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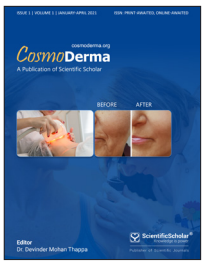

Review Article

Understanding skin aging: Exploring anti-aging modalities

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Received : 27 June 2023
Accepted : 11 July 2023
Published : 19 July 2023

DOI
10.25259/CSDM_123_2023

Quick Response Code:

ABSTRACT

With ever-improving life expectancy, skin aging has become the first casualty of exuberant health. People are progressively seeking remedies for their age-related skin problems. Understanding the aging process is unfolding newer realms in the molecular biology of the skin, giving us new insights to combat senescence more effectively. Epidermal dysfunction, compromised permeability homeostasis, elevated skin pH, diminished stratum corneum hydration, and dermal extracellular matrix aberrations with changes in its cellular composition are now well understood. Thus, a more scientific approach can be utilized while evolving various specific anti-aging therapies. The present communication attempts to address both the process of skin aging and various therapies to combat it in a concise yet succinct way.

Keywords: Skin aging, Cosmetic dermatology, Aesthetic dermatology, Anti-oxidants, Anti-aging

INTRODUCTION

Skin is the first defense against the external environment from physical and chemical stimuli and infective organisms. It has an immaculate power to shed and regenerate in an orderly time-bound fashion. Genetic factors, sun exposure, occupational activities, and time – all contribute to the aging process of the skin. Although aging changes also occur in other organs/systems of the body, the skin shows visible signs of aging to one and all. As the expectancy of life has increased throughout the world, we are encountering an increasing number of aging populations desperately seeking advice to delay or reverse the signs of aging. The present communication attempts to address these important aspects of both causes and remedies of this natural process.

THEORIES OF AGING

There are two basic theories of aging that have been put forward to explain the complexity beneath – Programmatic theory and Stochastic theory.

The programmatic theory is comprised of telomere shortening and cellular senescence. As the age advances, the human telomere shortens over 30%. Telomeres of patients with premature aging syndromes such as progeria are significantly shorter than their age-matched controls. Cellular senescence denotes a limited capacity of cells to undergo cell division leading to altered differentiation, irreversible growth arrests, and resistance to apoptosis.[1,2] The stochastic theory

postulates that a four-pronged process operates in the aging skin [Table 1].

EXTRINSIC SKIN CHANGES

As age advances, the tell-tale signs of aging start to display on the body gradually, which may vary from individual-to-individual, geographic areas, race, and occupation involving excessive sun exposure, etc. Face, hands, and feet are the first to show chronologic aging and photoaging.[3] Atrophy, wrinkling, laxity, sagging, pigmented blemishes, and dryness can be seen on the skin along with greying of the hairs. With time, they become more pronounced and disturbing; pigmentary changes also develop in sun-exposed areas. The liver spots, senile lentigo, and seborrheic keratoses keep developing and increase in number with time. Hair becomes grey, density may reduce, and the anagen phase of hair follicles progressively shortens. Paradoxically, eyebrows can become bushy in the elderly. In aging females, hirsutism may be a cause of concern – grey terminal hair on the chin even resists the hair removal lasers. Previously full face gives a look of weakening, wrinkling, and reduced facial musculature. The neck shows non-elastic wrinkled sagging skin. The nails may become lusterless and show thickening and longitudinal ridging [Figure 1]. The dry skin of the elderly is a continuous source of irritation and pruritus. Senile people, thus, become prone to xerotic skin conditions like asteatotic dermatitis. Pressure sores can develop over the skin of the pelvis due to loss of subcutaneous fat.[4]

