Vitamin D on Skin Aging

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The normal vitamin D3 status is important for a general prevention of premature aging maintaining a healthful skin aging. Vitamin D3metabolites including its classical (1,25(OH)2D3) and novel (CYP11A1-intitated) D3hydroxyderivatives exert many beneficial protective effects on the skin, which could influence the process of premature aging via many different mechanisms, leading to a delay or attenuation of both chronological skin aging and photoaging. Skin-resident cells (keratinocytes, fibroblasts, and sebocytes) are capable of locally activating vitamin D3and exhibiting a diverse biological effect such as photoprotection and immunosuppression, similar to the UVR-induced one.

Keywords: skin aging ; photoaging ; skin immune responses ; vitamin D ; vitamin D metabolites ; photoprotection

1. Introduction

Skin, like any other organs, undergoes progressive decline in its physiological, morphological, and functional features during aging [1,2,3,4]. The phenomenon of aging is natural and genetically predisposed. The functions of the skin are crucial for the homeostasis and survival. As the largest organ in the human body, the skin, together with the hypodermis (subcutaneous fat), is both the source and the target for several hormones and neuromediators [5,6,7,8,9,10,11,12,13,14,15,16,17], making it an independent peripheral endocrine organ [5,18]. The skin has also the capacity of producing the prohormone vitamin D and transforming it to active metabolites [19,20,21,22,23,24,25], which can exert several different effects on the main skin cells (keratinocytes and fibroblasts) [20,25,26,27,28,29] and immune cells [4,28,30,31] via the activation of the nuclear vitamin D receptor (VDR) [29,32,33,34,35]. Vitamin D plays a pivotal role in skin homeostasis contributing to its barrier function [20,29,36,37,38]. Moreover, as an essential part of a functioning immune system, active forms of vitamin D modulate the cutaneous immunity [8,30,39].

The gold standard of analyzing a vitamin D status is by measuring its major circulating metabolite, 25-hydroxyvitammin D 3 (25(OH)D 3), via high-performance liquid chromatography (HPLC) or liquid chromatography tandem–mass spectrometry (LC-MS/MS) [40,41,42]. Recently, a novel sensitive and specific LC-MS/MS method of the simultaneous measurement of 13 circulating metabolites of vitamin D 3 and D 2 was presented [43].

With advancing age, the capacity of the skin to produce vitamin D 3 decreases (irrespective of the season), and the degradation of its active forms increases [59,60]. It was found that the concentration of the precursor of vitamin D 3 in the skin, 7-dehydrocholesterol (7-DHC), declines approximately by 50% from age 20 to age 80 years [59]. Several other factors contribute to the vitamin D deficiency state in accelerated age, including limited sun exposure, insufficient dietary intake of vitamin D, or diseases causing malabsorption. The vitamin D deficiency, which is common in advanced age, can decrease the important physiological functions of the skin such as protection from the environment and prevention of cancer development [25,39,61,62,63,64,65,66].

In this review, we aimed to discuss the significance of vitamin D in the skin aging process.

2. Skin Aging—Your Skin Can Reveal Stories

The most prominent external stressors affecting skin and causing its premature aging include ultraviolet (UV) radiation [76,77], ambient pollutants [78,79,80,81,82], and smoking [57,83]. The continuous exposure of the skin to these environmental insults stimulates the production of reactive oxygen species (ROS) and generate oxidative stress [84,85]. The environmental factors can also cause an impairment of the epidermal barrier function [69] and alterations in skin microflora [86,87], leading to significant morbidity [2,88].

Chronic sunlight exposure, together with the persistence of cellular senescence, can drive an impaired regenerative capacity of the skin, chronic inflammation, and photoaging, which correlates with enhanced cancer risk [77,105,106,107]. Thereby, photoaging results in premature skin aging. Although some aging mechanisms share several similarities or

overlapping, photoaged skin differs from physiologically aged skin in the ECM changes. Photoaged skin is characterized by degraded collagen and accumulated aberrant elastin fibers and glycosaminoglycans, whereas physiologically aged skin is presented by the atrophy of dermal structures [108].

The negative impact of ambient pollutants on human health and the human skin is of growing concern [109]. Ozone (O 3) from the smog and PM, primarily contacting with the skin, is capable to stimulate ROS production and generate oxidative stress, leading to phenotypic features of extrinsic aging [69]. It was found that chronic exposure to PM leads to pigment spots and deep nasolabial folds [110,111]. Moreover, ultrafine particles (<0.1 μm) can penetrate tissues and localize in the mitochondria, causing an aberrant mitochondrial function because of the oxidative processes [112]. Additionally, the photo-pollution exposure may aggravate UVR-mediated skin aging [113].

Indeed, the human skin aging is mainly driven by oxidative events. An extensive ROS production and insufficient scavenging activity or a mitochondrial dysfunction are crucial events in oxidative stress-induced skin aging. The high levels of ROS lead to oxidative damage of lipids, proteins, genomic, and mtDNA, and also can deplete and damage the antioxidant defense systems of the skin (both non-enzymatic and enzymatic one) [85,127].

3. Effects of Vitamin D3 on the Skin

Summarizing, the biologically active classical and novel vitamin D 3 metabolites exert different affinities to multiple receptors in the skin and through their modulation they can influence different cutaneous pathologies. In addition to act on the VDR, the active forms of vitamin D can act on alternative nuclear receptors including RORs, AhR, LXR, and 1,25D 3-MARRS receptor. The active forms of vitamin D 3 have various functions, which partially overlap in their anti-inflammatory, antimicrobial, antiproliferative, prodifferentiation, antifibrotic, and antioxidative effects on the skin [20,38,63,141,145,178]. Along with the best characterized 1,25(OH) 2D 3, CYP11A1-derived products of vitamin D 3 and L 3 exhibit photoprotective properties against UVR-induced skin damage (**Figure 1**) [37,61,179,180,181,182,183].

