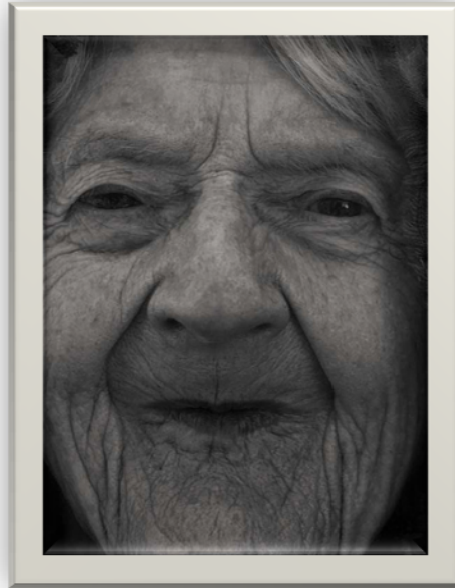


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THE AGEING SKIN

:: A BROAD VIEW ::

BY: MALVI PATEL

UNDER THE GUIDANCE OF:

DR. ABHA DOSHI

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THE AGEING SKIN

::A BROAD VIEW::

MALVI PATEL

INTRODUCTION

The skin is the most superficial part of the body. The signs of ageing are most visible in the skin. Although, ageing skin is not a threat to a person, it can have a detrimental effect on the psychology of a person. A look into the causes of skin ageing, the available treatments and preventive measures for this inevitable change is important to help both the already aged, as well as, the youth.

WHAT IS AGEING?[1]

Ageing is the process of growing old. It is a continuous time dependent and multifactorial phenomenon of reduction in size and number of cells and also reduction in the rate of many organic functions both at cellular and molecular levels. Skin is the largest and the most superficial organ of the body which is exposed to infection, disease and injury. It also shows the signs of ageing the earliest. Skin functions that have shown to decline are cell replacement, injury response, barrier function, sensory perception,

immune and vascular responsiveness, thermoregulation, sweat production, sebum production and vitamin D production.

THE SKIN[7]

Skin is the largest organ of the body in terms of surface area and weight. It covers all the external surface of the body. It protects the body, helps maintain a constant body temperature and provides sensory information about the surrounding environment. Of all the bodies organs skin is most exposed to infection, disease and injury.

STRUCTURE OF THE SKIN

Skin consists of 2 main parts the superficial, thinner portion is the epidermis and the deeper thicker part is the dermis. Deep to dermis is the subcutaneous layer which is not a part of the skin. The subcutaneous layer serves as a storage depot for fat and contains large blood vessels which supply the skin with nutrients. It also contains nerve endings called Pacinian corpuscles that are sensitive to pressure.

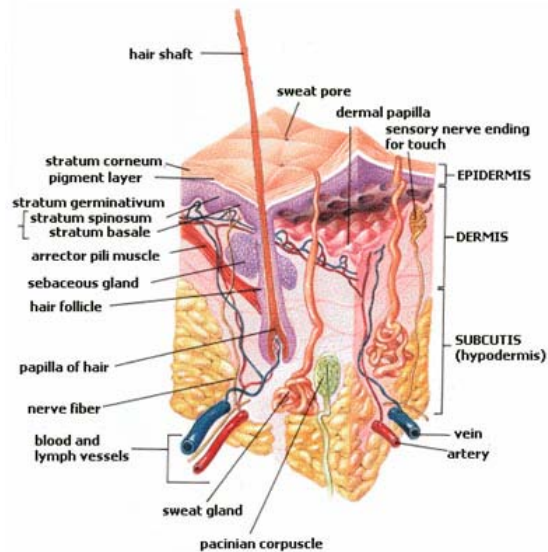


Figure 1 - The Structure of Skin

EPIDERMIS

It consists of 4 principle cells

i) Keratinocytes – They make up 90% of the epidermis layer of the skin and they produce the protein keratin. The protein protects the skin and underlying tissues from heat, microbes and chemicals. It also produces lamellar granules which release a water repellent sealant.

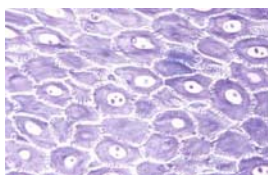


Figure 2- Keratinocytes as seen under a microscope

ii) Melanocytes – They make up 8% of the epidermis. It produces a pigment melanin which contributes to the colour of the skin and absorbs damaging ultraviolet light.

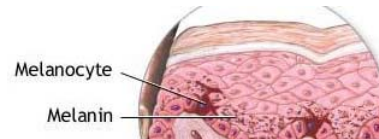


Figure 3- Melanocytes

iii) Langerhans Cells – They arise from red bone marrow and migrate to the epidermis. They participate in immune response against microbes that invade the skin and these cells are easily damaged by ultraviolet light.

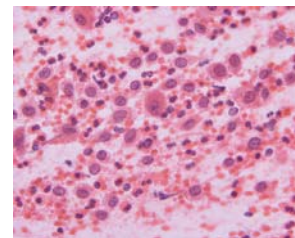


Figure 4- Langerhans Cells

iv) Merkel Cells – They are usually located in the deepest layer of the epidermis. These cells are in contact with the flattened process of a sensory neuron structure called tactile disc. Merkel cells and tactile disc together detect different aspects of touch sensation.

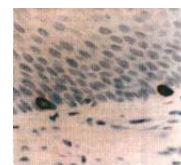


Figure 5- Merkel Cells

LAYERS OF EPIDERMIS-

Epidermis of the skin usually has 4 layers but few areas where exposure to friction is greatest e.g. fingertips, palms, soles, etc. have 5 layers.

The layers are:-

i) Stratum Basale – It is the deepest layer of epidermis and has a single layer of keratinocytes. It is also known as stratum germinativum.

ii) Stratum Spinosum – It is superficial to the stratum basale. It provides both strength and flexibility to the skin. This layer consists of 8-10 layers of keratinocytes.

iii) Stratum Granulosum – It is middle layer of the epidermis. It consists of protein called keratohyalin which converts tonofilaments into keratin. This layer consists of 3-5 layers of flattened keratinocytes. Also present in the Keratinocytes are membrane enclosed lamellar granules which release lipid rich secretion. This secretion fills the space between cells of stratum granulosum, stratum lucidum and stratum corneum. They act as a water repellent sealant that helps retard loss of body fluids and entry of foreign materials.

iv) Stratum Lucidum – This layer is present only in those areas which are prone to friction i.e. in thick skin. It consists of large amount of keratin and thickened plasma membrane. The layer is made up of 3-5 layers of flattened dead keratinocytes.

v) Stratum Corneum – This layer consists of 25-30 layers of flattened dead keratinocytes. These are continuously shed and replaced by cells from the deeper strata. This layer consists of mostly keratin and lipid secretions from lamellar granules which make this layer an effective water repellent barrier. Multiple layers of dead cells protect the deeper layers from injury and microbial invasion.

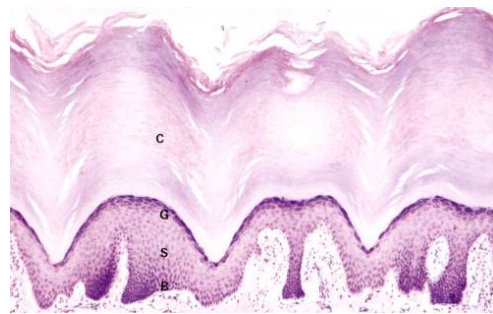


Figure 6- Layers of the epidermis: (B) Stratum Basale (S) Stratum Spinosum (G) Stratum Granulosum (C) Stratum Corneum

DERMIS

Dermis is composed mainly of connective tissues containing collagen and elastic fibers. Cells present in dermis include:-

i) Fibroblast – They provide the structural framework for many tissues and play a critical role in wound healing. They are also responsible for synthesizing the dermal proteins.

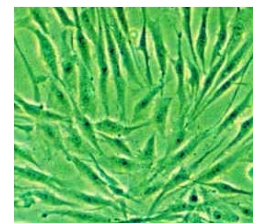


Figure 7- Fibroblasts

ii) Macrophages – They are also called as big eaters as their role is to phagocytose cellular debris and pathogens.

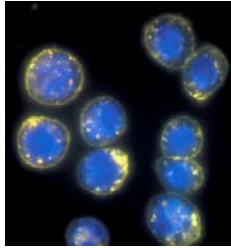


Figure 8- Macrophages

iii) Adipocytes – They are cells specialized in storing energy as fat.

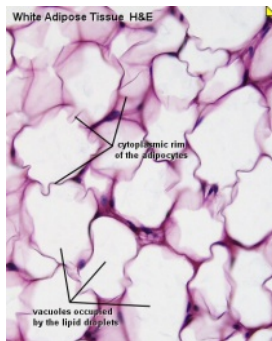


Figure 9- Adipocytes

Based upon the tissue structure dermis is divided into 2 regions

i) Papillary region – It is a superficial part of the dermis. The surface area of the papillary region is greatly increased by small fingerlike projection called dermal papillae. Some dermal papillae contain tactile receptors called corpuscles of touch or Meissner corpuscles these are nerve endings that are sensitive to touch. Also present in dermal papillae are free nerve endings which initiate signal which gives rise to sensation of warmth, coolness, pain, tickling and itching.

ii) Reticular region – It is the deeper part of dermis. In this region bundles of collagen fibers are interlaced in a net like manner. Adipose cells, hair follicles, nerves, sebaceous glands, sweat glands occupy the space between the fibers. Combination of collagen and elastic fibers in reticular region is responsible for providing the skin with strength, extensibility and elasticity.

DERMAL MATRIX COMPONENTS

I] COLLAGEN- is a primary structural component of the dermis and the most abundant protein found in humans. It is responsible for conferring the strength and support to human skin.

II] ELASTIN- it is a protein in the connective tissue that is elastic and allows many tissues in the body to resume their shape after stretching or contraction. It helps the skin to return to its original position when it is pinched or poked.

III] GLYCOSAMINOGLYCANS- It is a constituent of the dermal skin along with collagen and elastin and is responsible for conferring the outward appearance of the skin. They are composed of polysaccharides, with repeating disaccharide units attached to a core protein. They exhibit the capacity to bind water up to 1000 times their volume. The most important of the glycosaminoglycan family is hyaluronic acid. Others include

dermatan sulphate, chondroitin sulphate. They render normal skin plump, soft and hydrated and maintain proper water and salt balance.

Hyaluronic acid is found at the periphery of collagen and elastin fibers and where these fibers intersect. It is found in all connective tissues and is produced by fibroblast and keratinocytes in the skin. Hyaluronic acid is localized not only in the dermis but also in the epidermal intercellular spaces.

CUTANEOUS AGEING[2]

There are 2 primary skin ageing processes:-

i) Intrinsic Ageing/Natural Ageing is caused either by telomere shortening, mitochondrial damage, and endocrine dysfunction.

Intrinsically aged skin is smooth and unblemished and characterized by normal geometric patterns with some exaggerated expression lines. Histologically such a skin manifests epidermal and dermal atrophy, flattening of epidermal rete ridges, reduced number of fibroblasts and mast cells, increase number of collagen fibrils and increased ratio of collagen III to collagen I.

ii) Extrinsic Ageing by exogenous origin i.e. smoking, poor nutrition and solar exposure. These factors are responsible for premature ageing of the skin.

Extrinsically aged skin that results from cumulative effect of lifelong ultraviolet radiation exposure on the exposed area of skin i.e. face, chest, arms comprise rhytides, pigmented lesions (lentigens and patchy hyperpigmentation) and depigmented lesions (guttate hypomelanosis). There is loss in tone and elasticity is also observed along with increased skin fragility, benign lesions (keratoses and telangiectases). Histopathology of photo aged skin is characterized by elastosis, epidermal atrophy and distinct alteration in collagen and elastic fibers. Severe photo aged skin would exhibit fragmented thickened and more soluble collagen fibers.