INTRINSIC SKIN CHANGES

Epidermis

Stratum corneum has a brick-and-mortar model of compact cellular material. This efficiency maintains selective permeability and controls the transepidermal water loss.[5] Aging progressively impairs this optimum function of stratum corneum. The keratinocyte proliferation declines while the apoptosis increases with age leading to a reduction in the thickness of the epidermis.[6,7] Further, the structural proteins – filaggrin, loricrin, and cornified – envelope proteins markedly decline with aging. Side-by-side the intercellular cementing substance also shows lower production, contributing to the abnormal epidermal permeability.[8] Several other age-related complex enzymatic and biochemical changes including a low level of hyaluronic acid, further, contribute to altered epidermal function.[5-10] Other aging changes include elevation of skin surface pH beginning at 55 years of age, caused by a declining sebum content resulting in reduced triglycerides in the stratum corneum.[5] Other factors contributing to a higher pH include reduced levels of sodium hydrogen exchanger 1, secretory phospholipase 2, and filaggrin.[5,11-14] Finally, stratum corneum hydration gets significantly reduced with age [Table 2]. The underlying mechanisms include reduced contents of natural humectants and their metabolites, sebum, and glycerol. Aquaporin 3 levels decrease in the aging skin as well, further contributing to reduced epidermal hydration.[5,15,16]

Table 1: Stochastic theory of skin aging.[1-3]

Biological process	Features
Oxidative stress	Throughout life, cells accumulate a molecular oxidative damage due to decreased efficiency of anti-oxidant defense system.
DNA damage	A decreased DNA repair capacity over years can accelerate the aging of the cells.
Amino acid racemization	Substitution of the D-amino acids for the L-amino acids within the protein keeps occurring as time passes. This affects the protein function, reducing the deamidation of asparagine and glutamine, thereby reducing the rate of protein degradation.
Non-enzymatic glycosylation of proteins	This occurs when sugar aldehydes condense with the protein amino groups, resulting in altered degradation, loss of function, and brown discoloration of cells.

Dermis

In contrast to the dense cellular texture of the epidermis, the dermis is primarily composed of extracellular matrix (ECM). The components of the dermis include collagen fibers, elastic fibers, fibroblasts, immune cells, and skin appendages. With aging, there is a gradual reduction in both the quality and quantity of collagen and elastic fibers, clinically reflected in skin wrinkles and loss of elasticity [Table 3].[17-26]

Figure 1: Extrinsic skin changes seen in the mother (left) compared to her daughter (right).

Table 2: Epidermal molecular changes with aging.[5,11-16]

Changes	Effect of epidermis	Clinical effect on skin
Decreased sebum, NHE1, Filaggrin, and sPLA2	Increased skin pH	Cutaneous inflammation and pruritus
Decreased sebum, Filaggrin, AQP3, and stratum corneum lipids	Decreased stratum corneum hydration	Pruritus and xerosis
Decreased stratum corneum lipids, NHE1, sPLA2, and differentiated related protein	Decreased/Altered permeability barrier	Cutaneous inflammation and increased allergic reactions

NHE1: Sodium hydrogen exchanger 1, sPLA2: Secretory phospholipase 2, AQP3: Aquaporin 3

Table 3: Dermal molecular changes with aging.

Components	Features
Collagen[5,17-22]	• Collagen deficiency due to quantitative and structural changes. • Generation of ROS causing increased MMP expression and inhibition of TGF-β. This leads to decreased collagen biosynthesis and increased fragmentation. • Fibroblasts which normally adhere to ECM in young skin gets separated and reduced in size. • Aged fibroblasts produce more ROS which in turn aggravates the effects of increased MMP and inhibition of TGF-β.
ECM components[10,23-26]	• Elastic fibers, responsible for skin compliance and resilience (elasticity) get structurally changed and decreased in number. • In extrinsic aging and photoaging, there is paradoxical increase in abnormal and non-functional elastic fibers accumulated in dermis. • GAGs, a major component of ECM, are both sulfated (five types) and non-sulfated (One type – hyaluronic acid). They maintain the water content in tissues. Aging reduces their function and abnormal accumulation. • Proteoglycans, a family of conjugated proteins which impart mechanical strength to the skin, also become abnormal and less functional.
Appendages[5,17]	• Hair follicle changes vary greatly according to the site and gender. Hair cycles get shortened with greying of the hair, starting with scalp. The eyebrows of elderly become bushy and there is hirsutism in the elderly women with reduction of scalp hair. • Sebaceous and apocrine glands reduce in size, quantity, and function.

ROS: Reactive oxygen species, MMP: Matrix metalloprotein, TGF-β: Transforming growth factor-β, ECM: Extracellular matrix, GAGs: Glycosaminoglycans

ANTI-AGING MODALITIES

The scientific, in depth knowledge of the sophisticated aging and photoaging processes has led us to rational research, both for preventing and delaying the process of aging. Several approaches have been advocated to reverse the aging process to some extent. Everyday, new pharmacological, non-invasive, and laser/surgical intervention is being added to the ever-expanding basket of anti-aging therapy. It is worthwhile to briefly recount them [Figure 2].

