermore, pretreatment with topical anesthetic agents may be useful not only for adequate pain control, but also for skin hydration and it has been associated with a low rate of postoperative hypopigmentation and scarring when used with fully ablative resurfacing.[209]

Patient's eye should be protected with eye shield or wet cotton gauze. Dermatologists and assistants should use wavelength-rated spectacles. [200]

Postoperative Care

Postoperative care is crucial to avoid infection and scarring. Cold soaks of white vinegar one tea spoon to one cup water or aluminum acetate soaks reduce erythema, edema and provide antisepsis.[198] The skin should be kept moist.[198] The concept of promoting rapid healing via use of autologous platelet-rich plasma has recently been introduced.[210]

Occlusive dressings have been shown to speed healing, reduce inflammation and possibly improve results but they are exhausting, so they are used with aggressive fractional resurfacing only[211-213] usually topical light moisturizer and sunscreen may be used during re-epithelialization[198] Topical vitamin C can be used to encourage neocollagenesis and reduce erythema.[214, 215] but it is still controversial. .[216] Some studies have correlated beta-glucan application post-laser. Beta-glucan improves wound-healing ability, as it has antibacterial and anti-neoplastic properties.[217]

Complications of Fractional CO_2 Laser Skin Resurfacing [218]

Fractional CO_2 laser skin resurfacing complications can be classified according to severity in to mild, moderate, severe complications.

Mild complications include prolonged erythema, acne, milia, delayed purpra, superficial erosions and contact dermatitis.

Moderate complications are infection, pigmentary alterations, anaesthesia toxicity and eruptive keratoacanthomas

Hypertrophic scarring, ectropion formation and disseminated infections are the severe complications associated with fractional laser resurfacing

Prolonged Erythema

Immediate post-treatment erythema is an expected consequence of fractionated laser skin resurfacing that usually resolves within 3 to 4 days.[219]. It is defined as "Prolonged erythema" when it persists longer than 4 days with nonablative resurfacing or beyond 1 month with ablative treatment. It has been reported in fewer than 1% of nonablative treated patients, [220] while in ablative laser-treated patients it has been reported in more than 12.5% and usually resolves within 3 months.[221, 222] Both traditional non fractionated laser

and fractionated laser resurfacing treatments that use multiple laser passes or accidental stacking increase the risk of prolonged erythema.[223]

Infection

Viral, bacterial and fungal infections usually present during the first postoperative week. Proper diagnosis and treatment are essential to avoid further complications. The most common infection after fractional laser skin resurfacing is herpes simplex virus (HSV) infection reactivation, higher rates of infection occur with traditional (non-fractionated) laser treatment, with 2% to 7% of cases developing HSV reactivation.[206, 224]

Antiviral prophylaxis using oral antiviral agents should be initiated concomitant with or one day before treatment and continued for five to seven days to minimize the risk of HSV reactivation with fractional resurfacing in patients with prior history or full face ablative laser. Furthermore, patients with active HSV infection are contraindicated to have fractional skin resurfacing.[225]

The use of prophylactic systemic antibiotics in all patients is controversial, but it must be given in patients at high risk, especially those who are immunosuppressed or have documented mitral valve prolapse with regurgitation or other valvular heart disease. Bacterial super infection usually presents 1 to 3 days after treatment and is represented clinically by increased pain, focal intense erythema, increased exudate and erosions with crusting. [226, 227] After a wound culture, broad-spectrum empiric antibiotics should be initiated and further adjusted based on the culture results.

Although fungal infection are rarely seen, cutaneous candidiasis by Candida Albicans is the most common reported one after fractional laser skin resurfacing (usually 7–14 days after treatment) and should be treated with antifungal medications to prevent scarring. [226, 228]

Acne and Milia

After traditional non-fractionated laser resurfacing , transient acneiform eruptions occur in up to 80% of cases, and miliaoccur in more than 14% .While after fractional laser resurfacing, milia development has been reported in as many as 19% of treated patients but rates of acneiform eruptions were significantly lower (2–10%).[219, 220, 229-231] The avoidance of occlusive moisturizers and dressings or a change to non-comedogenic equivalents is therefore recommended.[219, 232, 233] Disruption of follicular units during treatment and aberrant follicular epithelialization during healing may further contribute to acne exacerbation.[234]

In moderate to severe acne flares, short courses of oral tetracycline–based antibiotics have been advocated. Antibiotics also can be prescribed during subsequent treatments to prevent future outbreaks. [230]

Pigmentary Alterations

Post-inflammatory hyperpigmentation (PIH) is much less frequent and hypopigmentation is an extremely uncommon complication with fractional laser skin resurfacing than with other ablative procedures. PIH is observed in 1% to 32% of patients, depending on the system used, parameters applied and skin phototypes treated. [220, 221, 225, 233, 235-237] Patients with darker skin phototypes (Fitzpatrick III-VI) have a higher likelihood of developing PIH. PIH is typically less

intense and of shorter duration than post non-fractional resurfacing. Hypopigmentation often has a delayed onset (6–12 months postoperatively), necessitating longer patient follow-up for definitive conclusions regarding its overall risk to be made. [238]