TELOMERE SHORTENING [2, 6]

Telomeres, the specialized structures found at the ends of eukaryotic chromosomes, have come under increasing scrutiny and are now believed to play an essential role in the intrinsic ageing process at a cellular level. Intact telomeres are integral in extending the lifespan of cells. With age, telomere length shortens. This telomeric erosion has come to be seen as a gauge by which to measure ageing, a veritable internal ageing clock, and the basis for one of the presently favored theories on ageing. One implication of this theory places ageing and cancer on opposite sides of the same coin. That is, telomerase, the cellular reverse transcriptase enzyme that stabilizes or lengthens telomeres, is expressed in about 85–90% of all human tumors but absent in many somatic tissues. Consequently, most cancer cells, unlike

healthy ones, are not programmed for apoptosis, or cell death. In other words, the presence of telomerase is associated with telomere stability and tumorigenesis, its absence with telomere shortening and somatic tissue ageing. Indeed, the natural, progressive shortening of telomeres may be one of the primary mechanisms of cellular ageing in skin. Telomeres and other cellular constituents also sustain low-grade oxidative damage as a result of aerobic cellular metabolism, which contributes to intrinsic ageing. Currently, there are no available topical skin care products, systemic drugs or other treatment options that target telomerase since experimental data does not adequately demonstrate that extending telomere length can be safely performed. One argument for eventual telomerase-based therapies is the belief that inhibiting telomerase may also have antiproliferative and apoptosis-inducing effects, not related to the role this ribonucleoprotein plays in shortening telomeres during cell division.

MITOCHONDRIAL DAMAGE [2, 6]

The mitochondria are considered as the power house of the cell as they generate energy to the cell, by the multistep process called oxidative phosphorylation or electron transport chain. They are responsible for ATP production from ADP and an inorganic phosphate molecule. Along with this ATP production a free radical is also generated. Free radicals are nothing but reactive oxygen species where the oxygen has unpaired electrons. Thus, the mitochondria

is the site of the highest reactive oxygen species turnover in the cell. The bad effects of this reactive oxygen species are lipid peroxidation and alteration of gene expression pathway causing degradation on dermal protein collagen which in turn causes accumulation of elastin.

ENDOCRINE DYSFUNCTION [6]

It is observed that with age there is reduction in the production of hormones. Estrogen is one such hormone the production of which reduces with age and lower levels of estrogen is associated with skin ageing and telomere shortening. The effects of reduced estrogen level causes loss of elasticity, reduced water holding capacity, increased pigmentation and decreased vascularity.

PHOTOAGING [2]

Skin ageing caused by sun exposure can occur even before intrinsic ageing. The changes that are observed due to photoaging are leathery appearance with wrinkle formation, impaired wound healing, appearance of lesions on the skin such as actinic and seborrheic keratoses, cutaneous horns, skin cancer, pigmentary alterations such as lentigens and hyperpigmentation and the most prominent feature is elastosis. The ultraviolet rays from the sun causes skin damage and accelerate ageing of the skin. There are 2 mechanisms by which the ultraviolet radiations act :-

i) Induction of matrix metalloproteinases – Matrix metalloproteinases are a group of enzymes of subfamily proteinases that are

responsible for the degradation of collagen. The ultraviolet light affects the post translational modification of these dermal matrix proteins (such as collagen) and induces wide variety of an ever increasing family of MMP's with proteolytic activity to degrade matrix protein. Thus, the induction of MMP's plays major role in the pathogenesis of photoageing.

ii) Ultraviolet Induced Mitochondrial Damage -

Ultraviolet radiations can cause mitochondrial damage in three ways:

- a) **Mitochondrial DNA Damage:** DNA is not just restricted in location within the nucleus but is also found in the mitochondria. The human mitochondrial DNA has a mutation frequency 50 folds higher than nuclear DNA. Ultraviolet rays can induce these mutations in the mitochondrial DNA. Thus being responsible in photoageing.
- b) **Production of Reactive Oxygen Species:** The Ultraviolet radiations are capable of exciting electrons in the outermost shell of the oxygen atom to a higher energy level. This excitation can cause the oxygen molecule in cells to split into the oxygen free radical. The oxygen free radicals can be of various kinds such as the hydroxyl radical (which is the most common). These free radicals are known as reactive oxygen species. These reactive oxygen

species can cause damage to the cell, in turn causing ageing.

- c) **Formation of uncommon D- β -Aspartyl residues:** UV radiations leads to the formation of D- β -Aspartyl residues in the elastic fibers of the skin. These uncommon D- β -Aspartyl residues have been reported in proteins of various elderly tissues.

SMOKING [1]

Studies have shown that smokers look older than non-smokers of the same age because smoking has an ageing effect on human skin, especially in the facial region. Mechanism of smoking induced ageing is not known, but invitro studies have shown that the tobacco smoke extract induces MMP-1 and MMP-3 mRNA in skin fibroblasts. However tobacco smoke has no effect on TIMP-1 (Tissue Inhibitor of Matrix Metalloproteinases) and TIMP-3 mRNA. In vivo studies have demonstrated that smoking induces MMP-1 mRNA in the skin but has no effect on TIMP-1 mRNA. These studies suggested that smoking showed multiplicative effect on facial ageing via the induction of MMP-1.

LIFESTYLE

The lifestyle of a person can also contribute to the ageing skin. Factors such as lack of sleep, alcohol consumption, stress, improper diet, and reduced intake of water, can all lead to minor signs of ageing.

CHARACTERISTICS OF THE AGEING SKIN

The changes undergone by skin as it ages, occurs throughout the epidermis, dermis and the subcutaneous tissue.

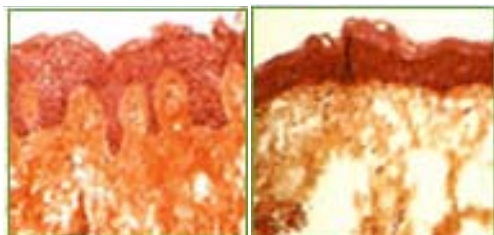


Figure 10- A histological comparison of the skin. To the left is the histological section of a young person, while to the right is the histological section of the skin of an aged person.

EPIDERMAL CHANGES [2]

The intersection of epidermis and dermis is known as the Dermal Epidermal Junction (DEJ). The DEJ is known to be altered with age. Aged epidermis shows a flattened DEJ with a correspondingly diminished connective surface area (2.64 mm² to 1.9 mm²). Loss of DEJ surface area may contribute to increased fragility of the skin and may also lead to reduced nutrient transfer between dermal and the epidermal layers. According to studies, on sun exposed and protected skin, from volunteers aged 6-84 years, it revealed that the epidermal thickness to be constant across the decades, but with thickness found to be greater in sun exposed skin. Spinous layer of a wrinkle was seen to be thinner at the base than flanks. The epidermis also showed fewer keratohyaline granules at the base as compared to flanks.

Decreased cell turnover- the epidermal turnover rate slows from 30% from 50%. The stratum corneum transit time was shown to be 20 days in young adults, and 30 or more days in older adults. Such a cell cycle lengthening in older adults coincides with a protracted stratum corneum replacement time, epidermal atrophy, slower wound healing, and often less effective desquamation. Older patients would thus require double the time to re-epithelialize following dermabrasion resurfacing procedures compared to younger patients. The cascade of changes related to decelerated cell turnover results in development in heaps of corneocytes that render a rough and dull skin surface.

DERMAL CHANGES [2]

Approximately 20% of dermis thickness disappears in older adults. Normal aged dermis is characterized by changes in collagen production and development of fragmented elastic fibers. A photoaged dermis exhibits disorganized collagen fibrils and accumulation of abnormal elastin containing material.

COLLAGEN

The primary structural component of the dermis and the most abundant protein found in humans, collagen is responsible for conferring strength and support to human skin. Over time, the structural proteins and main components of the skin deteriorate, resulting in the cutaneous signs of ageing. Intrinsically aged skin is characterized by epidermal and dermal atrophy as well as flattening of the rete ridges. It is well

known, however, that alterations in collagen play an integral role in the ageing process. This, in turn, partly explains the popularity of collagen-containing products intended for 'anti-ageing' purposes.

Of the dry skin mass, 70% is comprised of collagen. In aged skin, collagen is characterized by thickened fibrils, organized in rope-like bundles, that appear to be in disarray in comparison to the pattern observed in younger skin. In addition, lower levels of collagen are synthesized, *in vivo* and *in vitro*, by aged fibroblasts. The ratio of collagen types found in human skin also changes with age. In young skin, collagen I comprises 80% and collagen III comprises about 15% of total skin collagen; in older skin, the ratio of Type III to Type I collagen has been shown to increase, due, significantly, to an appreciable loss of collagen I. In addition, the overall collagen content per unit area of skin surface is known to decline approximately 1%/year. In irradiated skin, collagen I levels have been shown to be reduced by 59%; this reduction was found to be linked to the extent of photodamage.

Although collagen I is the most abundant and significant collagen type found in the skin, the effects of ageing are seen in other types of collagen in human dermis. An integral constituent of the DEJ, collagen IV imparts a structural framework for other molecules and plays a key role in maintaining mechanical stability. No significant differences have been found in collagen IV levels in sun-exposed skin

compared to unexposed skin, but significantly lower levels of collagen IV have been identified at the base of wrinkles in comparison to the flanks of the same wrinkles. The mechanical stability of the DEJ may be adversely affected by this loss of collagen IV, thereby contributing to wrinkle formation. Collagen VII is the primary constituent in anchoring fibrils that attach the basement membrane zone to the underlying papillary dermis. In one study, a significantly lower number of anchoring fibrils were identified in patients with chronically sun-exposed skin in comparison to normal controls. It was theorized by the researchers that wrinkles may form as a result of a weakened bond between the dermis and epidermis, due to anchoring fibril degradation. A more recent study showed such a loss of collagen VII to be more marked in the base of the wrinkle (as seen with collagen IV in the same study).

In the last 15 years, the pathogenesis of UVR induced collagen damage has been well understood and characterized. For instance, it is known that UVR exposure significantly up-regulates the synthesis of several types of collagen-degrading enzymes known as matrix metalloproteinases (MMPs). First, UV exposure leads to an increase in the amount of the transcription factor c-jun; c-fos, the other transcription factor involved in this mechanistic chain, is already abundant without UV exposure. Activator protein-1 (AP-1) is then formed by the combination of c-jun and c-fos. In turn, AP-1

activates the MMP genes, which stimulate the production of collagenase, gelatinase and stromelysin. Collagen degradation is mediated by AP-1 activation and by inhibition of transforming growth factor (TGF) β signaling.

Research in humans has shown that within hours of UVB exposure, MMPs, specifically collagenase and gelatinase, are produced. Multiple exposures to UVB engender a sustained induction of MMPs. Given that collagenase attacks and degrades collagen, long-term elevations in the levels of collagenase and other MMPs likely yield the disorganized and clumped collagen identified in photo-aged skin. Notably, these MMPs may represent the mechanism through which collagen I levels decline in response to UV exposure.

By characterizing the wide-ranging effects of UV in activating cell surface growth factor and cytokine receptors, researchers have been able to ascertain that skin ageing (extrinsic and intrinsic) is marked by elevated AP-1 activity and MMP expression, inhibited TGF β signaling, as well as reduced collagen synthesis and greater collagen degradation. These changes are likely to be exacerbated by photo-ageing.

ELASTIN

Alterations in elastic fibers are so strongly associated with photo-aged skin that 'elastosis', an accumulation of amorphous elastin material, is considered pathogenomonic of photo-aged skin.

Indeed, UV exposure induces a thickening and coiling of elastic fibers in the papillary dermis. These changes also occur in the reticular dermis as a result of chronic UV exposure. Examination by electron microscopy of elastic fibers in UV-exposed skin has revealed a reduction in the number of microfibrils and increases in interfibrillar areas, the complexity of the shape and arrangement of the fibers and the number of electron-dense inclusions. In addition, small amounts of sugar and lipids and an abnormally high level of polar amino acids have been found in elastin extracted from the skin of elderly patients. The underlying aetiology of age-related changes in elastin is not as well understood as such changes in collagen; however, matrix metalloproteinases are thought to play a role because MMP-2 has been demonstrated to degrade elastin. The initial response of elastic fibers to photodamage is understood, however, to be hyperplastic, resulting in a greater amount of elastic tissue.