PHARMACOLOGICAL AGENTS

Both oral and topical pharmacologic agents have been advocated for preventing, tackling, and delaying natural photoaging. It is believed that the prevention, especially that of ultraviolet radiation exposure from early childhood can go a long way in reducing extrinsic skin aging. Wearing protective clothing and using physical and chemical sunscreens, along with avoidance of sunlight, form a substantial denominator of any anti-aging treatment.

Oral agents

Antioxidants – Carotenoids, Vitamin C, Vitamin E, selenium, proanthocyanidins, and astaxanthins – have all been used orally for variable period of time for their anti-aging effects [Table 4].[27-30]

Topical agents

A wide variety of topical agents, both chemical and herbal have flooded the market in the past two decades. Scientific data are available on a variety of topical antioxidants (vitamins, flavonoids, and polyphenols). They all reduce the burden of free radicals in the tissues through regular applications. Another researched entity includes the cell regulators (retinol, peptides, and growth factors) which show a positive effect on collagen metabolism as well as production[27] [Table 5]. A combination of antioxidant and cell regulators in the same cream has been known to multiply the anti-aging potential of these agents.[31-50]

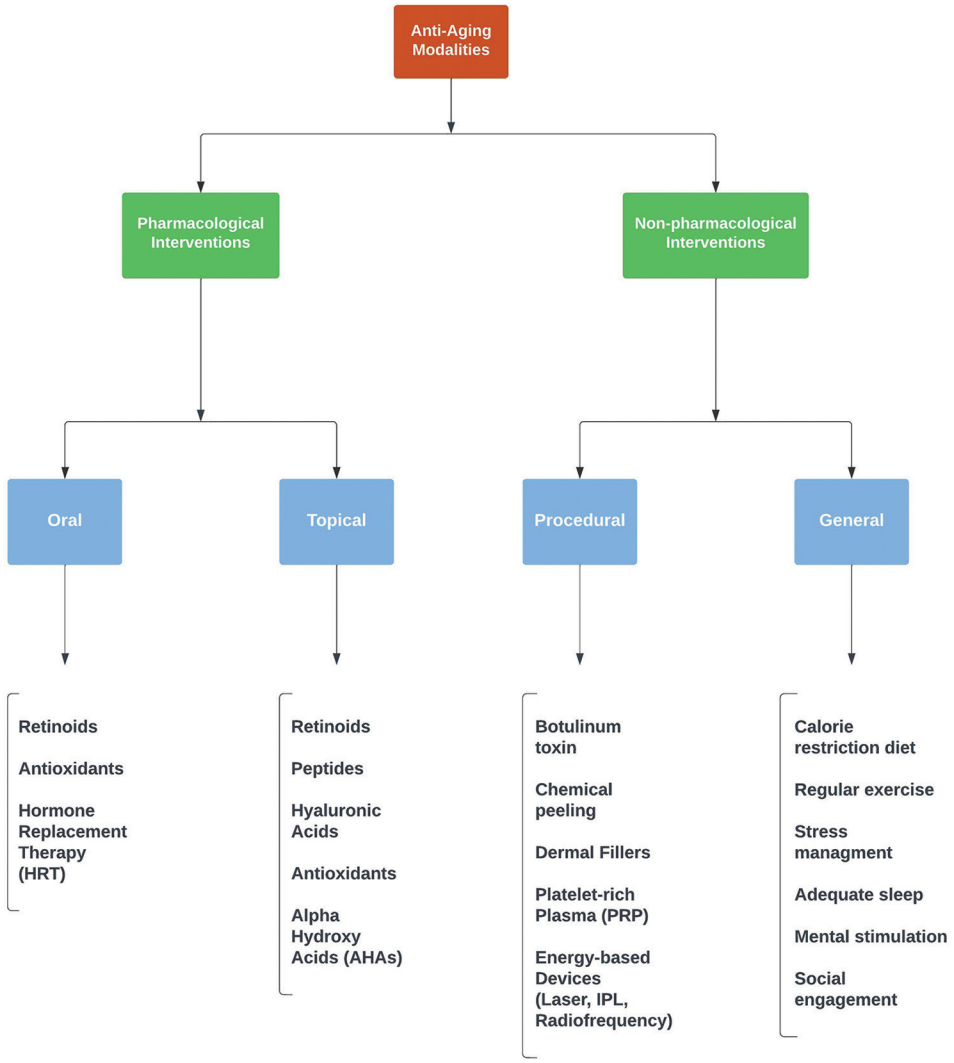

Figure 2: Broad classification of anti-aging modalities.

