Perceived Age and Life Style. The Specific Contributions of Seven Factors Involved in Health and Beauty

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ABSTRACT

Objectives: The skin is a dynamic, visible organ, showing the most obvious signs of aging. The mechanisms of extrinsic aging, most of them presented in this paper, are currently well known and also the only ones that can be counteracted. Therefore, the transition of this knowledge in the general population is of the most importance, in order to introduce healthy aging strategies, to prevent the development of chronic or malignant diseases and psychological burden related to old age.

Materials and methods: A thorough review of the literature has been performed in order to identify the main factors involved in skin health and aging.
INTRODUCTION ABOUT PERCEIVED AGE

One of the most interesting and true affirmations about skin is attributed to the zoologist Desmond Morris, respectively “Flawless skin is the most universally desired human feature”. The meaning of this declaration is about human’s need to “advertise” health, well being, and even fertility with a good looking skin (1).

During the 20th and 21st centuries, life expectancy has increased; therefore, healthy aging strategies are mandatory in order to prevent physical and/or mental diseases related to old age (2).

Skin, among all other organs, has a profound effect on general health in a dual way; skin is a powerful barrier against external factors, while also being actively involved in controlling the immune system. In addition, skin is considered an endocrine gland which produces hormones and neurotransmitters (3). But – a very important but – because of its visibility, skin health and skin appearance have the ability to influence self-esteem, mental status, social interactions and overall quality of life (4).

The skin represents the interface between external and internal aggressions, hence undergoes aging under the influence of both internal (intrinsic) factors and external (extrinsic) agents, two aging processes which are clinically and biologically different. While intrinsically skin aging is a result of natural decline in skin’s functions, the extrinsic aging is a consequence of chronic exposure to environmental factors (2), such as sun and ultraviolet exposure, pollution, diet, smoking and stress.

A very practical parameter for evaluating health is the comparison of perceived age with chronological age, and for adult patients the expression “looking old for your age” is an indicator of poor health. The concept of perceived age has been shown to be predictive of mortality in elderly individuals (5, 6) and is associated with a higher risk of both morbidity and mortality (7).

Perceived age is associated with genetic factors (8, 9) smoking, sun exposure, body mass index, socioeconomic status and depression (10).

Skin aging is strongly associated with perceived age (9), and facial skin aging is the most important parameter for the perceived age (11, 12). Sun damage, pigmented spots, skin wrinkling, skin color homogeneity, skin texture, lip size are all associated with perceived age (9).

Pigmentation and wrinkles (especially wrinkles around lips) and skin texture changes are signs that make a person look older earlier. Skin texture studies have shown that the effects of skin color distribution can account for up to 20 years of perceived age (13).

WHAT ARE THE MOST IMPORTANT FACTORS INVOLVED IN SKIN AGING?

Skin aging is a complex process comprising both intrinsic (or chronological) and extrinsic (or environmental) factors (14, 15).

Intrinsic aging is a “natural” process, caused by the accumulation of reactive oxygen species (ROS) resulting from oxidative cellular metabolism and influenced by genetic factors (ethnicity), anatomic variations and hormonal changes (natural decline of hormones’ and growth factors’ levels) (16, 17). Despite the fact that the causes of chronological aging have mainly been identified and understood, this process is considered uncontrollable.

Extrinsic aging is a result of chronic exposure to various environmental elements, such as sun and ultraviolet exposure (including tanning bed), pollution (18), smoking, diet, repetitive muscle movements (squinting, frowning, pursing, etc),
sleeping position and cutaneous or general diseases (19).

The process of aging induces the transformation of the face with changes that affect the shape (bone resorption, muscle atrophy, fat deposits redistribution), the texture (wrinkles), and the color of the face. Skin color is related to the distribution of skin chromophores and the structure of the dermis, which affects light scattering (20).

Practically, aging signs can be classified into four main categories: wrinkles/texture, loss of firmness of cutaneous tissues (ptosis), vascular disorders, and pigmentation heterogeneities (21).

**Sun, aging and perceived age**

Tanned skin has been promoted in modern Western culture as healthy and attractive, and the unexpected results were an increase in skin neoplasms’ rates, both melanoma and non melanoma skin cancers, and the acceleration of skin aging processes (22, 23) (Figure b).