The level of sun exposure determines the magnitude of the hyperplastic response. In aged elastic fibers, a secondary response to photodamage occurs but is degenerative, with decreases observed in skin elasticity and resiliency. Older skin that has experienced this degenerative reaction is characterized by changes in the normal pattern of immature elastic fibers, called oxytalan, that are located in the papillary dermis. These fibers form a network in young skin that ascends perpendicularly

from the uppermost section of the papillary dermis to just beneath the basement membrane. This network gradually disappears with age, however. Consequently, skin elasticity is also gradually lost with age. The phenomenon of sagging skin often observed in the elderly may, in fact, be due in large part to this loss of elasticity.

GLYCOSAMINOGLYCANS (GAGs)

GAGs, along with collagen and elastin, are among the primary constituents of dermal skin and are responsible for conferring the outward appearance of the skin. These polysaccharide chains, with repeating disaccharide units attached to a core protein, are also important molecules because they exhibit the capacity to bind water up to 1000 times their volume. There are numerous members in the GAG family, including hyaluronic acid (HA), dermatan sulphate (both of which are two of the most prevalent GAGs) and chondroitin sulphate.

These compounds render normal skin plump, soft and hydrated, and are believed to assist in maintaining proper salt and water balance. Several studies suggest that GAGs, particularly HA, have been found to be reduced in amount in photo-aged skin. Some studies offer conflicting reports, however, suggesting no changes in the level of GAGs in aged skin. The fact that HA is synthesized in the epidermis as well as the dermis likely accounts for this discrepancy in findings. In skin that ages intrinsically, the total HA level in the dermis remains stable;

however, epidermal HA diminishes almost completely.

Hyaluronic acid

Photoaged skin has been shown to be characterized by reduced levels of hyaluronic acid (HA) and elevated levels of chondroitin sulphate proteoglycans. Such patterns, intriguingly, are also observed in scars. HA is found in young skin at the periphery of collagen and elastin fibers and where these types of fibers intersect. In aged skin, such connections with HA disappear. It is possible that the decreases in HA levels, which contribute to its disassociation with collagen and elastin as well as reduced water binding, may be involved in the changes noted in aged skin, including wrinkling, altered elasticity, reduced turgidity and diminished capacity to support the microvasculature of the skin. As one of the primary GAGs, HA can bind 1000 times its weight in water, and may help the skin retain and maintain water. It is found in all connective tissue and is produced mainly by fibroblasts and keratinocytes in the skin. HA is localized not only in the dermis but also in the epidermal intercellular spaces, especially the middle spinous layer, but not in the stratum corneum (SC) or stratum granulosum.

Aged skin, which is less plump than youthful skin, is characterized by decreased levels of HA. The role of HA in skin hydration is not clear and HA does not penetrate the skin upon topical application; however, this has not stopped many companies from putting

HA in topical skin care products and claiming efficacy. HA is used successfully, however, as a temporary dermal filling agent in soft tissue augmentation procedures.

MELANOCYTES

With age there is a reduction in number of melanocytes in range of 8-20% per decade. The skin of older patients is less protected by sun because melanin which is reduced in the elderly tend to absorb carcinogenic UV radiations. Therefore older people are more susceptible to develop sun induced cancers. For this reason, protection of the skin from UV exposure is highly recommended.

VASCULATURE

Aged skin is seen to be relatively avascular. The loss of vascular network is especially notable in papillary dermis with the disappearance of the vertical capillary loops. Reduced blood flow, depleted nutrient exchange, inhibited thermoregulation, decreased skin surface temperature, skin pallor is associated with reduction in vascularity.

SUBCUTANEOUS TISSUE

Site-specific changes, including gains and losses, are known to occur in subcutaneous tissues that also influence the appearance of the elderly and their skin. Subcutaneous fat diminishes in the face, dorsal aspects of the hands and the shins. Fat amasses with ageing, though, in other regions, particularly the waist in women and the abdomen in men.

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CHANGES IN SKIN APPEARANCE

Dry skin [2]

Dry, scaly skin is frequently seen in the elderly. The degradation or loss of skin barrier function with increasing age is partly accountable for this manifestation. The recovery of damaged barrier function has been demonstrated to be slower in aged skin, resulting in greater susceptibility to developing dryness. This is a multifactorial process due, in part, to lower lipid levels in lamellar bodies and a decrease in epidermal filaggrin. Increased trans-epidermal water loss (TEWL) is also exhibited by aged skin, leaving the stratum corneum more susceptible to becoming dry in low-humidity environments. In addition to dryness, aged skin is often characterized by roughness, wrinkling, skin pallor, hyper- or hypopigmentations, laxity, fragility, easy bruising and benign neoplasms.

Benign neoplasms in ageing skin [2]

With age, the appearance and surface texture of skin can change dramatically, as represented by the development of acrochordons (skin tags), cherry angiomas, seborrheic keratoses, lentigos (sun spots) and sebaceous hyperplasias, among other lesions and cutaneous alterations. Patients of dermatologists and plastic surgeons often request removal of these benign neoplasms. Various destructive treatment

modalities are available, including hyfrecation and sundry laser options.

PRODUCTS AND TREATMENTS FOR SKIN AGEING

SUNSCREEN AGENTS [1, 8, 9]

Solar radiation is composed of infrared radiations (770nm and longer wavelengths), visible light (400-770nm) and UV radiations (290-400nm). Infrared and visible light causes reddening of skin which will appear immediately and subside rapidly, and UV rays are the cause of erythema.

UV radiation is further divided into:

UV-A range (320-400nm)- the peak being at 340nm. It causes direct tanning, photo-oxidation of melanin present in the upper layer of the skin, and are weak in producing erythema.

UV-B range (290-320nm)- the peak being at 297.6nm. It causes sunburn as well as irritating reaction. It leads to formation of melanin and development of tan.

UV-C range (less than 200nm). These rays are generally filtered off by the ozone layer. It is damaging to tissue and can cause skin cancer, erythema but not tanning.

As seen earlier sun is leading cause of extrinsic ageing, and hence it is imperative to ameliorate this area in the skin care regimen.

Sunscreen agents should either act by scattering or by absorbing the sun's radiant energy. Depending on the mechanism by which they block the radiation, they are classified as physical (scatter) and chemical (absorb) sunscreens. The sunscreen agent is thought to prevent cellular damage and thus prevent dehydration. It may be chemical, physical, or a combination of both.

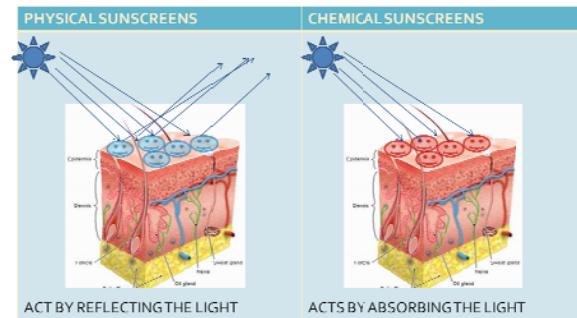


Figure 11- Diagram showing how physical and chemical sunscreens act

The best cosmetic a person can wear for preservation of his or her youthful appearance is a sunscreen. It can cause an apparent reversal of some photoaging and keep the skin youthful looking. Physical sunblocks are important for individuals who must be absolutely protected from the sun. They also are important to protect the most vulnerable parts of the body, such as the ears, nose tips, shoulders, and cheeks. There are several types of UVB and UVA chemical sunscreens.

Patients should avoid the sun during the peak hours of sunshine, wear protective clothing, and use sunscreens while outdoors. The constant use of a photoprotector can promote an apparent reversion of photoaging giving skin a younger aspect. A great improvement may

occur with suppression of exposure or photoprotection, even when started late in life. There is formation of neocollagen and new elastic fibers, giving the same aspect as seen in nonexposed skin.

The extent to which a sunscreen product can protect from sunburn and other harmful effects of exposure to sunlight varies with individual skin type. A measure of how well a sunscreen agent can block the sun's rays is by the SPF (Sun Protection Factor) value of the sunscreen. SPF is defined as UV exposure to produce minimal erythema dose on protected skin and the exposure that will produce the same erythema on unprotected skin. SPF is measured using the following formula:

$$\text{SPF} = \frac{\text{MED of Protected Skin}}{\text{MED of Unprotected Skin}}$$

Larger the SPF value, greater the protection the sunscreen can confer. An SPF 15 or above offers greatest protection from sunburning, permitting no tanning.

MOISTURIZERS [1, 8, 9]

In old age, dryness of skin is observed. To prevent this dryness, moisturizers are used. Water is the only material that would plasticize the outer dead layers of the epidermis, to give the much desired attribute called soft, smooth skin. If water is lost more rapidly from stratum corneum than it is received from lower layers of the epidermis the skin becomes dehydrated and loses its flexibility.

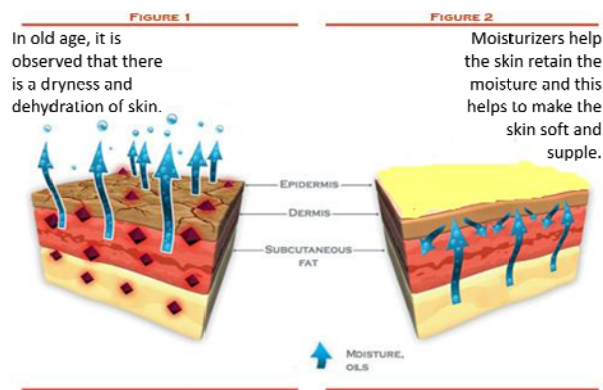


Figure 12- Shows how moisturizers prevent water loss from skin surface.

Dryness of aged skin is mainly due to UV exposure. There are three approaches to restore water content of skin:

1) Occlusives:

A thin film is formed over the skin which prevents water loss. Occlusion of the skin results in an immediate decrease in the rate of water loss through the epidermis. This has the desired effect of causing the stratum corneum to become more hydrated and making it softer and supple. However this effect is transient, and the water loss is higher than the pretreatment value, but this drawback does not reduce its usefulness in moisturizing. Many non-permeable substances may be used such as mineral oils, vegetable oils, lanolin, silicones, extracts from plants (such as aloe vera extract, bamboo and cactus extracts).

More recently skin substantive barrier materials based on quaternary ammonium complexes have become available, which seems to be able to prevent trans-epidermal water loss without putting an occlusive or greasy barrier. These act not only as

moisturizers but also as emollients i.e. skin conditioners; e.g. Quaternium 19, hydroxyethylcellulose derivatives.

2) Humectants:

Their role is to attract water from the atmosphere to supplement the skin's water content. Although popular in use it is debated that externally applied water will not increase the flexibility of the stratum corneum. In fact, it can have precisely the opposite effect. Humectants mostly used in moisturizers are glycerol, ethylene glycol, propylene glycol and sorbitol, either alone or in admixtures. In a test conducted, none of the humectants had any effect in increasing the uptake of water by the skin. Sodium Lactate which is one of the water extractable materials in the skin was found to increase the uptake of water. It acts as a buffer as well as humectant and is compatible with most other cosmetic materials.

3) Restoration of deficient material:

To restore skin moisture depends on the determination of the precise mechanism of the natural moisturization process. To assess what is gone with the dry skin and to replace any material which maybe deficient. Researchers demonstrated that there is natural moisturizing factor (NMF) in the skin. This NMF can be removed by the means of water, polar solvents, and detergent solutions. It is found that NMF is of amino-lipid nature, and maybe a mucoprotein complex or a lipomucopolysaccharide complex.