Table 4: Antioxidant defense of the skin.[27-30]

Endogenous defense (innate)		Exogenous defense (dietary)
Enzymatic • Superoxide dismutase • Glutathione peroxidase • Catalase	Non-enzymatic • Albumin • Bilirubin • Thiol • Glutathione • Uric acid • Nutritional factors	• Ascorbic acid (Vitamin C) • Tocopherol (Vitamin E) • Carotenoids • Copper • Selenium

CHEMICAL PEELS

Another substantial therapy widely used for age diminishing is different varieties of chemical peels. They have shown promising results when used either alone or with combination of different agents [Table 6].[51,52]

ENERGY-BASED DEVICES

A selective heat-induced denaturalization of dermal collagen which results in subsequent reactive synthesis is the principle behind various types of light devices. Laser, intense pulsed light, and radiofrequency can be effectively employed for rejuvenation,

Table 5: Topical pharmacological agents with anti-aging potential.[17,32]

Agents	Preparation	Regimen	Efficacy
Retinol[33,34]	0.04–1%	1–3 times/week, up to 6 weeks	Improvement in epidermal thickening, wrinkling with histopathological confirmation.
Retinoic acid[35]	0.01–0.1%	1–2 times/week, up to 3 months	Clinical improvement in wrinkling, pigmentation, sallowness, and texture.
Retinaldehyde[36]	0.05–0.1%	1–2 times/week, 1–3 months	Better tolerated, significant improvement in profilometric score.
Glycolic acid[37]	25–50%	Once a week, up to 4 weeks	Reduction in fine wrinkles and solar elastosis. Improves skin texture.
Lactic acid[38]	5–12%	Twice daily, up to 3 months	Increased firmness of epidermis and dermis. Clinical improvement in skin texture, fine lines, and wrinkles.
Mandelic acid[39]	4–6%	Twice a day for 4 weeks	Significant increase in skin firmness and elasticity; reduced fine lines.
α-lipoic acid[40]	5%	Twice a day for 12 weeks	Mean epidermal and dermal thickness improvement; significant reduction in photoaging.
Hyaluronic acid[41]	0.1%	Twice daily for 2 months	Significant improvement in skin hydration, elasticity and reduction of wrinkle depth.
Niacinamide[42]	4–5%	Once daily for 8-12 weeks	Significant improvement in skin texture and wrinkling.
L-ascorbic acid[43]	5%	Once daily for 6 months	Decrease in deep furrows with microscopic evidence of neocollagenesis.
Vitamin E[44]	1% with ferulic acid and vitamin C	Daily for 4 days, followed by UV irradiation	Increased photoprotection to solar simulated UV radiation.
CoQ10[45]	1%	Twice daily for 3 months	Reduction in wrinkle score.
Phenols (Green tea, Berry)[46]	10% cream+300 mg oral	Twice daily for 8 weeks	Significant improvement in elastin content of the skin.
Ferulic acid[44,47]	0.5% with vitamin C	Daily for 4 days, followed by UV irradiation	Increased photoprotection to solar simulated UV radiation.
Signal peptide[31,48]	5% niacinamide, pal-KTTS cream	Daily for 8 weeks	Significant improvement in wrinkles in comparison to retinoic acid.
	GEGK cream	Daily for 8 weeks	Increased formation of procollagen, hyaluronic acid, and fibronectin.
Carrier peptide[49]	GHK-Cu cream	Daily for 8 weeks	Significant improvement in wrinkles, reduction in fine lines, and increase in skin density.
Neurotransmitter inhibitor peptides[50]	Acetyl hexapeptide-3 with tripeptide-10 cream	Daily for 60 days	Significant reduction in wrinkles.

