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Beneficial effects of UV radiation other than via vitamin D production

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Most of the positive effects of solar radiation are mediated via ultraviolet-B (UVB) induced production of vitamin D in skin. However, several other pathways may exist for the action of ultraviolet (UV) radiation on humans as focused on in this review. One is induction of cosmetic tanning (immediate pigment darkening, persistent pigment darkening and delayed tanning). UVB-induced, delayed tanning (increases melanin in skin after several days), acts as a sunscreen. Several human skin diseases, like psoriasis, vitiligo, atopic dermatitis and localized scleroderma, can be treated with solar radiation (heliotherapy) or artificial UV radiation (phototherapy). UV exposure can suppress the clinical symptoms of multiple sclerosis independently of vitamin D synthesis. Furthermore, UV generates nitric oxide (NO), which may reduce blood pressure and generally improve cardiovascular health. UVA-induced NO may also have antimicrobial effects and furthermore, act as a neurotransmitter. Finally, UV exposure may improve mood through the release of endorphins.

Introduction

Solar ultraviolet (UV) radiation has been used since ancient times to treat various diseases. This has a scientific background in the fact that a large number of molecules (chromophores) in different layers of the skin interact with and absorb UV. These interactions may have both positive and negative biological implications. In this review we only concentrate on the positive effects other than those directly related to vitamin D production.

Cosmetic Tanning

Some Africans and Asians avoid sun and use bleaching products to lighten skin, while many Caucasians seek the sun for tanning to achieve a bronze skin to "look good."[1–3] UV radiation from the sun or from artificial sources increases skin pigmentation.[4,5] There are three phases of tanning: immediate pigment darkening (IPD), persistent pigment darkening (PPD) and delayed tanning (DT).[6,7] IPD occurs during the first minutes of exposure to UVA, and then fades within few hours.[6,8] PPD appears within hours of higher doses of UVA exposure and persist up to several days or weeks.[7,9] DT develops over 3–7 days after UVB exposure, and then remains for weeks.[10] The mechanisms of UVA- and UVB-induced pigmentation are different.[11] UVA induces IPD and PPD through oxidation of pre-existing melanin or melanogenic precursors.[6] IPD is oxygen dependent, and reactive oxygen radicals are considered to be responsible for this process.[7,12,13] PPD is also due to the upward movement of melanosomes toward the surface of the skin.[10] Persons with lightest skin (skin type I) do almost not tan, while IPD and PPD are strongest in moderately and darkly pigmented skin.[14,15] DT results from synthesis of melanin in the melanocytes, followed by melanin distribution to neighboring keratinocytes.[6,7,10]

The levels of UV radiation from the sun vary with latitude, altitude, weather, time of day and season of year. Facultative pigmentation (i.e., that induced by UV) decays during winter months at higher latitudes due to low temperatures and low UV levels. Some people want to maintain facultative tanning throughout the year for cosmetic purposes. They often use sunbeds or travel south for sunny vacations. Indoor tanning is popular, not only among Caucasians in countries with low annual UV levels (Northern countries),[16,17] but also in countries with high annual UV levels (Australia).[18,19] Sunbeds have several times higher UVA fluence rates than found in solar radiation under relevant conditions,[19,20] and, due to this, IPD and PPD are pronounced after sunbathing. Additionally, under certain conditions UVA-induced pigmentation lasts longer than UVB-induced DP.[9] This can be partly explained by the facts that UVB-induced tanning is located in the upper layers of the epidermis, while UVA-induced tanning is primary localized in the basal cell layer.[11] However, high doses of UV radiation from sun or indoor tanning devices lead not only to tanning, but also to erythema, local and systemic immunosuppression, DNA damage, photoaging and photocarcinogenesis.[17,21,22]

Photoprotection

UV radiation from sun and sunbeds is the main risk factor for skin cancer.[23–27] Human skin adapts to chronic UV exposure by increasing melanogenesis, thickening of the horny layer, activating of antioxidant molecules, the DNA repair systems, and secretion of cytokines.[28–31]

Melanin provides protection of structures in and below the skin against free, UV-induced radicals. Thus, it acts as a direct shield

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from UV and visible light radiation. UV radiation causes DNA damage in the nuclei of keratinocytes, resulting in activation of p53, which transcriptionally upregulates the expression of the gene encoding proopiomelanocortin (POMC).[32] The POMC precursor polypeptide is processed into several bioactive products, including α-melanocyte-stimulating hormone (α-MSH), adrenocorticotropic hormone (ACTH) and β-endorphin.[32,33] After secretion, α-MSH binds to the melanocortin 1 receptor (MC1R) located on melanocytes and activates melanin production.[32,33] The anti-inflammatory effects of α-MSH and ACTH may help relieve irritation and local inflammation in UV-exposed skin.[33,34]