Research revealed the fact that the first subclinical signs of skin damage induced by ultraviolet exposure (UV) are already present at 15 years old (24), in the setting of normal sun exposure, while visible skin modifications are found even in unexposed skin areas by early 30s (19, 22).

In the late 19th century, two famous dermatologists, Unna (25) and Dubreuilh (26), recognized the negative effects of intensive sun exposure on the face, by comparing the face of sailors and farmers with indoor workers (Figures c, e).

Seventy years later, Albert M. Kligman identified the structural changes in human skin after sun exposure and the differences between intrinsic and extrinsic skin aging processes (27). Lavker confirmed the work of Kligman and also described the profound structural differences between sun exposed and sun protected skin (28). In 1986, Kligman and Kligman (29) introduced the term “photoaging” in order to differentiate intrinsic from extrinsic aging of the skin.

Photoaging is a combination between solar tissue damage and the normal ageing process, and is the result of repeated exposure to various sources of ultraviolet radiations (including sun and the use of tanning beds), and chronic UV exposure, which is responsible for both aesthetic effects and clinical injuries (22, 30).

Acute exposure to UV is associated with sunburn, DNA modifications, and immune suppression, but chronic, long-term exposure can lead to premature skin aging (photoaging) and skin cancer (photocarcinogenesis) (31, 32).

Ultraviolet B – UVB (290-320 nm), ultraviolet A – UVA (320-400 nm) (33) and Infrared A – IRA (770-1400 nm) (34-37) are all associated with extrinsic skin aging processes.

The mechanisms involved in UV-induced skin aging processes are multiple and complex, respectively mitochondrial damage, arylhydrocarbon receptor (AhR) signaling, receptor-initiated signaling telomere-based DNA damage and protein oxidation (15, 38).

The most important signs of long term sun exposure (or use of tanning beds) are changes in visible colour, surface texture (22, 23) with early appearance of dyschromia and lentigines, loss of normal translucency or pink glow, the appearance of telangiectasia and purpura (22, 23), but also texture alterations such as increased roughness and the development of fine rhytides which progress to deeper folds and creases (22, 23).

Flament et al. sustain that UV exposure seems to be responsible for 80% of visible facial aging signs (21), and chronic UV exposure is associated with photo-induced damage (loss of pigmentation and vascular homogeneities, loss of skin elasticity and degradation of skin texture).

The impact of sun exposure (photoaging) on facial aging is strongly connected with chronological aging, and several authors have estimated that this ratio could be very important (39), up to 80% estimated by most authors (17, 40), while other publications have even discussed a ratio closer to 90% (41). Pigmentary changes are the more visible and most specific of these effects, therefore this aspect has been described and explained very often in the literature (39, 42-44).

**Sugar and perceived age**

A very interesting article published in 1945 highlighted the correlation between serum and cutaneous sugar levels and the fact that the levels of sugar in the skin decreased after the assumption of a hypoglycemic diet (45). Refined carbohydrates or high glycemic foods induce peaks in insulin levels, followed by generalized inflammation processes.
The correlation between diet and skin health has become an obvious subject in the past years. One important mechanism proved to be involved in this connection is represented by the advanced glycation end products (AGEs), which have the ability to exert their negative effects by impacting on both intrinsic and extrinsic skin ageing mechanisms. Food is the source of sugars, which are involved in the production of AGEs but, additionally, some foods contain preformed AGEs (46), which induce changes in cutaneous collagen, elastin and fibronectin.

Changes in collagen and elastic fibers are followed by the appearance of rhytides, sagging of skin, and loss of elasticity (Figure d). But diet, through ingestion of sugar, can accelerate these signs of aging, as it promotes cross-linking (through glycation) of collagen and elastin fibers (47).

Glucose and fructose (from diet) bond to the amino acids from collagen or elastin, leading to the production of advanced glycation end products (AGEs), process which is accelerated by hyperglycemia. Accumulation of AGEs in skin is strongly associated with increased stiffness and reduced elasticity (46).

Glycation (Maillard reaction) is a non-enzymatic reaction between digested sugars (glucose, fructose) and proteins, lipids or nucleic acids (48) that leads to the formation of advanced glycation end products (AGEs).