Sodium-2-pyrrolidone-5-carboxylate has been identified as a naturally occurring humectant and has been shown to be useful in moisturizing dry flaky skin. Furyl glycine and furyl hydantoin have been recommended to be used in moisturizers.

Facile addition of water on skin is not sufficient to plasticize it. Water in the skin is bound in protein lipid complexes, possibly in the dead cells, and only in this form it is effective in keeping the skin soft. Simple application of water soluble components of NMF such as sodium pyrrolidone carboxylate, and sodium lactate are inefficient as they do not have affinity for most layers of the skin. Administration of NMF using novel drug delivery systems such as niosomes should be looked into.

A condition called Xerosis in which there is continuous loss of water from the stratum corneum through evaporation from the surface, generally occurs in the elderly. The cells accumulate giving the skin a white and scaling aspect. Such skin show thicker fissured and disorganized horny layer. Moisturizers can be helpful as they decelerate the loss of humidity from the surface of the skin. Fine wrinkles are more visible when the skin is too dry, and thus hydration can make wrinkles less obvious.

ANTIOXIDANTS [1, 6, 8]

The ageing process is believed to be due in part to free radicals, also known as reactive oxygen species. Free radicals are composed

of oxygen molecules with an unpaired electron and are produced by several exogenous and endogenous factors such as UV exposure, pollutants, stress, smoking and normal metabolic processes. Free radicals are responsible to induce alteration in gene expression pathways, which in turn contribute to the degradation of collagen and accumulation of elastin.

Antioxidants neutralize these free radicals by supplying another electron delivering an electron pair to an oxygen molecule and stabilizing it in the process. E.g. vitamin A (retinol), vitamin C (ascorbic acid), vitamin E (tocopherol), β -carotene, bioflavonoids and many others found in nature (e.g. resveratrol- an antioxidant found in high concentration in red grape skin and berries).

Topical application of α -tocopherol or ascorbic acid decrease UVB induced erythema and edema, and decreased the number of sunburnt cells. Carotenoid preparations and synthetic phenolic antioxidants similarly are reported to reduce UVB induced erythema and retard development of squamous cell carcinoma.

FILLERS [1, 3]

Facial fillers have expanded and enhanced non-surgical option in facial rejuvenation. Age changes in face include alteration in skin quality, volume depletion of soft tissue and bones and gravitational descent of facial muscle. The cumulative results are fine lines, wrinkles, folds and furrows. Facial fillers are designed to address rhytids (folds

and furrows) and soft tissue loss. It can be used anywhere, especially useful in the lower third of the face.

Injectable fillers maybe used in forehead, glabella, nasal tip, eyelids, cheeks, nasolabial folds, melolabial folds and lips. Filling agents use their volume occupying properties to replace lost subdermal fat and dermal proteins.



Figure 13- A dermal filler being injected in the upper lip

Collagen

Collagen lays the structural foundation of the skin. With age the amount of collagen in the skin decreases. Collagen dermal fillers were developed as logical replacement for dermal constituent lost thru ageing.

Bovine Collagen:

They are the original non autologous injectable fillers. This collagen is derived from cow hides. There are three types of bovine collagen available in the market: Zyderm I, Zyderm II and Zyplast. Zyderm I composes of 3.5% collagen packed in phosphate buffer solution along with 0.3% lidocaine. It is usually injected in superficial papillary dermis. Zyderm II consists of 6.5% collagen by weight. It is injected in the mid dermis region of the skin. Zyplast provides longer duration of correction as in this collagen fibrils are cross linked with glutaraldehyde, thus, inhibiting degradation by collagenase. Zyplast is generally injected

in deep dermis. Lidocaine in solutions improves comfort of injection and also inhibits activation of eosinophils that play a role in bruising and edema. Collagen's platelet aggregating effect may also inhibit bruise formation. Allergy testing prior to administration of these products is required via small skin inoculation as some patients are known to develop hypersensitivity to bovine collagen following repeated injections. Many recommend a second test a few weeks after the first, as the first test would act as the sensitizing dose.

Zyderm I requires over correction by 100% to compensate the loss of saline from injected material. With Zyderm II 50% over correction is recommended. While no over correction is required in case of Zyplast fillers. As the saline is absorbed a network of collagen forms to restore skin contour. After a period of a month, host connective tissue grow into the network giving it texture and appearance of normal host tissue. The injected collagen is eventually detected as foreign substances and degraded by collagenase and inflammatory cells. Eventually the foreign body reaction clears the material within a duration of less than 6 months.

Human Collagen:

The FDA approved human collagen are Cosmoderm and Cosmoplast. They are used for the restoration of lip border, correction of facial wrinkles, acne scars and other soft tissue contour deformities. These products contain purified collagen from human fibroblast cell culture. Processing renders the product free from immunological cells

and melanocytes. It obviates need to allergy testing. Zyderm, Zyplast, Cosmoderm, Cosmoplast are packed in syringes containing 0.3% lidocaine as local anesthesia. Cosmoplast, like Zyplast, contains collagen fibrils linked with glutaraldehyde for increased duration of action. Human collagen is easier to use than bovine collagen, with smoother injection and less lump formation. The advantage of injectable collagen cultured from the patient's own skin may represent an attractive but expensive alternative.

Hyaluronic Acid

It is a major component of the connective tissue matrix in the dermis. Unlike collagen its chemical structure is uniform throughout living species thereby decreasing its immunogenicity. Older skin has lower levels of Hyaluronic acid with resultant loss of tissue hydration. Hence, use of Hyaluronic acid fillers seems ideal, but lasts only 1-2 days in natural form, as it is locally degraded and eventually metabolized to carbon dioxide and water in liver. Thus to increase the longevity of Hyaluronic acid fillers, they are stabilized by cross linking process. Cross linked hyaluronan is called hylan. Hylans or hyaluronic acid gels are swollen with water and have unique attribute of dynamic viscosity. Under pressure of injection the gel can pass through a small gauge needle. On removal of the shearing force, viscosity increases and thick gel, that is unlikely to migrate develops at site of tissue implantation. Unique characteristic of hyaluronic acid

fillers is isovolemic degradation. Concentration of gel decreases during reabsorption, but volume remains same until last molecule of hyaluronic acid are degraded. Such an implant maintains 95% of initial space filling volume till last of material is completely reabsorbed. It is approved for mid to deep dermal implantations for correction of moderate to severe facial wrinkles, effective for lip shaping and augmentation. No allergy testing is required for these products.

There are four hyaluronic acid preparations approved by the FDA.

Restylane is FDA approved. Restylane is produced from cultures of *Streptococcus equi*. The resulting hyaluronic acid chains are chemically stabilized through permanent cross-linking with epoxides. Restylane is 1% crosslinked. During processing, the hyaluronic acid concentration increases approximately 4-fold to 20mg/ml and the small gel-particle size is formed (400nm). Low levels of impurities, high concentration of hyaluronic acid, and minimal cross-linking help increase the biocompatibility of Restylane with native hyaluronic acid. This helps achieve maximum implant residence time. Other preparations of Restylane that are not yet FDA-approved are Restylane Fine Lines (indicated for superficial lines and more superficial implantation) and Restylane Perlane (indicated for volume contouring and deeper implantation). Each has identical hyaluronic acid concentrations

(20 mg/ml), but differs in the size of the particles. Viscosity is proportional to the size of the particles (Restylane Perlane has the largest particles, Restylane Fine Lines has the smallest particles).

Hylaform (INAMED Aesthetics) is FDA-approved. It uses hyaluronic acid derived from the dermis of rooster combs that is chemically cross-linked with divinyl sulfone. It does contain a small amount of avian protein. The concentration of hyaluronic acid is 5.5 mg/ml. The total cross-linking of hyaluronic acid in Hylaform is 20%. The greater degree of cross-linking in Hylaform may reduce biocompatibility within the dermis and, along with a decreased concentration of hyaluronic acid compared to Restylane, result in decreased duration of the cosmetic effect. Hylaform Plus (INAMED Aesthetics) is similar to Hylaform except for its larger particle size (750 compared with 500nm) and is intended for deeper dermal implantation.

Captique (INAMED Aesthetics), like Restylane, is non-animal stabilized hyaluronic acid dermal filler produced by bacterial fermentation. Like the other INAMED hyaluronic acid products, the concentration of hyaluronic acid is 5.5 mg/ml with 20% cross-linking.

INAMED Aesthetics has submitted a premarket approval application to the FDA for a new line of hyaluronic acid fillers called Juvederm. This bacterially derived product differs from the other hyaluronic

acid products in that it is a homogeneous gel, rather than gel particles, with the potential for increased biocompatibility and duration.

Each of the hyaluronic acid preparations is injected intradermally. If injected too deep or intramuscularly, the duration of effect may be reduced due to product absorption. If injected too superficially, there may be visible areas of excess fullness and/or skin discoloration. Treatment recommendations are to inject to 100% of the desired volume with no need to overcorrect. Hyaluronic acid as compared to collagen do not contain local anesthesia.

Complications of using hyaluronic acid are

- Increased viscosity compared to collagen result in more discomfort during injection.
- Increased bruising may be noted as structure of hyaluronic acid is similar to heparin.
- Excess bruising will decrease duration of action of product by inflammatory mediators and generating free radicals.

The treatment may last up to 9 months.

Biologic Combination Fillers

Cymetra is micronized form of Alloderm. Alloderm is an acellular dermal matrix derived from donated human skin tissue. It acts as a framework to allow in growth of native tissues. In addition to collagen it also contains dermal elements, elastins and proteoglycans. They are preserved as freeze

dried particles which can be reconstituted before use in 1ml lidocaine or saline. Host fibroblast and collagen infiltrate the implanted material. It lasts for 4-6 months. And skin testing is not necessary. As its effect is dependent on the host's ability to elicit fibroblast ingrowth and neovascularization, the results can be variable.

Autogenous Fat

Is the original dermal filler material. It can be harvested from abdomen, thigh and buttocks. Subdermal injection of fat cells in the face has advantage of using self tissue and potential of achieving permanent results (7 years or more). Disadvantage of this filler is that there is unpredictable degree of localized reabsorption with resulting unpredictable cosmetic effect.

Poly-L-Lactic Acid

It is a FDA approved filler. Sculptra is injectable poly-L-lactic acid, a synthetic polymer of the alpha hydroxy acid family. Allergy testing is not required. Microparticles of poly-L-lactic acid is 40-63 µm in diameter and suspended in sodium carboxy methyl cellulose gel. Particle size is large enough to avoid phagocytosis by dermal macrophage or passage through capillary, but small enough to be injected. It is supplied as powder that can be reconstituted with 3-5ml sterile water for injection. It should be reconstituted for at least 2 hours in advance for full hydration. Lidocaine may be added to decrease pain of injection. It is injected in subcutaneous

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tissue or in deeper parts of dermis. After implantation poly-L-lactic acid degrades and ultimately gets metabolized to carbon dioxide and water. Collagen production in response to implant provides long term volume correction. Because of the mechanism, it is avoided to give over correction. Post injection massage is recommended. Sculptra should probably be thought of as a diffuse volume enhancement rather than a wrinkle filler. Sculptra is not recommended for lip augmentation or very superficial fine lines. Duration is 18-24 months.

Radiesse

It is used for correction of facial lipoatrophy and nasolabial folds. Its primary component is calcium hydroxy apatite spheres, ranging from 25-45 μm in diameter, suspended in an aqueous gel with glycerin and sodium hydroxy cellulose. Hydroxy apatite is a mineral component of bone, so its biocompatibility is excellent and no allergy testing is required. The product is highly viscous but can be injected with 27 gauge needle. Subdermal or intramuscular placement is recommended because of its viscosity. Massage after injection is very important. Treated areas resemble native soft tissue due to collagen in growth. The carrier vehicle is gradually absorbed, degraded and undergoes phagocytosis. Fibrous encapsulation of particles takes place, which limits their migration. With time the hydroxyl apatite particles will degrade to calcium and phosphate ions. Implant material persists for at least 6 years with no evidence of bone formation.

