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Review

Anti-Aging Interventions: The Biochemistry of the Holistic Approach for Skin Aging

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Abstract

Aging is defined as the accumulation of damage, and several factors have been recognized as "factors of aging". A sensible holistic approach is appropriate to reduce the rate of accumulation of damage, while maintaining the well-being of the individual. The holistic approach of L-Raphael defines seven fields of intervention: Outdoor management, Physical management, Medical management, Nutritional management, Stress management, Aesthetic management, and Leisure management. These interventions apply to skin aging as well. Perhaps all of the known factors of skin aging induce the synthesis of intercellular adhesion molecule 1 (I-CAM 1) in endothelial cells. I-CAM 1 molecules bind circulating immune cells, who then exit the blood vessels, enter the dermis, and initiate an inflammatory process, which entails three oxidative bursts and the release of proteolytic enzymes. The micro-inflammatory theory of skin aging describes the different factors that accelerate the rate of aging and recommends biochemical interventions. These biochemical interventions fit the seven holistic managements quoted above. The principal factor of skin aging is known to be solar exposure, which generates DNA damage that triggers an inflammatory reaction. Hence the importance

of Outdoor management that recommends protecting against UV and using boosters of DNA repair such as Nicotinamide. Anoxia associated with stationary standing positions induces the synthesis of I-CAM and consequently of varicose veins and of spider veins. Well-managed physical exercise is therefore recommended to avoid the onset of anoxia. Medical management of cutaneous hygiene helps avoid the damage provoked by the response to local infections. Tailored targeting of the skin microbiome might be an additional tool in that sense. Glycated proteins induce I-CAM 1. The skin of people with diabetes is particularly affected, and nutrition management could avoid favoring conditions that facilitate protein glycation. Psychological stress provokes the release of I-CAM 1-inducing neuropeptides in the skin. Stress management is very important to maintain skin inflammation-free. The aesthetics of the skin suffer because of tobacco smoking. This is especially true when the skin is exposed to UV. Tobacco smoke is vasoconstrictive and reduces nutrient supply to the skin. Undernourished cells undergo necrosis and trigger inflammatory responses. Leisure management and balanced time use are crucial. Sleep deprivation does negatively affect skin health, and sleep is a necessary condition for global well-being.

Keywords
Skin aging; micro-inflammation; damage accumulation; holistic approach; damage removal; avoiding damage

1. Introduction

Perhaps one reason that added to the difficulties of studying aging was the lack of a proper definition of aging itself. One definition of aging was “the loss of the physiological characteristics of youth”. In the absence of a definition of youth, aging remained undefined. And indeed, if things can be defined by defining their contrary, this definition is ambiguous, because the contrary of aging is not “youth” but “eternal youth”.

To achieve “eternal youth,” one individual should be able to return to the *status quo ante* every time a molecular modification occurs, and this consideration allows one to define aging as “accumulation of damage” [1]. In this frame of definition, quantitative biochemical measurements can be performed in the course of a treatment that could thus be tested for its pro-ageing or anti-ageing properties, and kinetic studies will allow one to measure the “rate of ageing” in controlled experiments, being understood that ageing begins at birth.

Aging and longevity are sometimes used interchangeably. This is not correct: longevity is a property of the individual organisms, whereas aging applies to the organs, which can age at different rates. Sometimes the failure of an organ hinders the study of its aging. Skin is a particularly appropriate organ to study aging insofar as aged skin is not known to be a factor limiting longevity.

2. Aging and Skin-Aging

Aging is not a genetically programmed phenomenon. Aging is dictated by the environment and by individual behavior as well as by the anabolic, catabolic, and metabolic pathways that can generate oxidative stress. Genes and their products can make an individual better than another one

at removing randomly generated damage, and this can improve the overall longevity of the individual. But there is no genetically programmed generation of damage meant to obliterate the body after the transfer of the genes to offspring, as it was assumed by the Disposable Soma Theory.

On the other hand, every organ of the body is exposed to a variety of environmental and endogenous factors that can be damaging and can affect in different modes the rate of aging of every individual organ. For instance, the lungs of smokers are more exposed to cancerogenic molecules than their spleens, and the skin of sun worshippers is more exposed to ultraviolet radiation than their livers. Since damage to the skin does not affect the longevity of the individual, the studies on skin aging were the first ones to provide valuable insight into mechanisms related to the accumulation of damage.