CoQ10: Coenzyme Q10, KTTS: Lysine-threonine-threonine-lysine-serine, GEGK: Gly-Glu-Lys-Gly, GHK: Glycil-L-histidyl-L-lysine, UV: Ultraviolet

Table 6: Chemical peels.[51,52]

Type	Agents	Effect
Superficial peel	α-β-, lipohydroxy acid, trichloroacetic acid (10–30%)	Exfoliation of epidermal layer without going to basal layer.
Medium depth peel	Trichloroacetic acid (30–50%)	Exfoliation up to upper reticular dermis.
Deep peels	Trichloroacetic acid (>50%), phenol	Penetrate lower reticular dermis

resurfacing, and tightening of the skin. Laser resurfacing has been shown to be very encouraging in reversing the photoaging by causing extensive dermal remodeling, regeneration of cellular organelles, and stimulation of neocollagenesis.[53-55]

DERMAL FILLERS AND INJECTABLE SKIN REJUVENATORS

Dermal fillers can be injected within or beneath the skin to improve the blemishes and to cause soft tissue augmentation. They very useful in treating permanent wrinkles like crow's feet and prominent nasal labial furrows[27,56] [Table 7].

BOTULINUM TOXIN AND PLATELET-RICH PLASMA (PRP)

Although it has an insignificant effect on skin aging or skin texture on a molecular level, the botulinum toxin is often prescribed for slowing down the visible aging process by acting on dynamic wrinkles.[57] It is used in various dilutions at various sites and repeated after variable intervals of several months. PRP derived from fresh whole blood of the subject has a very high concentration of platelets which harbor various growth factors including platelet-derived growth factors, transforming growth factors, vascular endothelial growth factors, and insulin-like growth factors. All these growth factors are known to regulate processes including cell migration, attachment, proliferation, and differentiation; promoting ECM accumulation by binding to specific cell surface receptors. This in turn induces the synthesis of collagen and other matrix components by stimulating the activation of fibroblasts, resulting in skin rejuvenation.[27,58]

ANTI-AGING DIET

Calorie restriction has remained a longstanding advice that delays age-associated diseases and extends the lifespan of an individual. Time and again, claims of intermittent fasting, ketogenic diet, protein restriction, time-restricted feeding, diet restriction of certain amino acids, and fast-mimicking diets have been advocated in natural anti-aging regimens. Although the effects seem to be highly variable and inconsistent, some anti-oxidant properties of such diets causing the elimination of reactive oxygen species may be beneficial to some extent.[59]

Table 7: Dermal fillers.[27,56]

Types	Agents
Autologous	• Fat • Cultured human fibroblasts
Collagen	• Bovine-derived • Human-derived (from tissue culture)
Hyaluronic acid	• Non-animal stabilized • Viscoelastic (from bacterial fermentation)
Synthetic/ Pseudosynthetic	• Silicon • Polymethacrylate microsphere suspended in aqueous polysaccharide gel • Alkyl-imide gel polymer

HORMONE REPLACEMENT THERAPY (HRT)

The progressive decrease of hormone synthesis with age makes it logical to use HRT in select individuals – both males and females, with overall benefit in the quality of life and halting signs of aging.[27,60] Melatonin is one such example, other being estrogen and progesterone. Obese men with Type-2 diabetes mellitus have a low testosterone level and can be advised a controlled testosterone therapy, improving their stamina as well as skin tone.[61]

CONCLUSION

With increasing longevity, improved comforts, better standard of living, and abundant social interactions, the humankind is getting more concerned about their physical appearance and youthful personality. The first blemish on the face or a fine line on the forehead can be a significant cause for concern for any self-conscious socialite person. Understanding the aging mechanism has translated into a plethora of modalities available for preventing and delaying aging. Social media has also increased awareness about the use of beautifying creams promising a glowing, youthful skin. Thus, an ever-increasing number of people approach skin specialists for various procedures and cosmeceuticals to prevent their skin from signs of senescence. Sunscreen common to all age-defying agents can also be used prophylactically to prevent photoaging, the spectrum of which has now included visible light, infrared rays, and anti-pollutants. The future is getting more and more promising in the field of senescence and skin rejuvenation. An accurate understanding of the aging process up to genomic levels has made it possible to identify novel targets for better prevention, maintenance, and reduction of chronological aging and photoaging.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Srivastava G, Srivastava G. Understanding skin aging: Exploring anti-aging modalities. CosmoDerma 2023;3:109.