Radiesse is used for deeper folds, furrows and creases. It is more effective in reducing facial wrinkles in nasolabial and melolabial folds than collagen fillers. It is avoided in the lip.

Artefill

Polymethylmethacrylate microspheres are used for facial volume augmentation. Artefill is composed of polymethylmethacrylate microspheres suspended in 0.3% lidocaine, 3.5% bovine collagen, 0.3% NaCl, and phosphate buffer pH 7.3. Microspheres comprise 20% of the mixture and 80% collagen. Range of sphere size is from 30 to 40 μm . It is small enough to allow subdermal placement using 26 gauge needle, but large enough to prevent phagocytosis. Allergy testing is required. Collagen is rapidly broken down by collagenase and phagocytized by macrophages within 1-4 months. During the same period, microspheres become encapsulated with collagen fibers by the body's own fibroblasts. Artefill is placed within deep dermis or sub dermis and is not designed for treatment of fine wrinkles. Initially degradation of collagen vehicle takes place. 50-75% of the product left behind is maintained because of polymethylmethacrylate.

Polymethylmethacrylate microspheres remain permanently. Accordingly, patients should be advised that complete correction will require two to four treatment sessions, at intervals of 3-4 months. Overcorrection at the initial treatment session should be avoided as the body may respond better by

being able to encapsulate a smaller quantity of product more frequently. Patients should be advised to minimize facial expressions for 3 days after treatment to reduce likelihood of muscular contractions pushing the substance more deeply into the subcutaneous tissue.

As with nonbiologic fillers, the success of ArteFill depends on the amount of connective-tissue reaction that mounts in response to the microspheres. Younger individuals have a greater response than do the elderly. The polymethylmethacrylate microspheres remain permanently. Results in some patients have endured 10 years.

Injectable Liquid Silicone

A silicone is a polymer synthesized based on the element silicon. Silicon is the 7th most common element in the universe and the 2nd most common in the earth's crust. It can exist as solids, gels, foams, liquids depending on degree of polymerization. Silicone is inert, clear, and oily, liquid derived from silica and composed of polymerized dimethylsiloxane.

Silikon and Adatosil are two products found commercially. They differ in their viscosity

such that Silikon (1000 centistokes) is more preferred as compared to the higher viscosity Adatosil (5000 centistokes). It is injected using a micro droplet technique. The formulation flows easily through the 27-30 gauge needles. Minute volumes are injected at multiple sites into deep dermis. A grid of injections spaced at 1-3mm is created in the area requiring augmentation. Over correction with this filler should be avoided. The injected silicone disperses rapidly and becomes individually encapsulated by fibrous tissue. It is used for volume augmentation in lips and is effective in reducing fine lines. It is the most permanent and least antigenic filler.

Complications of Dermal Fillers

No procedure is free from complications and dermal fillers are no exception. A myriad of complications have been reported in detail. Some issues related to potential complications are discussed elsewhere in this paper. The technique of injection can create complications if filler material is inadvertently administered at the improper skin depth (skin changes,

Table 1- Table showing list of FDA approved dermal fillers

| Product | Material | Depth of dermal implantation | Duration | Relative advantages | Relative disadvantages | Notes |
|----------------|---|------------------------------|----------------|--|---|---|
| Zyderm I | Bovine collagen | Superficial | 3 – 6 months | Long history of use, material contains lidocaine | Allergic reactions, requires skin testing | Xenogenic |
| Zyderm II | Bovine collagen | Mid | 3 – 6 months | Long history of use, material contains lidocaine | Allergic reactions, requires skin testing | Xenogenic |
| Zyplast | Bovine collagen | Deep | 3 – 6 months | Long history, material contains lidocaine | Allergic reactions, requires skin testing | Xenogenic |
| Cosmoderm | Human collagen | Superficial | 3 – 4 months | Does not require skin testing | Short duration of effect | Allogenic |
| Cosmoplast | Human collagen | Mid to deep | 3 – 4 months | Does not require skin testing | Short duration of effect | Allogenic |
| Restylane | Nonanimal stabilized hyaluronic acid | Mid | 4 – 6 months | Safe, easy to use, no allergy testing | Pain with injection if blocks not used | Xenogenic, smaller gel-particle size in Restylane Fine Lines. |
| Hylaform | Hyaluronic acid from rooster combs | Mid | 3 – 6 months | Safe, easy to use, no allergy testing | Pain with injection if blocks not used, contains some avian protein | larger gel-particle size in Restylane Perlane |
| Hylaform Plus | Hyaluronic acid from rooster combs | Deep | 3 – 6 months | Safe, easy to use, no allergy testing | Pain with injection if blocks not used, contains some avian protein | Xenogenic, lower concentration of hyaluronic acid and more cross-linking than Restylane |
| Captique | Nonanimal stabilized hyaluronic acid | Mid | 3 – 6 months | Safe, easy to use, no allergy testing | Pain with injection if blocks not used | Xenogenic, lower concentration of hyaluronic acid and more cross-linking than Restylane, larger particle size than Hylaform |
| Cymetra | Micronized dermis (human cadaver) | Mid to deep | 3 – 4 months | No allergy testing | Donor-related risks, short duration, cost | Allogenic |
| Autogenous fat | Fat | Deep to subdermal | Variable. | Safe; patient's own tissue, abundant supply | Donor-site morbidity, variable results, requires processing | Autogenic |
| Sculptra | Poly-L-lactic acid | Subdermal | Months – years | Long-lasting, no allergy testing | G-nodule formation | Synthetic |
| Radiesse | Calcium hydroxyapatite spherules | Subdermal to intramuscular | 2 – 5 years | Long-lasting, no allergy testing | Nodule formation, especially in lips | Synthetic, cosmetic use is off-label |
| ArteFill | Polymethylmethacrylate spherules | Deep to subdermal | Permanent | Long-lasting | Requires allergy testing for bovine component | Synthetic |
| Silicone | Injectable liquid silicone (1000 centistokes) | Deep | Permanent | Permanence, long clinical experience | Permanence, migration | Synthetic, cosmetic use is off-label |

excessive lumps), at the improper location (product misplacement), or in the improper volume (palpable lumps, contour deformity).

Acute hypersensitivity reactions can occur with any substance but remain a serious concern for materials containing bovine or other animal products. Potential transmission of bovine spongiform encephalopathy (BSE) remains a risk, but is difficult to quantify.

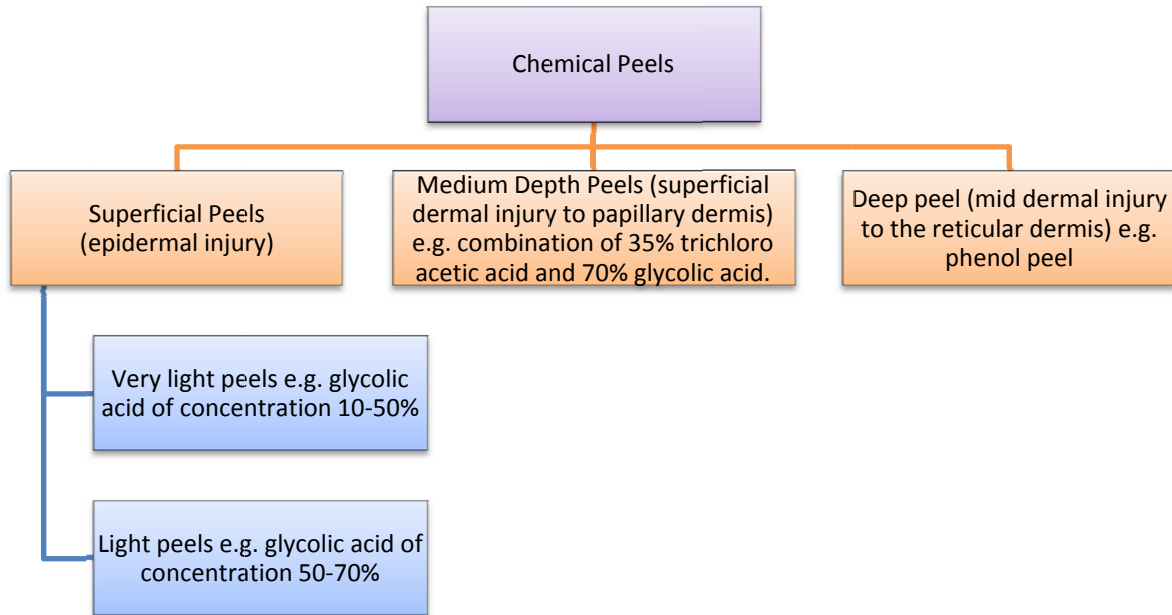
All fillers create some form of histological soft-tissue reaction that evolves over time. Granuloma formation can occur with any substance that is injected. Granulomatous tissue reactions have been reported even with biologic products, including hyaluronic acid preparations. These granulomas can be treated conventionally with incision/drainage or excision. Hyaluronic

acid reactions can be treated uniquely with hyaluronidase. Fillers containing alloplastic materials seem more likely to develop histopathologic foreign-body reactions with granuloma formation. These potential complications are unique when compared with traditional surgery and warrant unique informed consent of the patient receiving filler agents.

CHEMICAL PEELS [1, 5, 11]

It is a skin treatment technique used to improve and smooth skin texture using chemical solution that would cause the skin to blister and eventually peel off. The new skin layer would be smoother. The advantages of chemical peels are that they are efficient in facial skin rejuvenation, safer in comparison to surgical procedures, easy to use, inexpensive, patients have relatively rapid recovery time.

Classification of Chemical Peels:



Preoperative evaluation of the skin is done to determine a suitable chemical peel for use. The skin is evaluated on the basis of:

1) Fitzpatrick skin type: The Fitzpatrick skin type classification is as seen below.

| Type | Skin color | Features |
|------|-----------------|--------------------------------|
| I | White, freckled | Always burns, never tans |
| II | White | Usually burns |
| III | White to olive | Sometimes burns, average tan |
| IV | Light brown | Rarely burns, easily tans |
| V | Dark brown | Very rarely burns, profuse tan |
| VI | Black | Never burns, deeply pigmented |

Based on this classification, I-III can undergo all type of peeling; while, IV-VI are challenging for medium or deep peels.

2) Glogau's ageing changes: The Glogau's ageing scale is as seen below.

| Type | Description | Features |
|----------------|---------------------|---|
| I (Mild) | No/minimal wrinkles | Early photoaging No keratoses, pigmentary changes Age: 20s-30s Minimal/no makeup |
| II (Moderate) | Wrinkles in motion | Early to moderate photoaging Early actinic keratoses Sallow color Smile lines begin Age: Late 30s-40s Little makeup |
| III (Advanced) | Wrinkles at rest | Advanced photoaging Dyschromias, telangiectasias Actinic keratoses Persistent wrinkling Age: 50s or greater Always wears makeup |
| IV (Severe) | Only wrinkles | Severe photoaging Yellow-gray skin Dynamic/gravitational wrinkling throughout Actinic keratoses ± skin malignancies No normal skin Age: 60s or greater Makeup with poor coverage (cakes/cracks) |

According to this scale, people with skin type I-II should preferably go in for superficial peels; and III and IV should go in for medium to deep peels for better results.

Chemical Peel Solutions

The commonly used solutions are

1] **Alpha Hydroxy Acids (AHA):** They are naturally occurring organic carboxylic acid e.g. glycolic acid (obtained from sugarcane juice), lactic acid (obtained from sour milk and tomato juice). These are the mildest and produces light peels. AHAs can be mixed with face wash and creams in small concentrations as part of your daily skin care regimen to improve skin texture.

2] **Beta Hydroxy Acids (BHA):** They are milder as compared to AHAs. They are preferred over AHAs because of their ability to get deeper into the pores.

3] **Jessner's peel:** is a combination of salicylic acid, resorcinol and lactic acid. It is thought to break intracellular bridges between keratinocytes.