Over the years, a variety of environmental and biochemical factors have been recognized as factors of skin aging. They all share the common feature of being able to trigger an inflammatory response, more particularly by inducing the synthesis of I-CAM 1 (Intercellular Adhesion Molecule-1) [2]. This molecule is instrumental in recruiting circulating immune cells that bind to it, perform diapedesis, cross the walls of the blood vessels, cross the dermis, and reach the cells or the other targets that must be disposed of. This path is accompanied by three oxidative bursts and by the release of proteases, first to perform diapedesis, then to cross the dermis, and finally to dismantle the target. These bursts increase the number of molecular damages provoked by the first insult.

Inflammation has been observed to play a major role in the acceleration of aging, also in other anatomical zones of the human body, for instance the joints [3] and the brain [4], and it has been observed that specific behaviors could delay or alleviate the onset or the severity of aging-linked impairment. Indeed, mental exercise was shown to delay the onset of Alzheimer's disease ([5]), and muscular exercise is used as a tool to improve the mobility and the independence of the elderly in nursing homes ([6]).

These and other behavioral observations lead L-Raphael to propose a holistic approach to the fighting of aging, based on seven behavioral determinants. The rate of aging can be reduced by appropriate management: Outdoor Management, Physical Management, Medical Management, Nutritional Management, Stress Management, Aesthetic Management, and Leisure Management. The environmental and behavioral factors of skin aging can be tackled by appropriate anti-aging biochemicals that fit in one or another of the seven determinants above, also called the "Pillars of skin beauty".

3. The Seven Ways of Managing the Factors of Skin Aging

3.1 Outdoor Management

The most efficient single factor of skin aging is, without a doubt, the exposure to ultraviolet radiation (UV). Skin chronically exposed to UV acquires so many characteristics of aged skin that historically the aging of the skin was thought only in terms of solar radiation-induced aging. Wrinkles, cutis rhomboidalis, lentigo senilis, Milian's citrine skin, and Favre-Racouchot syndrome are examples. Still, a few examples of the pleiotropic effects of excessive chronic exposure of human skin to UV radiation include UV-induced mutations that can transform normal cells into cancer cells.

When a UV photon is absorbed by DNA, it can provoke the formation of Pyrimidine Dimers (PyPy). Pyrimidine Dimers trigger the inflammatory response [7], and inflammatory cells are recruited into the epidermis to remove sun-damaged, necrotic epidermal cells. Over time, this process can

damage the dermis; newly synthesized collagen lacks a template, and the organization of elastic fibers is perturbed, resulting in loss of elasticity, thinning of the dermis, and wrinkle formation. Outdoor management recommends avoiding excess UV, either by using appropriate sunscreens or appropriate fabrics [8]. Topical sunscreens and soothing post-UV treatments should contain appropriate antioxidants such as Mannitol to eliminate the Hydroxyl radical, Vitamin E to scavenge superoxide, and β-carotene or another singlet oxygen scavenger. *In vivo*, topically administered α-tocopherol has been shown to avoid UV-induced spongiosis in human epidermis [9]. The presence of nicotinamide is also recommended insofar as Vitamin B3 activates energy production, boosts DNA repair and restores the immune response, three properties that are impaired by UV radiation [10-13].

3.2 Physical Management

Ever since ancient times, it has been reported that the secret of successful aging was *mens sana in corpore sano*, a healthy mind in a healthy body, and the body can be maintained healthy *via* physical exercise. One observation in non-physically active people is that they develop varicose veins. An elegant experiment by Remacle and coworkers [14] showed that cultured endothelial cells maintained in hypoxia synthesize I-CAM 1. Anoxia, the absence of Oxygen, is the condition experienced by endothelial cells in the veins of people constrained to a standing position without moving for many hours. So, one can conclude that when the blood is in anoxia, circulating immune cells are recruited and perform diapedesis. Once out of the vessel, they lack a target and, while missing a chemotactic signal to guide them, they digest the smooth muscle surrounding the vein. In the long term, the vessel walls collapse, and the vein becomes varicose. The same happens to people living or practicing sports at low temperatures. While practicing sport is recommended to achieve successful aging, low temperatures provoke the release of I-CAM 1 in the blood that triggers a micro-inflammatory reaction. People chronically exposed to low temperatures may develop spider veins, superficial blood vessels whose walls have collapsed, with the same consequences as described for the varicose veins, above [15].

3.3 Medical Management

It is well known that wounds and infections trigger inflammation. When not properly attended, severe wounds heal *via* a "damage and remodeling" pathway that ends with the closing of the wound and the replacement of connective tissue with scar tissue, a typical example of tissue where damage has accumulated (in scar tissue, the damage consists of the loss of the organization of the fibers). Bacterial and fungal infections trigger inflammation in the nearby tissue and, when neglected, can achieve permanent morphological damage by digging holes and leaving scar tissue. Less widely recognized is that skin is a steroidogenic tissue and that several lines of evidence indicate that the internal hormonal status is programmed to support, whenever required, a micro-inflammatory reaction. (For an early discussion of this topic, see reference [2]).