In the etiology of secondary complications in diabetes (49), glycation plays an important role because it induces changes in the structural and functional properties of proteins.

The glycation process was first described by Maillard in 1912, in association with diabetes mellitus and other pathologies (50). Later on, Hodge (51) identified the fact that glycation may be induced by certain methods of food thermal processing, such as roasting, frying or grilling.

AGEs formation is accelerated by hyperglycemia, cooking temperatures over 120°C, increased rate of protein turnover, presence of oxygen, reactive oxygen species, or active transition metals (52).

Collagen is a very good candidate for extensive modification through glycation (53) because it is a protein with slow turn-over rate, therefore especially susceptible to modification by glycation, and it contains several basic amino acids with free amino groups, which, as mentioned above, bond with glucose and fructose inducing AGEs. In addition, collagen in the skin has a half-life of approximately 15 years and thus can un-
Collagen represents a vital protein for the mechanical properties of the skin and is involved in several cellular processes, so the impact of glycation is more extensive.

Glycation modifies collagen's biomechanical properties with increased stiffness and vulnerability to mechanical stimuli (55), influences its ability to interact properly with surrounding cells and matrix proteins (56), and affects the cross-linking of collagen fibers (57). The process of collagen turnover and replacement with functional proteins (58) is impaired because glycated collagen is highly resistant to degradation by matrix metalloproteinases (MMPs).

Collagen is not the only protein affected by glycation, since elastin and fibronectin are also involved (59-61). Very interestingly, glycated collagen is first observed at 20 years and it reaches a 30–50% increase at 80 years of age (54, 60).

Glycation also affects proteins, lipids and nucleic acids with negative consequences on enzyme-substrate interactions, protein-DNA interactions, protein-protein interactions, DNA regulation and epigenetic modulation.

Glucose levels are connected with skin aging and extensive exposure to hyperglycemic conditions are associated with premature cellular senescence in human skin fibroblasts (62, 63).

In conclusion, glucose is associated with skin aging processes via formation of AGEs (55, 64) and the induction of premature cellular senescence (62-64). Moreover, Noordam et al showed that higher glucose levels are associated with higher perceived age, independently from confounding factors (66).

**Smoking and perceived age**

In 1856, Solly (67) published the first paper concerning the correlation between smoking and premature skin aging, showing that smokers present a sallow complexion, wrinkled skin and gaunt facial appearance. After more than 100 years, Ippen (68) reported the same correlation in German women, and in 1969 Harry Daniell recognized that smokers look older than non-smokers (69) and that wrinkles are a common clinical feature of smokers (70).

In 1985, Model (71) coined the term smoker’s face with a long list of signs typically associated with smoking for at least 10 years, and Kadunce et al. (72) were the first to evaluate a possible relationship between cigarette smoking and wrinkling, with age, sex, sun exposure and skin pigmentation.

According to Kadunce (72), smoking is an independent risk factor for premature facial wrinkling, after controlling sun exposure, age, sex, and skin pigmentation.

Helfrich (73) studied the connection between aging in photoprotected areas and smoking, concluding that, in photoprotected areas, years of smoking and number of packs smoked per day are strong indicators of premature skin aging.

Smoking is an independent important factor in skin aging, noticed in identical twin studies, which concluded that 5-year difference in smoking history is associated with changes skin (74).

Smoking is associated with wrinkling in a dose-response relationship (75), and some authors observed that smoking represents a greater contributor to facial wrinkling than even sun exposure (76). Tobacco smoke contains at least 3800 constituents (77), and the negative effects on the skin are the result of both direct action of its components on the epidermis, and indirect actions (via blood circulation) on the dermis (78, 79).

A good example of direct effect of smoke on the epidermis is the low level of moisture observed in the stratum corneum of the face, which is followed by the development of facial wrinkles (80).

Squinting of the eyes and pursing the lips represent other factors involved in wrinkle formation (81), respectively contraction of the facial muscles contribute to wrinkles formation around the mouth and eyes (crows feet) (82) (Figure a).

Cutaneous microvasculature is constricted by acute and long-term smoking (83), and nutrient deprivation in cutaneous tissues (17).

The effects on microcirculation are associated with a negative impact on wound healing (84), and face-lifting is one of the procedures preferably not performed on smokers because of the disturbed vascularization (85, 86).