4] **Trichloroacetic acid (TCA):** used in intermediate to deep peeling with concentration ranging from 20-50%. Depth of penetration is directly proportional to concentration. E.g. 50% TCA can penetrate reticular dermis, however concentrations higher than 35% have increased risk of scarring but are preferred over phenol peels for dark skin patients.

5] **Phenol peels:** they are the strongest among the chemical peel solutions. It produces deep skin peel. Effects of a phenol peel are long lasting (up to 20 years). Improvements are quite dramatic, a single treatment usually achieves the desired effects. The treatment requires several months to heal, and needs sun protection for life. Phenol peels are cardiotoxic, and is excreted by hepatic and renal routes thus

cannot be administered for patients with cardiac, renal or hepatic complications. A typical phenol peel formulation consists of 3mL liquid phenol, 2mL tap water, 8 drops of liquid soap, and 3 drops of cotton oil.

Procedure of Application of Chemical Peels

1. A suitable chemical peel is chosen as per the requirement.
2. Patient must be educated about the process and a signed consent must be obtained from the patient undergoing medium or deep peel.
3. Skin should be washed thoroughly and should be defatted using acetone.
4. Delicate areas that need protection should have petroleum jelly applied to it.
5. Medications given prior to procedure include:
 - a. Oral antibiotics and antivirals- in case of deep peels, where patients are susceptible to viral and bacterial attacks.
 - b. Sedatives and anti-inflammatory agents such aspirin or other non-steroidal anti-inflammatory drugs- to alleviate swelling and discomfort during the procedure.
 - c. Anesthesia can also be given prior to the procedure.
 - d. Agents such as tretinoin or hydroquinone can be given before and after a peel to help skin heal faster.

6. Peeling agent is applied with the help of 4x4 gauze, cotton swabs or foam applicator.
7. Apply beginning with the forehead and finishing with the chin.
8. Feather the peeling agent into the hair line and the shadow of the mandible.
9. The acid should not form pools in the facial folds, nor drip from the face.
10. The number of coats varies depending on the depth of peel desired.
11. The peel frost or facial whitening indicates the depth of the damage and acts as an indicator to stop the peeling procedure.
12. The peeling process is stopped by neutralization (not all acids require neutralization e.g. salicylic acid, Jessner's and phenol peels, as they are neutralized by skin itself). Neutralization can be achieved by cold water, or wet cool towels applied to the face following frost. Other agents such as bicarbonate sprays can also be used.
13. Reapplication of the peeling agent maybe necessary if the frost is uneven or is not white enough.

Complications of Chemical Peels

Superficial peels generally show no complications, however, medium and deep peels have the following:

- Prolonged erythema
- Pigmentary changes
- Millia (white heads)
- Possible infections
- Scarring
- Skin atrophy

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- and textural changes.

BOTULINUM TOXIN [1, 12]

Toxin botulinum, is a sterile, vacuum dried purified form of botulinum toxin type A indicated for the treatment of strabismus, blepharospasm, and other related condition. It acts by inhibition of acetylcholine release of the motor endplates. It temporarily denervates specific muscles responsible for certain facial rhytids including the glabellar furrow, horizontal forehead lines, horizontal neck lines, and crow's feet.

The genus Clostridium has more than one hundred and twenty seven species, grouped by morphology and function. The anaerobic, gram positive bacterium Clostridium botulinum produces a potent polypeptide neurotoxin, botulinum toxin, which causes a neuromuscular illness in humans and animals known as botulism in higher concentrations. However, in extremely low concentration the toxin is helpful as it causes flaccid paralysis of the muscles and thus relaxing the wrinkles and expression lines.

Harmful Effects of Clostridium Bacteria

Clostridium botulinum and its spores are commonly found in soil and the bacterium can grow in improperly sterilized and sealed food containers of home based canneries, which are the cause of many of the cases of botulism. The effects of botulism typically appear 18 to 36 hours after eating the

foodstuffs infected with a *Clostridium botulinum* culture or spores. The botulinum toxin can apparently pass unattenuated through the lining of the gut and attack peripheral motor neurons. Symptoms of botulinum toxin intoxication can progress from difficulty walking, swallowing, and speaking to paralysis of the respiratory muscles and death.

Toxicity of the Toxin

Botulinum toxin type A is the most lethal natural biological agent known to man. About 50 picograms of botulinum toxin (purified neurotoxin complex) type A is a LD₅₀ in mice. On a molar basis, botulinum toxin type A is 1.8 billion times more lethal than diphtheria, 600 million times more lethal than sodium cyanide, 30 million times more lethal than cobrotoxin and 12 million times more lethal than cholera. One unit (U) of botulinum toxin is defined as the LD₅₀ upon intraperitoneal injection into female Swiss Webster mice weighing 18-20 grams each. In other words, one unit of botulinum toxin is the amount of botulinum toxin that kills 50% of a group of female Swiss Webster mice.

Types of Botulinum Toxins

Seven generally immunologically distinct botulinum neurotoxins have been characterized, these being respectively botulinum neurotoxin serotypes A, B, C₁, D, E, F, and G, each of which is distinguished by neutralization with type-specific antibodies. The different serotypes of botulinum toxin vary in the animal species

that they affect and in the severity and duration of the paralysis they evoke. For example, it has been determined that botulinum toxin type A is 500 times more potent, as measured by the rate of paralysis produced in the rat, than is botulinum toxin type B. Additionally, botulinum toxin type B has been determined to be non-toxic in primates at a dose of 480 U/kg which is about 12 times the primate LD₅₀ for botulinum toxin type A.

Although all the botulinum toxins serotypes apparently inhibit release of the neurotransmitter acetylcholine at the neuromuscular junction, they do so by affecting different neurosecretory proteins and/or cleaving these proteins at different sites. Botulinum toxin A is a zinc endopeptidase which can specifically hydrolyze a peptide linkage of the intracellular, vesicle associated protein SNAP-25. Botulinum type E also cleaves the 25 kiloDalton (kD) synaptosomal associated protein (SNAP-25), but targets different amino acid sequences within this protein, as compared to botulinum toxin type A. Botulinum toxin types B, D, F and G act on vesicle-associated protein (VAMP, also called synaptobrevin), with each serotype cleaving the protein at a different site. Finally, botulinum toxin type C₁ has been shown to cleave both syntaxin and SNAP-25. These differences in mechanism of action may affect the relative potency and/or duration of action of the various botulinum toxin serotypes.

Mechanism of Action

The botulinum toxins apparently bind with high affinity to cholinergic motor neurons, are translocated into the neuron and block the presynaptic release of acetylcholine.

Regardless of serotype, the molecular mechanism of toxin intoxication appears to be similar and to involve at least three steps or stages. In the first step of the process, the toxin binds to the presynaptic membrane of the target neuron through a specific interaction between the heavy chain (H chain) and a cell surface receptor; the receptor is thought to be different for each serotype of botulinum toxin and for botulinum toxin. The carboxyl end segment of the H chain, H_C , appears to be important for targeting of the toxin to the cell surface.

In the second step, the toxin crosses the plasma membrane of the poisoned cell. The toxin is first engulfed by the cell through receptor-mediated endocytosis, and an endosome containing the toxin is formed. The toxin then escapes the endosome into the cytoplasm of the cell. This last step is thought to be mediated by the amino end segment of the H chain, H_N , which triggers a conformational change of the toxin in response to a pH of about 5.5 or lower. Endosomes are known to possess a proton pump which decreases intra endosomal pH. The conformational shift exposes hydrophobic residues in the toxin, which permits the toxin to embed itself in the endosomal membrane. The toxin then translocates through the endosomal

membrane into the cytosol.

The last step of the mechanism of botulinum toxin activity appears to involve reduction of the disulfide bond joining the H and L chain. The entire toxic activity of botulinum and botulinum toxins is contained in the L chain of the holotoxin; the L chain is a zinc (Zn^{++}) endopeptidase which selectively cleaves proteins essential for recognition and docking of neurotransmitter-containing vesicles with the cytoplasmic surface of the plasma membrane, and fusion of the vesicles with the plasma membrane. Botulinum neurotoxin, botulinum toxin B, D, F, and G cause degradation of synaptobrevin (also called vesicle-associated membrane protein (VAMP)), a synaptosomal membrane protein. Most of the VAMP present at the cytosolic surface of the synaptic vesicle is removed as a result of any one of these cleavage events. Each toxin specifically cleaves a different bond.

Preparation of Botulinum Toxin Type A

The botulinum toxin type A complex can be isolated and purified from an anaerobic fermentation by cultivating *Clostridium botulinum* type A in a suitable medium (e.g. a medium composed of meat and milk products). Raw toxin can be harvested by precipitation with sulfuric acid and concentrated by ultrafiltration. Purification can be carried out by dissolving the acid precipitate in calcium chloride. The toxin can then be precipitated with cold ethanol. The precipitate can be dissolved in

sodium phosphate buffer and centrifuged. Upon drying there can then be obtained approximately 900 kD crystalline botulinum toxin type A complex with a specific potency of 3×10^7 LD₅₀ U/mg or greater. This known process can also be used, upon separation out of the non-toxin proteins, to obtain pure botulinum toxins, such as for example: purified botulinum toxin type A with an approximately 150 kD molecular weight with a specific potency of 1.2×10^8 LD₅₀ U/mg or greater; purified botulinum toxin type B with an approximately 156 kD molecular weight with a specific potency of 1.2×10^8 LD₅₀ U/mg or greater, and; purified botulinum toxin type F with an approximately 155 kD molecular weight with a specific potency of 1.2×10^7 LD₅₀ U/mg or greater.

Products of Botulinum Toxin

Commercially available botulinum toxin containing pharmaceutical compositions include Botox.RTM. (Botulinum toxin type A neurotoxin complex with human serum albumin and sodium chloride) available from Allergan, Inc., in 100 unit vials as a lyophilized powder to be reconstituted with 0.9% sodium chloride before use), Dysport.RTM. (Clostridium botulinum type A toxin haemagglutinin complex with human serum albumin and lactose in the formulation), available from Ipsen Limited, as a powder to be reconstituted with 0.9% sodium chloride before use), and MyoBloc™ (an injectable solution comprising botulinum toxin type B, human serum albumin, sodium succinate, and sodium

chloride at about pH 5.6, available from Elan Corporation).

ESTROGENS [1, 4]

Skin ageing process increases rapidly after age of 50, especially in women. Skin ageing is influenced by genetic, environmental and hormonal factors. Estrogen affects several skin functions such as, elasticity, water holding capacity, pigmentation and vascularity. It prevents skin ageing by influencing skin thickness, skin wrinkling and skin moisture.

Effects of Estrogen

a) Estrogen Effect on Skin Thickness and Collagen Content

Postmenopausal women with osteoporosis had skin that was atrophied with decreased skin thickness, skin collagen content and reduction in bone marrow density. It was observed that there was decreased in Type I and Type III collagen as well as, decrease in type III/type I ratio in comparison to premenopausal women. Skin collagen decline was closely related to the number of years following menopause. With the correlation noted between skin collagen decline and postmenopausal years, studies have attempted to decipher the effects of estrogens on skin collagen. Several studies have shown that estrogen therapy has had beneficial effects on collagen content and skin thickness.

b) Estrogen Effects on Skin Moisture

Ability of skin to hold water is by two mechanisms

- 1) Using Stratum Corneum Lipids
- 2) Using Dermal Glycosaminoglycans.