It is therefore important, to fight skin aging and maintain the skin in healthy homeostasis, to keep an open dialogue with a medical professional who can help minimize the inflammatory response. The medical professional will be able to recognize hormonal imbalance when it occurs and provide the appropriate treatment to restore the balance. In the case of wounds and infections, the medical

professional might think not only of the administration of antibiotics but also of pre- and post-biotic ingredients to hinder the growth of the pathogenic strains without affecting the microbiome.

3.4 Nutritional Management

The discovery of the role of some nutrients in human health is one of the major successes in preventative medicine in the history of science. The discovery of vitamins was the consequence of the scientific approach considering that not all diseases are provoked by a pathogenic agent, as is the case for the diseases provoked by bacterial, fungal, and viral infections, and that some diseases, some of which can have fatal issues, are the consequences of impaired metabolism because of the absence of a nutritional element.

Scurvy, Pellagra, Beriberi, Rickets, Ophthalmological problems, Anemia, and Egg White Toxicity are diseases provoked by the absence, respectively, of Vitamin C, Vitamin B3, Vitamin B1, Vitamin D, Vitamin A, Vitamin B12, and Vitamin B8, and can be cared for by administering the appropriate vitamin. Vitamin E was discovered because its absence hinders proliferation in rodents, and it was later discovered that it possesses a beneficial antioxidant efficacy in humans.

When the mechanism of action of vitamins was elucidated, it was observed that one vitamin can have more than just one effect. For instance, Vitamin C (ascorbic acid) can be used in skin care as an acid exfoliator, and can also be used as a hydro-soluble antioxidant together with the lipo-soluble antioxidant Vitamin E. In addition, Vitamin C is necessary to achieve the maturation of ceramides in the epidermis as well as collagen in the dermis.

Topical Vitamin B3 helps restore the immune response and the energy production that are impaired after UV radiation, as well as to boost DNA repair [11-13]. Vitamin D induces heat shock proteins in cultured human keratinocytes and increases the Minimal Erythema Dose in humans when applied topically [16]. Other experiments have shown that Vit D enhances apoptosis of malignant cells and has a defined anti-cancer characteristic [17].

It was also realized that, when nutritional additives are used in skin care, the topical application is the preferred route of administration, for two relevant reasons. The first reason is that, to achieve a defined concentration of the vitamin in the skin, one needs a small amount for topical application and does not need to ingest the large amounts of the vitamin which would be necessary to increase the concentration in the skin to the desired values. The second reason is that some vitamins, when ingested, do not reach the skin because they are trapped in the adipose tissue, as is the case for Vitamin E.

Some nutritional supplements can be administered by the general route and extend their benefits to the skin. Ingested β-carotene imparts a slightly orange color to the epidermis where it efficiently scavenges singlet Oxygen, the most damaging of the Reactive Oxygen Species. Ingested probiotics have been shown to reduce the pruritus and scores in patients affected by Atopic Dermatitis. *Bifidobacterium animalis subsp. lactis,* or placebo was administered by the general route to 44 A.D. patients. Pruritus was alleviated in patients receiving probiotic treatment. Anti-pruritus metabolite Kynurenic acid was found in patients with improved pruritus [18].

In addition to considering using nutritional additives, one should avoid those nutritional behaviors favoring the synthesis of I-CAM 1, such as the ingestion of excess ethanol or provoking the formation of glycated proteins. People chronically ingesting excess ethanol undergo the appearance of spider veins, superficial blood vessels whose walls have collapsed because ethanol

provokes the release of circulating I-CAM 1 with the same consequences as described for the varicose veins, above [15]. When a protein binds non-enzymatically to glucose, it acquires the capability of triggering the synthesis of I-CAM 1 [19], thus provoking the brittle skin that is an undesired characteristic of the skin of people suffering from diabetes [20, 21]. In this sense, nutritional management aimed at controlling ingested material to avoid the occurrence of well-documented, undesired biochemical phenomena is an important avenue for discovery in the fight against accelerated aging.

It should also be noted that ingesting hydrolyzed collagen only means ingesting a mixture of free amino acids whose composition mirrors that of collagen I. Once ingested, these amino acids will be metabolized and used, among other things, to produce any one of the several thousand proteins coded for by human genes. And hydroxyproline, that is the amino acid resulting from collagen I maturation *via* the Vitamin C-catalyzed hydroxylation of proline, will not be used to make new collagen, but will enter the blood circulation, will be filtered by the kidneys, and will be excreted in the urine.