Although UVA- and UVB-induced pigmentations are visually identical, only UVB-pigmentation results in a protection which is as large as corresponding to a factor of about 2 to 3 against DNA photodamage and erythema.[11,35,36] This protection is equivalent to using a sunscreen with a sun protection factor (SPF) of 2 to 3.[4]

UVA tanning is not involved in melanin production, nor in photoprotection.[7,11,36] The evolutionary role of IPD still remains unknown. Recently we have proposed that the biological role of IPD is protection of folates against photodegradation, which would be of large evolutionary importance for early hominids.[37] We found that IPD had an absorption spectrum covering a number of endogenous photosensitizers in skin, such as porphyrins and riboflavin.[38]

UVB induces hyperkeratosis and thickening of the stratum corneum, thus reducing UV transmission.[30,31,39] However, the relative importance of stratum corneum thickening and pigmentation in photoprotection is debated.[30,31,39]

UVA photons excite endogenous chromophores (photosensitizers) in human skin which lead to generation of reactive oxygen and nitrogen species that can cause damage by themselves or enhance the damaging effect of UVB. UVA can cause immunosuppresion in human skin. A number of recent studies demonstrate that UVA radiation can provide immunoprotection and also inhibit UVB-induced immunosuppression through modulation of various cytokines and enzymes, such as expression of heme oxygenase-1 (HO-1).[40] UVA exposure increases expression of HO-1 that mediates antioxidant, anti-inflammatory, anti-apoptotic and anti-proliferative effects, and protects cells and tissues against oxidative stress and tissue injury.[40,41]

Actinic or solar elastosis is an accumulation of abnormal elastic tissue in the upper and middle dermis, which may be related to activation of the human elastin promoter by UV radiation or elastin degradation due to an influx of neutrophils that diffuse to the dermis in response to cytokine production after UVB exposure.[42] Solar elastosis is generally considered to be a biomarker for cumulative sun exposure.[42] However, solar elastosis is a protective factor for sporadic basal cell carcinoma.[43] Furthermore, it has been positively associated with melanoma survival.[44] Prognosis for melanoma of the back (low solar elastosis) is worse than that for the face (high solar elastosis).[45–47] Melanomas with elastosis occur at later ages than melanomas without elastosis.[48] Consequently, sun exposure is associated with increased survival from melanoma.[44] Melanoma is more frequent among people with indoor occupations than among people getting large accumulated UV exposures (farmers, fishermen, etc.).[49] Chronic UV exposure reduces and/or delays the development of melanoma.[47] Holiday sun exposure is not always associated with an increased melanoma risk, and even a protective effect of regular weekend sun exposure has been observed, particularly for limb tumors.[50] Outdoor activities (without sunburn, associated with increased risk of melanoma) in childhood are associated with a lower risk of melanoma.[51] The observed effects could be mediated independently by photoadaptation (development of solar elastosis) and by higher vitamin D levels.[47,50,52]

Mood Enhancing Effects

Most people judge sun exposure in non-erythemic doses as pleasant. Exposure to sunlight has been linked to improved energy and elevated mood.[53] Tanners feel more relaxed and less tense than non-tanners.[54] The belief that people look better with a tan may partly explain this phenomenon.[53] Additionally, exposure of keratinocytes to UV radiation leads to production of an opioid β-endorphin via stimulation of the POMC promoter.[55–57] This β-endorphin released into the blood during UV exposure may reach the brain in sufficient concentrations to induce mood enhancement and relaxation.[58] However, only one study has demonstrated increased β-endorphin levels in blood after UV exposure of healthy volunteers[59] while three other studies have not found increased levels of β-endorphin.[60–62] At the same time even anxiety associated with the needles used for blood sampling could affect endorphin levels.[62] Other indirect evidences also suggest that endorphins are released to blood. It has been demonstrated that frequent tanners almost always choose sunbed emitting UV radiation.[54] In another study was shown that the use of the opioid antagonist naltrexone, used for treatment of opioid dependence, reduced UV preference and even induced withdrawal symptoms in frequent tanners.[63] Chronical and frequent exposure to UV radiation may result in a tanning addiction and in a pattern of behavior similar to other types of substance-related disorder.[3,64–66]