Smoking accelerates the molecular mechanisms involved in aging, with reduced activities of fibroblasts, decreased collagen synthesis, induced matrix metalloproteinases expression and abnormal accumulation of elastic fibers and proteoglycans (80).
Smoking accelerates AGEs formation and increases their deposition in various tissues, including the skin (87, 88). The effects of smoking on the epidermis and dermis are similar to those resulting from chronic UV radiation exposure (89, 90).

**Skin care**

Extrinsic aging, responsible for 80% of the visible signs of skin aging (21, 91), includes – beside UV and sun exposure – pollution, smoking and diet, daily skin care habits. One of the first mention of skin care was made (92) in 1883, but we must not forget Cleopatra and her famous rituals of skin care.

Cosmetics are defined by the Food and Drug Administration (FDA) as “articles intended to be applied to the human body for cleansing, beautifying, promoting attractiveness, or altering the appearance” (93). Practically, cosmetic products must protect the skin and reinforce its beauty and attractiveness (94).

An important step was made through the association of cosmetic products with active ingredients in order to reduce the damage and aging of the skin (95).

Cosmeceuticals are topical cosmetic—pharmaceutical hybrids intended to enhance health and beauty through ingredients that influence the skin’s biological function (96), therefore cosmeceutical fits the niche between drugs and cosmetics (97). Cosmeceutical products are used not only for skin, but also for body and hair, for photoaging, wrinkles and hyperpigmentation (98).

The use of nanotechnology to develop effective cosmeceuticals is an important step forward, because these small particles are readily absorbed into the skin and repair damage easily and more efficiently (99). They can be used for perfumes that last longer, sunscreens to protect the skin, antiaging creams to fight back the years, and moisturizers to maintain skin’s hydration.

The most important products used for skin care are sunscreens (physical or chemical) because of their ability to prevent photoaging. A sunscreen is defined as the agent that protects the skin against UV damage, sunburn, wrinkles, and pigment changes.

Other important skin care products are antioxidants, like N-acetyl cysteine (NAC) (100) or vitamin C (101). Vitamin C (101) used as topical product stimulates the collagen producing activity of the dermis and leads to clinical improvement in photoaged skin.

Retinol, a vitamin A derivative, increases collagen production, glycosaminoglycan expression, procollagen I immunostaining and inhibits UV induction of collagen degrading enzymes in photoaged skin (102). Up to date, tretinoin and tazarotene are the only two retinoids FDA approved as antiaging drugs. Tretinoin induces the synthesis of collagen 1 and decreases the quantity of abnormal elastin. Tazarotene improves mottled hyperpigmentation and fine wrinkles. Higher concentrations of tazarotene demonstrated the best efficacy, found to be comparable to tretinoin (103). Regarding pregnancy, tazarotene carries a pregnancy category X and tretinoin pregnancy category C.

Peptides (fragments of amino acid chains) such as Pal-KTTS and tripeptide copper complex-GHK-copper peptide, could stimulate collagen synthesis (104).

Alpha hydroxy acids, first described in 1974 by Van Scott and Yu (105), are organic acids with the most recognizable compounds in this class represented by glycolic acid, lactic acid, and salicylic acid. They modify cell turnover and stimulate collagen synthesis by fibroblasts (106).

The skin care formulation can improve both the external aspects of skin, while also protecting its health, texture and integrity, providing moisture, nutrition and photoprotection (107).

In the specific case of female acne patients, Matsuoka et al. (108) demonstrated that providing instructions on skin care and cosmetics to female acne patients improves quality of life compared to patients to whom no instructions are given.

In conclusion, protection, prevention, cleansing and moisturizing are the key components of an effective skincare routine. Daily use of sunscreens is extremely important, because most sun damage results from everyday, incidental ultraviolet exposure.

**Stress**

Stress is associated with potentially harmful stimuli, and its negative effects are the result of physiological or psychological disturbance to homeostasis (109-111). Some factors, such as dura-
tion of the stressful condition and personal or individual reaction, are associated with variation of the body’s defense mechanisms (112).

High risk for cardiovascular diseases, immune dysfunction and neuropsychiatric diseases (113-116) are the result of chronic stress, but a direct link between psychological stress and aging is still missing (117).