Postmenopausal women not taking estrogen experienced dry skin compared to those with estrogen therapy. Transdermal estrogen therapy leads to an increased water holding capacity of stratum corneum. Estrogen therapy has shown to increase dermal water holding capacity in animals and increase in glycosaminoglycans within 2 weeks of estrogen therapy, while in humans it has shown increased hydroscopic qualities.

c) Estrogen Effect on Skin Wrinkling

Wrinkles show an alteration of dermal collagen, elastic fibers and marked decrease in glycosaminoglycans. Application of estrogen creams showed a marked improvement in fine wrinkles. Postmenopausal women using estrogen were less likely to develop skin wrinkles. Estrogen also causes increase in collagen and glycosaminoglycans in the dermis, which may explain the decrease in skin wrinkling with estrogen treatment. Treatment with estriol ointments to the skin showed changes in skin elastic fibers.

d) Estrogen Effects on Hair Growth

Hair growth encompasses 3 stages which are known to be influenced by estrogens. These stages are

- 1) Growing or Anagen Stage
- 2) Structural regression or Catagen Stage

3) Resting or Telogen Stage

High estrogen levels (during pregnancy) prolongs the growing phase of hair follicle and low estrogen levels (post partum) result in significant hair loss (as anagen phase enters the telogen phase simultaneously), called androgenetic alopecia or female pattern hair loss observed after menopause. Estrogen treatment has shown increased anagen and decreased telogen as compared to placebo.

Mechanism of Estrogen Effect in Skin

Estrogens regulate cell function by binding to two nuclear receptors ER- α and ER- β . Mechanism of estrogen action on skin is not well known. There are controversies regarding expression of ER- α and ER- β . ER- α and ER- β are members of nuclear hormone family of intracellular receptors which is activated by hormone 17- β -estradiol. Function of estrogen receptor is as a DNA binding transcription factor which regulates gene expression. There are two receptors α and β , each encoded by a separate gene (ESR1 and ESR2). Hormone activated estrogen receptors form dimmers ER- α ($\alpha\alpha$) and ER- β ($\beta\beta$) or homodimer ER- $\alpha\beta$ ($\alpha\beta$). While one group of researchers found that ER- β is predominant receptor of skin, others found that both receptors are equally present in the skin.

Estrogen Therapy For The Skin

1) Hormone Replacement Therapy-

HRT consists of two components i.e., Estrogens and Progestogens. Use of estrogen alone is associated with an increased risk of endometrial hyperplasia. Thus progestogens are incorporated in HRT to protect the endometrium. As the estrogen component, natural 17- β -estradiol is often used in Europe, whereas the conjugated equine estrogen (CEE) derived from pregnant mare's urine is the preferred product in the US.

HRT carries a small increased risk of serious complications, and the risk

increases with duration of the therapy. Recently, recognized experts have provided practical guidelines for postmenopausal HRT and have reviewed the risk of complications. Endometrial cancer occurs up to 4 times more frequently in women with a uterus who take unopposed estrogen than in non-users. The risk may be reduced by adding progestogens. Breast cancer risk increases slightly with HRT prescribed longer than 5 years. Venous thromboembolism is rare but increases with estrogen use.

The indication for HRT is the treatment of menopausal symptoms (hot flushes, sweating, insomnia, fatigue, depressed mood and urogenital atrophy). The dose and regimen of HRT need to be individualized, based on choosing the lowest appropriate dose in relation to the severity of symptoms and on the menopausal age. Lower dose HRT has been shown to be effective and minimizes the side effects. Usually after 3-4 years of hormonal treatment, it is possible to stop HRT with no recurrence of menopausal symptoms. Currently, experts believe that limited, short-term use of HRT (<5 years) administered in the early phase of menopause is relatively safe among healthy women. Long term HRT may

be appropriate if symptoms persist. In this case, appropriate counseling on the risks and benefits of the long term HRT should be provided. HRT can offer long term benefits in the CNS, CVS, and skeletal systems. Specifically, it has been demonstrated that HRT is very effective at preventing osteoporosis. However, there are still controversies about the long term use of HRT because of the risk of breast cancer with prolonged use of estrogens. In patients at high risk of osteoporosis, prevention should be continued independently of management of menopausal symptoms, using alternatives to HRT such as selective estrogen receptor modulators (SERMs).

Beneficial effects of HRT on skin ageing have been documented by several studies. An analysis showed that HRT prevents dry skin and wrinkling. Women under long term substitution had one-third fewer wrinkles than non-substituted patients. In a pilot study involving different regimens of HRT on skin ageing, patients were assigned into three groups based on their regimens-

- a) Transdermal estrogen and progesterone
- b) Transdermal estrogen
- c) Oral estrogen and progesterone

And one group was kept as a control. Epidermal moisture, skin elasticity, and skin thickness were significantly improved in all treated groups. A comparison of epidermal hydration and skin elasticity revealed no significant differences between UV exposed and non-exposed measurement sites, suggesting that both intrinsic and photoageing may be improved by HRT.

A leading parameter of skin ageing is skin thickness, which reflects the status of collagen tissue. As previously reviewed, many studies have demonstrated beneficial effects of HRT on skin collagen content. HRT also affects skin elasticity; it has been reported that HRT also limits age-related increase in cutaneous extensibility, thereby exerting a preventive effect on skin slackness.

Despite such beneficial effects of HRT on skin ageing, HRT cannot obviously be recommended solely to treat skin ageing in menopausal women. Prevention of skin ageing with HRT should be regarded as an additional benefit for menopausal women who receive this treatment for other menopausal symptoms.

2) Topical Estrogen Treatment-

Studies have showed that topical estrogen may prevent skin ageing, as seen with HRT. It was observed that treatment with topical 0.01% estradiol and 0.3% estriol on skin aging on the face of perimenopausal women for a period of 6-months showed significant improvement similar to that seen in studies using HRT. Both treatments showed increased skin moisture and improvement of elasticity and firmness of the skin with decreased wrinkle depth. No hormonal side effects were noted, either clinically or by hormone monitoring. Serum hormone levels and the appearance of vaginal smears showed no significant change as compared to before treatment.

A group of scientists (Creidi et. al) examined the effect of a topically applied conjugated estrogen cream (Premarin) in 54 women. After a 24-week treatment period, they found that Premarin cream produced better results than the placebo cream; the difference was statistically significant for skin thickness and fine wrinkles. Premarin cream was well tolerated locally. The general safety of Premarin cream was also excellent; no women had any serious drug-related study events. However, in contrast to the previous study, a modification of the vaginal

maturation index was seen in women using Premarin cream, demonstrating that the CEE (Conjugated Equine Estrogen) has permeated the skin and exerted its effect on the vaginal mucosa. Indeed, it is known that CEE and 17- β -estradiol differ in their total estrogenic potency. This suggests that estradiol creams may provide a safer therapy for skin ageing compared to CEE creams, since they seem not to induce systemic effects.

It is clear that topical estrogen is effective treatment for skin ageing. Menopausal women who are not receiving HRT and who do not have any contraindications to HRT would be candidates for topical estrogen therapy.

Since studies have demonstrated a sharp decline in skin thickness and collagen in the years following menopause, particularly in the initial postmenopausal years, it would be critical to begin the treatment within the first postmenopausal years. Additional studies are needed to definitively demonstrate the safety of this treatment. Further investigations should determine the highest effective concentration of estrogens that can be used without the risk of possible systemic side-effects. Based on previous work on the use of topical estrogen for

vaginal atrophy in postmenopausal women, it is expected that short term use of topical estrogen (<5 years) should prevent skin ageing without serious risks. Indeed, recent studies have demonstrated the efficacy and safety of a low dose of 17- β -estradiol for postmenopausal vaginal atrophy. Neither an increase in systemic estradiol, nor any estrogenic side effects (such as endometrial hyperplasia) have been observed with this treatment. The choice of the form of estrogen is also important: as previously discussed, CEE, which possesses a greater estrogenic potency than 17- β -estradiol, may induce systemic side effects. Estriol, a low potency estrogen that has considerably lower affinity for the estrogen receptor, is commonly prescribed in Europe for topical treatment of menopausal urogenital symptoms. This treatment has been demonstrated to be safe, with no increase risk of endometrial hyperplasia and so may be useful for topical treatment of skin ageing.

Such topical estrogen treatment for skin ageing will need to be administered by dermatologist experienced in endocrinology, given that the concentration and application areas must be observed in order to avoid systemic side-effects.

3) Selective Estrogen Receptor Modulators (SERMs)

SERMs act at the level of the estrogen receptors; they bind to ER- α and ER- β . They appear to have either estrogenic or antiestrogenic effects, depending on the tissue. In some tissues such as bone, they mimic the effects of estrogen, while in others they act as antiestrogens and block unwanted estrogenic effects on uterine and breast tissues. Because of this tissue specificity activity, SERMs are potentially a versatile drug class that offers the prospect of developing individualized, targeted treatments for menopause-associated morbidity. SERMs and estrogen agonist molecules that are currently available or in development are shown in the table 2 below.

The question of whether estrogen alternatives such as phytoestrogens and SERMs are effective estrogens for the prevention of skin aging in postmenopausal women remains unanswered. However, preliminary data indicate that such treatment may be of benefit for skin aging treatment.

Effect of phytoestrogenic SERMs on skin ageing

Phytoestrogens are plant-derived molecules that structurally resemble endogenous estrogens, containing a

diphenolic chemical structure that can directly bind to estrogen receptor. They have a relative greater affinity for ER- β than for ER- α . Phytoestrogens exhibit some

estrogen agonist-like properties but can also act as partial estrogen receptor antagonists. Because of their mixed agonist/antagonist estrogen receptor profile,

Table 2- Shows list of SERMs and Phytoestrogens that are available or in development

| <i>Triphenylethylene derivatives</i> | <i>Benzothiophene derivatives</i> | <i>Dihydronaphthalene derivatives</i> | <i>Tetrahydronaphthalene derivatives</i> | <i>Benzopyran derivatives</i> | <i>Pure steroidal antiestrogens</i> | <i>Phytoestrogens</i> |
|--|--|---------------------------------------|--|------------------------------------|--|-----------------------|
| Tamoxifen (Nolvadex [®] , Zeneca Pharmaceuticals) | raloxifene (Evista [®] , Eli Lilly) | trioxifene | lasofoxifene (Pfizer) | levormeloxifene | ICI 182,780 (fulvestrant Faslodex [®]) | genistein |
| 4-Hydroxy-tamoxifen (active metabolite of tamoxifen) | arzoxifene (LY353,380-JCI, Eli Lilly) | nafoxidene | | ormeloxifene (Centchroman) | ICI 164,384 | genistein |
| Toremifene (Fareston [®]) | zindoxifene | | | EM800 (SCH57050) | RU 39411 | daidzein |
| Ospemifene (FC-1271a) (active metabolite of toremifene) | ZK 119010 | | | EM652 (active metabolite of EM800) | | daidzein |
| Droloxifene | ERA-923 | | | | | formononetin |
| Clomifene (Clomid [®] , Seraphene [®]) | bazedoxifene (Wyeth) | | | | | equol |
| Miproxifene phosphate (TAT-59) | | | | | | coumestrol |
| Idoxifene | | | | | | |
| GW 5638 | | | | | | |
| GW 7604 | | | | | | |
| MDL-103,323 | | | | | | |

phytoestrogens have received considerable attention as potential alternatives to estrogen. Studies have demonstrated that genistein may prevent photoageing in human skin. Other studies have reported that genistein and daidzein stimulate hyaluronic acid production in human keratinocyte culture. A recent European study had examined the effect of a cosmetic cream preparation including isoflavone (Novadiol) in 234 postmenopausal women and had showed improvement in the skin dryness and wrinkles after 12 weeks of treatment.

Effect of SERMs on skin ageing

An effective SERM for the skin would exert estrogen agonist action in skin and estrogen antagonist action in the breast and uterus. The ideal SERM for skin would also exert estrogen action in brain, bone and in the vagina. Among different SERMs currently available or under development, only raloxifene has been studied for its effects in skin. Raloxifene is used in prevention and treatment of postmenopausal osteoporosis. It also decreases the risk of breast cancer and does not stimulate the endometrium. Recent studies have demonstrated that raloxifene exerts stronger stimulative effects on collagen biosynthesis than estradiol in human

skin fibroblasts and might reverse some of the postmenopausal changes in skin.