To minimize the risk of PIH, fractional resurfacing of darker skin should be at lower density settings and longer treatment intervals.[235, 239] Patients should avoid sun exposure at least 2 weeks before and after fractional skin resurfacing.[235, 240] PIH often resolves without treatment,[241] application of topical bleaching and mild peeling agents (e.g. retinoic, azelaic, ascorbic, glycolic acid) and judicious use of sunblock can hasten its resolution.[232]

Scarring

Hypertrophic scarring is a known and rare complication of ablative skin resurfacing using CO_2 and Er: YAG lasers. [232, 242] Fractional ablative resurfacing can also induce such scarring. [226, 228] The first signs of potential scar formation are focal areas of erythema and induration 2 to 4 weeks after treatment.

The neck is a well-recognized site that is especially susceptible to the development of scarring because of the small number of pilosebaceous units and poor vasculature in this region, which are essential for wound healing.[243] In addition, the thin skin of the neck renders it more susceptible to thermal injury.

Other scar-prone anatomic locations that also require more conservative treatment protocols include the periorbital and mandibular regions. So, only experienced physicians using more cautious treatment parameters should perform fractional ablative resurfacing of the neck,.[228]

In general, patients with a prior history of radiation or surgical procedures involving the neck or eyelids or those who have experienced postoperative wound infection, contact dermatitis, or keloid scarring have the highest risk of scarring. [232, 242]

The use of topical corticosteroids or silicone gel products, intralesional corticosteroid injections and pulsed dye laser therapy is the early treatment of hypertrophic scarring in such settings.[244, 245]

Ectropion Formation

Cicatricial ectropion is a rare and serious complication that has recently been reported after fractional CO_2 laser treatment.[226] The lower eyelid is typically involved, especially in patients with a previous history of eyelid surgery or limited preoperative skin elasticity in the periocular. To minimize ectropion formation, the use lower energy density settings is recommended.

Eruptive Keratoacanthomas

Keratoacanthomas were described in association with ablative laser treatment of the face,[246] and in two cases after fractional resurfacing with a history of actinic keratoses[247].

Anesthesia Toxicity

Rarely occurs, especially with lidocaine gel.[248] A number of symptoms suggestive of lidocaine toxicity were evident, including agitation, anxiety, light-headedness,

palpitations, slight nausea, perioral tingling and tachycardia. A theoretical increase in percutaneous absorption of lidocaine induced by fractional photothermolysis is a possible explanation for this reaction. Consequently, complete removal of topical anesthesia before laser treatment is postulated to minimize this risk.

Delayed Purpura

Delayed purpura arising more than 3 days after fractional laser skin resurfacing has been reported. [220, 249] Avoidance of nonsteroidal anti-inflammatory drugs, aspirin and other blood thinners in the immediate postoperative period is recommended to decrease the risk of purpura. Patients should also avoid traumatizing their skin through rubbing or scratching because of skin fragility during the recovery period.[250]

Superficial Erosions

Small linear abrasions, ranging between 2 and 16 mm, have occurred after fractional laser treatment. [225, 251] The most susceptible body sites are the upper lip, lower orbital rim and forehead, presumably because of incomplete contact of the hand piece with the skin.[219, 220] Newer modifications of the laser hand pieces have reduced the incidence of this complication. [251]

Contact Dermatitis

The incidence of post fractional laser dermatitis is rare and, in most cases, represents an irritant contact variant.[252]Allergic reactions to topical ointments (e.g., antibiotics) can occur, so their use should be avoided during the reepithelialization process.[218] Patients should be instructed to refrain from using any non-prescribed topical natural or herbal remedies to prevent additional irritation.

Promising and newly introduced therapies for skin rejuvenation:

Low temperature atmospheric plasma

Many types of low-temperature plasma devices have been developed for medical applications but their detailed functions and working mechanisms are unclear. Low-temperature microwave plasma device was suggested to induce the expressions of some anti-aging-related genes in skin cells without causing cellular damage. [253]

Stem Cell Therapy & Stem Cell Factors:

The use of body's stem cells and growth factors is another therapeutic modality for repair of damaged tissue and cell-based therapy.[254]

Several cytokines and growth factors are involved in stimulating fibroblast collagen synthesis for skin rejuvenation, have been shown to be part of the secretome of adipose-derived stem cells (ADSCs),[255] suggesting that these cells may be suitable for promoting repair of atrophic and photo-damaged skin. Animal studies have shown that subcutaneous ADSC injections increase dermal thickness and collagen density in aged mice, [256] and reduce wrinkles induced by UVB-irradiation.[257] Suggested mechanisms include paracrine activation of dermal fibroblasts and dermal angiogenesis.[256, 258]