3.5 Stress Management

Psychological stress is known to affect the overall health of the individual, and a stressed individual can be identified because of characteristic skin aspects such as dark circles around the eyes and a pale-yellowish skin tone. The link between psychological stress and skin damage was pointed out (see, for instance, [15]). As much as hurt limbs release nervous signals that reach the brain to signal that damage is occurring and that some reaction has to be considered, so much stressed brain releases neuropeptides that, from nerve endings, enter the skin, which is a highly innervated tissue. Free neuropeptides in the skin can trigger the synthesis of I-CAM 1 and recruit circulating immune cells in the dermis. As is the case for anoxia, immune cells recruited by free neuropeptides do not have a target, lack a chemotactic signal to follow, and exert their destructive action randomly in the dermis, thus accelerating the process of skin aging. A correlation was found between psychological stress and poor skin conditions [22, 23]. Topical anti-inflammatory treatment can help protect against skin damage from psychological stress. Still, a proper organization of one's life and priorities is certainly helpful in reducing the extent of stress and therefore of the rate of skin aging. As a matter of fact, stress might induce people to smoke cigarettes and/or to consume alcoholic beverages without moderation. We have discussed above the effects of ethanol consumption. Cigarette smoke, in addition to poisoning the lungs and being a complete carcinogen, is a vasoconstrictive factor that limits the delivery of circulating nutrients to the skin. As such, it impairs skin homeostasis and might provoke cell death with the consequent triggering of an inflammatory reaction. It has been clinically shown that cigarette smoking exacerbates the skin aging effects of solar exposure [24].

In general, cigarette smoking affects one's skin. It exacerbates undesired conditions such as psoriasis, chronic dermatoses, polymorphous light eruptions [25], and the biochemical analysis of the skin of smokers has uncovered a remarkable effect of smoking on proteins and lipids participating in the so-called barrier function [26].

3.6 Aesthetic Management

Visible signs of aging are “molecular damage that became visible”. Seborrheic keratoses can be removed by delicate scalpel handling, and lentigo senilis can be removed by appropriate laser ablation. Dermabrasion is the method of choice to improve the appearance of lentigines and scars on the skin [27], and cryosurgery [28] can also be utilized in this respect. Fat mobilization can be tackled by injection of appropriate fillers, and the removal of wrinkles might require plastic surgery. These are extreme interventions consequent to the neglect of one’s skin over the years. These interventions will never be successful when the individual subject to these interventions maintains deleterious habits such as sun worshipping, cigarette smoking, alcohol drinking, abusing psychotropic substances, and the like.

3.7 Leisure Management

One might expect that indulging in leisure versus being a workaholic should improve one’s overall health. That can be true provided one follows an appropriate time management and does not “burn the candle from both ends”. This is to say that sleep should not be neglected: the absence of sleep is deleterious for one’s skin [29, 30]. Melatonin is both an excellent antioxidant and anti-inflammatory drug [31] and is being discussed as an excellent tool against skin aging [32]. Since it is the molecule that signals sleep, Melatonin is used in creams to be topically applied before bedtime. Generally, one applies 1 gram of cream on one’s face. This means that when the cream contains 1% melatonin, 10 mg of the molecule are applied. This quantity corresponds roughly to the amount of melatonin secreted nightly by the pineal gland, and its beneficial effects have been tested clinically.

4. Conclusion

Eternal youth has been defined above as the capability to return to the *status quo ante* after every molecular modification. Such a thing is undesirable insofar as it is associated, for instance, with the incapacity of memorizing and of reasoning. The goal of the fight against aging is not to reverse the clock: that is a meaningless buzzword! The fight against aging is to achieve what is called “successful aging”. This consists of *adding life to our years, not years to our lives*. This is why the discipline of Molecular Gerontology was created by the European Network for the Study of the Biology of Aging. The work presented in this paper summarizes the biochemical reasons for the commonsense, experience-based suggestions to maintain the body and the skin in good shape, and recommends a few experimentally proven, effective treatments to limit the rate of skin aging.

Author Contributions

Both authors discussed the topics to be described in the review. Dr Giacomoni wrote the text and discussed it thouroughly with Dr Morganti.

Competing Interests

The authors have declared that no competing interests exist.

AI-Assisted Technologies Statement

The authors did not use generative artificial intelligence in the writing of this manuscript.

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