To Summarize Estrogen Treatments

The skin is an estrogen responsive tissue. A better understanding of the hormonal regulation of skin physiology and skin ageing may provide the basis for development of new hormonal treatment for skin ageing. HRT cannot be recommended solely to treat skin ageing in menopausal women but may be considered as an additional benefit in the treatment of menopausal symptoms. Topical estrogen application is highly effective and safe if used by a dermatologist with an expertise in endocrinology. Phytoestrogens appear to be effective but their possible side-effects have not been well investigated. SERMs are drugs that offer exciting opportunities for the future treatment of skin ageing but, while great strides have been made in developing effective SERMs for menopausal symptoms such as osteoporosis, the challenge of developing an effective estrogen alternative for skin ageing treatment remains.

PLASTIC SURGERY [1,5]

It is a medical specialty that uses a number of surgical and non-surgical techniques to change the appearance and function of a person's body. It is also referred to as cosmetic surgery. Plastic in Greek is 'plastikos', means to mold or to shape. The

various techniques that can be used to ameliorate skin ageing are as follows:

1) Surgical Procedures

- a. Blepharoplasty- surgical procedure to reshape the upper and lower eyelids by removal or repositioning of excess tissue as well as reinforcement of surrounding muscles and tendons.



Figure 14- A patient undergoing blepharoplasty

- b. Rhytidectomy (Face Lift)- to lift up the tissue and skin and underlying muscles in order to have tighter and smoother face.

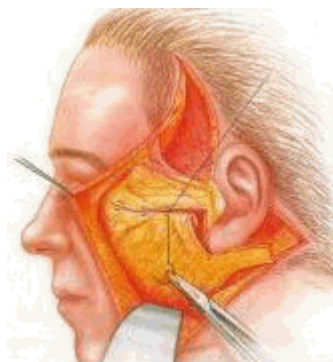


Figure 15- A diagram showing how rhytidectomy

2) Non-Surgical Procedures

- a. Dermabrasion- Surface of epidermis of the skin is removed by abrasion.
- Microdermabrasion-

Uses: It is used for reducing superficial wrinkles, scars, large pores, acne, and age spots. It restores smoother and more useful appearance.

Technique: In this technique there is a mechanical device which directs a stream of fine abrasives (aluminum oxide crystals) using compressed air. Depending on the particle flow rate, the vacuum pressure, the movement of the hand piece and the number of passes, different depths of abrasions are achieved. As these particles hit the skin the superficial layer i.e. stratum corneum, is abraded off.

After Treatment Requirements: After the treatment the patient may experience redness for the first few hours. Creams and ointments may be applied to the area to keep them moist as they heal. The skin may appear as if the person has got a minor sun burn for 2-3 days and will be more sensitive to sunlight, therefore, use of SPF 15 and greater sunscreen is essential.

Advantages: It is highly effective with low risk. It shows rapid facial skin rejuvenation with a minimal to no downtime. It can be used for all ages and skin types. The technique gives minimal discomfort with no use of anesthesia and no bleeding or visible desquamation. The technique leaves the skin with only temporary erythema.

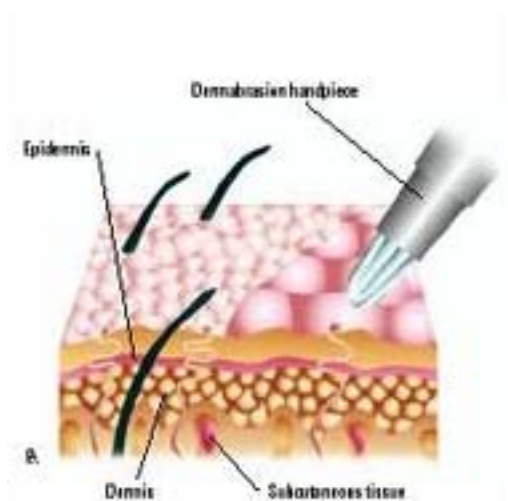


Figure 16- Diagram of a dermabrasion machine

Disadvantages: Skin exfoliation to a depth of 15-25 μ m has been seen with two passes, so this is a superficial treatment for wrinkles on the surface only and not deeper wrinkles. For deeper wrinkles, other methods would have to be used. Particles along with the abraded superficial cellular debris are aspirated into a close separate container and discarded. Thus new particles have to be used for each treatment cycle.

Histological Benefits of Dermabrasion:

The procedure leads to fibroblast stimulation, new dermal collagen deposition, epidermal thickening, normalization of stratum corneum, thickening of the papillary dermis with increased deposition of collagen and elastin and an increase in fibroblast. Microcirculatory changes in reticular dermis are also seen.

b. Laser Resurfacing-

For more than a decade, carbon dioxide laser skin resurfacing has offered precise cutaneous ablation for facial rejuvenation. The controlled removal of epidermis and variable portions of the dermis with associated heating results in predictable collagen shrinkage, remodeling, and dermal tightening. This improves skin texture and appearance. Laser energy on tissue can be reflected, scattered, transmitted, or absorbed, with the latter feature producing the photothermal or photochemical effects on tissue. By creating a pulsed delivery system that dwells on tissue for less than the thermal relaxation time (which for skin is estimated at approximately 695 μ s), the surrounding thermal damage is limited while still delivering sufficient energy (irradiance, measured in joules/s/cm^2) to vaporize tissue. The fluence (energy density) estimated to vaporize tissue is approximately 4 to 5 J/cm^2 per pulse. In super- or ultrapulsed systems, the pulse duration may range from 600 microseconds to 1 millisecond. This technical advance has allowed lasers to become a popular method of cutaneous resurfacing.

Laser skin resurfacing is an ablative technique that offers comparable results to superficial, medium or deep chemical peels with greater surgeon precision and control. The carbon dioxide laser wavelength of 10,600 nm is absorbed by tissue water, resulting in approximately 50 to 70 μm of ablation in a single pass with a similar amount of thermal necrosis. With additional passes, less ablation occurs, and greater thermal necrosis is seen.



Figure 17- A patient undergoing laser ablative therapy

As with chemical peels, removal of the epidermis places the skin at higher risk of infection, inflammation, and desiccation. The risks of complications are related to this as well as the depth of resurfacing. Although the indications and complications of laser resurfacing are similar to those of medium and deep chemical peels, full face resurfacing results in a complex postoperative course. Persistent erythema and (for many surgeons and patients) an unacceptable rate of late permanent

hypopigmentation have resulted in a recent reduction in demand, yet for severe photoaging, this may be the optimal treatment for skin rejuvenation, especially in those patients with lighter skin types.

The erbium:yttrium-aluminum-garnet Er:YAG laser wavelength of 2940 nm offers precise ablation with minimal thermal damage. This laser is absorbed by water approximately 13 times more efficiently than CO₂ laser radiation. With short pulses, thermal damage of 10 μm or less occurs with ablation. However, this results in increased dermal plexus bleeding during resurfacing. The skin vaporization threshold for the Er:YAG laser is approximately 0.5 to 1.7J/cm². The depth of ablation of an Er:YAG laser is approximately 4 μm of tissue per each joule per square centimeter. With larger spot sizes, and higher repetition rates, ablation rates of up to 70 μm per second can be attained. Erbium laser resurfacing has an advantage of safely resurfacing skin on more pigmented patients (Fitzpatrick skin types III–VI). Although carbon dioxide laser resurfacing is the optimal treatment modality for severe cutaneous photoaging, the Er:YAG laser offers a level of safety for those patients who are at risk of pigmentary abnormalities.

More recently, the introduction of hybrid lasers allows deeper penetration with improved hemostasis. A variable pulsed Er:YAG laser, a dual-mode ablation/coagulation pulsed Er:YAG laser, and a combined Er:YAG and CO₂ laser are all modulated lasers that offer deeper ablation and greater thermal damage for improved hemostasis. Initial reports offer promise that these lasers provide good efficacy when compared with carbon dioxide or Er:YAG laser systems alone.

Full skin cryopeeling can eliminate precancerous lesions, wrinkles, improves texture, pigmentary problems associated with photoageing. Surgery or dermabrasion improves the skin contour because new collagen and epidermis replaces the abraded skin and gives a smoother appearance to the skin.

MAKE UP [1,8,9]

Cosmetic are the best product to hide the signs of ageing but not to prevent the signs of ageing. The most commonly used make up products to hide the signs are:

- 1) Lip liners – lips, mainly the inferior, show alterations due to sun exposure, dryness, scaling, loss of the limits between semimucosa and skin, and atrophy are characteristics of photoaging. Thus, a careful use of a lip liner can avoid the vertical bleeding of lipstick onto the wrinkles of the borders

of the lips. It can also enlarge the appearance of thin, atrophic lips and correct the lip line if there is an irregularity due to the removal of a skin cancer or other type of lesion along the vermilion border. Hence, use of specific products for photoprotection of the lips is essential.

- 2) Lip balms – they are essential as they help in preventing the lips from drying
- 3) Eye liners and mascara – they can help enhance the beauty of the eyes. If the upper lid has sagged too much, a thin line of color applied just above the lash line may be the best way to hide the signs. Use of mascara incase where the upper lids hang heavily can help lift the lashes up and around the sagging lids may be helpful
- 4) Face powders and Foundation make up – are used to hide the visible defects

Adverse Reactions to Cosmetics

The stratum corneum of the elderly is less capable to act as a barrier; thus, it is frequent to see allergic and irritant reactions to cosmetics. They are caused by endogenous and environmental factors and, besides an irritative dermatitis, cosmetics can produce allergic reactions also in elderly patients. They may be acute reaction, irritant dermatitis, mechanical irritation, acneiform eruption, phototoxic reaction, subjective irritation, such as burning, stinging, or itching, contact urticaria syndrome, and delayed hypersensitivity reactions.

CONCLUSION

Although ageing is inevitable, the best a person can do is take steps to slow it down. The cosmetic ageing changes that occur in the skin are not a threat, but show marked effect psychologically in a person; especially with regard to a person's self perception, self esteem, and quality of life.

Intrinsic ageing of the skin cannot be slowed down, but control of the extrinsic factors that affect the skin can be made to help reduce the ageing in skin. Attenuation of skin ageing can be done in several ways, which include topical, injectable, oral and surgical therapies. The limitation of sun exposure by avoiding the sun during the peak tanning hours (between 10:00 a.m. and 2:00 p.m.), the use of a sunscreen with a high sun-protection factor, and the use of protective clothing when exposed to the sun are the most important advice physicians can offer to their patients at any age. Even if this sun protection treatment is started later at old age, the constant use of a photoprotector can promote an apparent reversion of photoageing, giving a younger aspect to the skin. Other topical treatments such as moisturizers can also be used to reduce the visibility of fine lines while also helping the old skin regain its moisture content.

Introduction of oral antioxidants in the form of vitamins in the diet or medication can also help ameliorate oxidative damage to

the skin. Oral estrogen taken by postmenopausal women in HRT can also help decrease the ageing in skin. Although HRT is not recommended as a treatment for skin ageing, the amelioration of ageing skin seen when HRT is given can be explained as an added benefit to the patients receiving this treatment. Topical estrogens and SERMs should also be looked into as possible treatments for ageing skin in postmenopausal women.

Use of chemical peels in aged skin to help refresh the skin surface, provides an effective treatment for removing old and damaged skin and allowing new smoother skin to take its place. While injectable fillers can be used to artificially replenish the lost dermal constituents such as collagen. Use of botulinum toxins to ease the wrinkles, by flaccid paralysis of the muscles, can be made.

Plastic surgery can be looked into as a last resort to help aged skin as they are expensive and can have complications. Surgeries such as blepharoplasty and rhytidectomy are quite common, while non-surgical procedures like microdermabrasion and laser resurfacing may provide a better treatment modality.

Finally, make-up can be used to hide inconsistencies in the skin, but cannot be used to reverse ageing.

Despite all these available treatments, it is more important that a person takes the

ageing process as it comes well. If a person feels young at heart, then that is more important as compared to cosmetic changes. It is thus appropriately said by the great artist Pablo Picasso that- “youth has no age”.

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