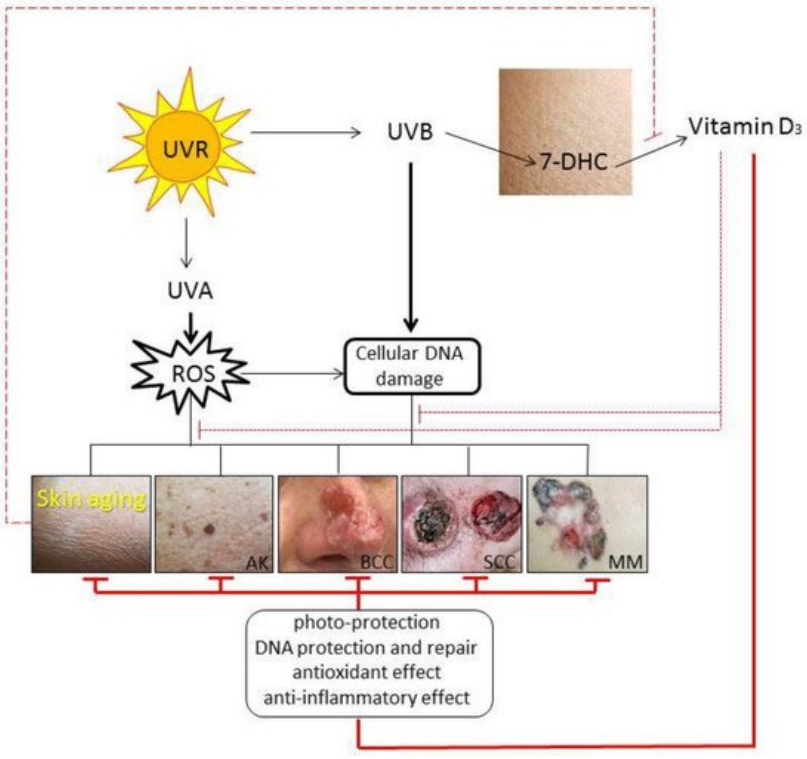

Figure 1. Photoprotective effects of vitamin D_3 in premature skin aging and cutaneous cancerogenesis. Abbreviations: 7-DHC, 7-dehydrocholesterol; AK, actinic keratosis; BCC, basal cell carcinoma; SCC, squamous cell carcinoma; MM, malignant melanoma.

The normal vitamin D 3 status is important for a general prevention of premature aging maintaining a healthful skin aging [213,214]. Vitamin D 3 metabolites including its classical (1,25(OH) 2D 3) and novel (CYP11A1-intitated) D 3 hydroxyderivatives exert many beneficial protective effects on the skin, which could influence the process of premature aging via many different mechanisms, leading to a delay or attenuation of both chronological skin aging and photoaging. Skin-resident cells (keratinocytes, fibroblasts, and sebocytes) are capable of locally activating vitamin D 3 [23,36,215] and exhibiting a diverse biological effect such as photoprotection and immunosuppression, similar to the UVR-induced one [179,216].

Chronic UVR irradiation, mainly UVB [232] and UVA [233], induces DNA damage and the formation of CPDs that potentially lead to premature skin aging and carcinogenesis. CYP11A1-derived D 3 and L 3 hydroxyderivatives, along with 1,25(OH) 2D 3, demonstrate photoprotective and reparative properties by increasing the expression and phosphorylation of p53 with its translocation to the nucleus [61,229,234,235]. The P53 gene family, in particular its isoform p63, might be an important molecular target for vitamin D action in premature aging and cancer [236], which are promoted by similar mechanisms [237].

Additionally, 1,25(OH) 2D 3 can induce rapid and dose-dependent reduction in skin cell apoptosis, and it can increase CPDs repair and decrease the oxidative DNA damage through non-genomic energy-conserving autophagy and mitophagy [227], thus contributing to the intrinsic skin photoprotection mechanism [242].

4. Conclusions and Future Perspectives

Vitamin D 3 and its active metabolites exert a variety of antiaging and (photo) protective effects on the skin. These are achieved through immunomodulation that include anti-inflammatory actions and regulation of keratinocytes proliferation and differentiation program to build the epidermal barrier necessary to maintain skin homeostasis. In addition, they induce antioxidative responses, inhibit DNA damage and induce DNA repair mechanisms to attenuate premature skin aging and cancerogenesis. Similar actions can be assigned to lumisterol metabolites. Therefore, active forms of vitamin D 3 including its canonical (1,25(OH) 2D 3) and noncanonical (CYP11A1-intitated) D 3-hydroxyderivatives as well as L 3-derivatives are promising agents for the prevention, attenuation, or treatment of premature skin aging, when applied topically. It is expected that they will attenuate photoaging and perhaps repair the existing damage induced by external stressors. The mechanism of action would involve interaction with nuclear receptors including VDR, AhR, LXR, reverse agonism on RORα and RORγ, and nongenomic actions through 1,25D 3-MARRS receptor and interaction with the nongenomic binding site of the VDR. The regulatory mechanism affected by D 3 and L 3 derivatives would include the activation of Nrf2 and p53 and the downregulation of NFκβ signaling pathways or the regulation of mitochondrial functions. To prevent skin aging, vitamin D 3 and lumisterol or their derivatives could be administrated orally and/or topically. Other forms of parenteral application of the vitamin D 3 precursor should be considered to avoid channeling its metabolism to 25(OH)D 3, which is not recognized by CYP11A1 enzyme [243]. The efficacy of topically applied vitamin D 3 and L 3 derivatives needs further clinical evaluation in future trials.

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