However, the effect of stress could be mediated through autonomic nervous system (SAM), renin-angiotensin system (RAS) and hypothalamus-pituitary-adrenal (HPA) system, because these systems are involved in inflammation, oxidative stress and DNA damage (117).

Cumulative DNA damage, immune dysfunctions and oxidative stress are the most accepted theories regarding aging, and stress is actively involved in each of the above mentioned mechanisms (118). Genetic and cellular repair are negatively influenced by chronic immune dysfunction and reactive oxidation species (ROS), so this could be another pathway of stress implication in aging (119).

Catecholamines (epinephrine and norepinephrine) are released from the adrenal glands (109, 110) under psychological stress and the pathway stress – catecholamine release – DNA damage and immunosuppression represents one of the most well defined molecular link between stress and aging (109, 120).

Elevated cortisol levels (resulted from chronic stress) are associated with important changes in extracellular matrix, respectively suppression of hyaluronan synthase and a reduction in collagen mass (121, 122).

In conclusion, psychological stress activates the SAM, RAS, HPA and cholinergic systems, which contribute to immune dysfunction, ROS, and DNA damage (109, 110, 123, 124), with skin aging as a possible final result.

Sleep

Sleep represents an important process, which is essential for individual’s physiological, cognitive and behavioural functionality (125-128), and with an important impact on long term health (129).

Some authors revealed the increased risk of health problems and the reduction of longevity associated with small deviations from the average sleep duration in the long term (129, 130).

In the first clinical trial on sleep quality, skin function and aging (131), the authors demonstrated that increased signs of skin aging and slower recovery of the skin barrier after ultraviolet (UV) radiation are associated with poor quality of sleep. The poor quality of sleep is also associated with patient’s worse self assessment and facial appearance.

Sleep loss could also impact sexual behavior and collaboration, because sleep is connected with attractiveness, which has an important impact in many social contexts (132).

The notion of beauty sleep is actually very important, because sleep deprived people are perceived as more fatigued, less attractive, and even less healthy than when they are rested (133).

Sleep deprivation is associated with increased signs of intrinsic skin aging (fine lines, uneven pigmentation, reduced elasticity) (134), with much slower recovery rates after skin barrier disruption and lower satisfaction with appearance.

If we compare people with a normal night sleep with the same persons but sleep deprived, the sleep deprived ones look more fatigued, with hanging eyelids, redder eyes, more swollen eyes, darker circles under the eyes, paler skin, more wrinkles and fine lines around the eyes, the corners of the mouth as being more droopy and more sad (135).

In conclusion, the sleep is not connected only with good health (136, 137), but is also a link between attractiveness and health (132).

Second

Intrinsic aging is a genetic process, associated with natural degeneration of the cell functioning and loss of extracellular matrix (16), with fine wrinkles, dry, thin, and pale skin (138, 139) as the most representative markers.

In contrast with extrinsic aging, the chronological process is less clear and, to date, almost impossible to counteract. In the context of world’s population life expectancy rise, the aging process poses new challenges for both healthcare systems and society. Skin cancer incidence has increased significantly in the past decades, independently of age, as a result of increased sun exposure and lifestyle changes (2).

As the famous quote states “You never get a second chance to make a first impression”, every second is becoming ever more important in the
quest for healthy aging in general and skin aging in particular, in order to prevent chronic degenerative or malignant diseases (Figure 1), and last but not least, psychological and social burden.

CONCLUSIONS

The changes in society dynamics in the last two centuries has led to an important increase in the worldwide life’s expectancy. People are wealthier and spend more and more time engaging in leisure outdoor activities, sun bed use and sunny vacations. Besides the economic and social positive results, the unwanted long-term effects are wrinkled, saggy, uneven complexion or even tumor growths and skin cancers. In addition, the prevalence of mental disability related to old age has also increased.

In this context, skin aging occupies a central place, because it is a reflection of the general health status and, due to its visibility, it has a strong social and psychological impact. The mechanisms of extrinsic aging, most of them presented in this paper, are currently well known and also the only ones that can be counteracted. Therefore, the transition of this knowledge in the general population is of the most importance, in order to introduce healthy aging strategies, to prevent the development of chronic or malignant diseases as well as the psychological burden related to old age.

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