Phototherapy

Already several thousands of years ago sunlight (heliotherapy) was used to treat a variety of skin conditions in Egypt, Greece and Rome.[67] At that time, the importance of UV radiation was not recognized, because UV rays were not discovered before 1801.[67] In 1903, Niels Ryberg Finsen was awarded the Nobel Prize "in recognition of his contribution to the treatment of diseases, especially lupus vulgaris, with concentrated light radiation, whereby he has opened a new avenue for medical science." Finsen discovered that UV radiation was beneficial in treating lupus vulgaris, a skin condition caused by *Mycobacterium tuberculosis*. UV radiation was the only effective treatment against tubercle bacilli in the skin before the introduction of antituberculous chemotherapy in the 1950s.[68,69] Finsen believed that UV radiation killed *Mycobacterium tuberculosis*, but the detailed mechanism of action is not known.[68] In 1958 it was demonstrated that the UV radiation in Finsen's lamps can lead to vitamin D production.[70,71] It has been suggested that increased levels of vitamin D could be involved in bacterial killing, and it was

considered as the mechanism of effect of UV therapy on lupus.[70,71] However, a few years ago Wulf's group in Denmark tried to find which wavelengths could be emitted by Finsen's equipment and which mechanisms could lead to the photoinactivation of *Mycobacterium tuberculosis*.[68] Their experiments have suggested that only glass quartz was used in the treatment. This means that only wavelengths longer than 340 nm (UVA) could be emitted through Finsen's lenses.[68] They have also detected that *Mycobacterium tuberculosis* contains the water soluble porphyrin coproporphyrin III which has its highest absorption peak at 398 nm (the Soret band).[68] Exposure of coproporphyrin III to UVA and blue light leads to the production of singlet oxygen and the photoinactivation of bacteria in the process known as photodynamic therapy (PDT). A mechanism like that operating in PDT seems to be a most plausible explanation why Finsen's therapy worked.[68]

Modern phototherapy. In our days phototherapy is a valuable option in the treatment of many psoriatic and nonpsoriatic conditions, including atopic dermatitis, sclerosing skin conditions such as morphea, scleroderma, vitiligo, and mycosis fungoides.[72] Phototherapy is the treatment of certain skin disorders with UV radiation which can be produced by the sun, fluorescent lamps, short arc lamps with UV filters and lasers. Depending on the shape of the spectrum of radiation emitted by the source, phototherapy can be divided into broadband UVB (290–320 nm), narrow band UVB (310–315 nm), monochromatic UVB (308 nm from an excimer laser), broadband UVA (320–400 nm) and UVA-1 (340–400 nm).[73,74] For a detailed review see references 72–79.

Mechanism of action. UVB radiation reaches the epidermis and the upper dermis where it is absorbed by DNA, trans-urocanic acid (trans-UCA), and cell membranes.[73] Absorption of UVB by nucleotides leads to the formation of DNA photoproducts, primarily pyrimidine dimers. UVB exposure reduces the rate of DNA synthesis. In addition, UVB radiation causes photoisomerization of trans-UCA to cis-UCA which has immunosuppressive effects. Furthermore, UV radiation can affect extranuclear molecular targets (cell surface receptors, kinases, phosphatases, and transcription factors) located in the cytoplasm and in the cell membanes.[73]

Keratinocytes, circulating and cutaneous T lymphocytes, monocytes, Langerhans cell, mast cells and fibroblasts are all targeted by narrowband UVB.[73] Narrowband UVB induces also local and systemic immunosuppressive effects which may particularly contribute to the beneficial effects of this light source.

UVA radiation penetrates more deeply into the skin than UVB, and reaches not only epidermis, but also dermis with blood vessels affecting dermal dendritic cells, dermal fibroblasts, endothelial cells, mast cells, and granulocytes.[80] UVA radiation is absorbed by pyridine nucleotides (NAD and NADP), riboflavins, porphyrins, pteridines, cobalamins and bilirubin.[80] Porphyrins and riboflavins are photosensitizers. UVA effects are dominated by indirect DNA damage caused by reactive oxygen species such as singlet oxygen. The ability of UVA radiation to cause skin erythema is approximately 10^3 to 10^4 times lower than that of UVB. As UVA-1 is even less erythematogenic than broadband UVA, much higher doses of UVA-1 can be tolerated by the patients. UVA-1 phototherapy works mainly through induction of apoptosis of skin infiltrating T cells, T-cell depletion and induction of collagenase-1 expression in human dermal fibroblast.[40,81]

Psoriasis. Traditionally, broadband UVB phototherapy has been used to treat psoriasis, which is an inflammatory skin disease, characterized by keratinocyte hyperproliferation with 1–2% prevalence in the general population. However, now more often narrowband UVB or monochromatic UVB are used for the clearance of psoriasis. Narrow-band UVB clears psoriasis faster and produces longer remissions than broadband UVB.[74,77] Action spectra for UV-induced erythema, DNA damage, photoimmunesuppression, squamous cell carcinoma and vitamin D synthesis are very similar, all in the UVB spectral region of 280–310 nm.[38] Narrowband UVB do not contain the most erythemogenic and carcinogenic wavelengths. Even though UVB phototherapy is a standard treatment for psoriasis, the mechanisms underlying its efficacy are incompletely understood. UVB exposure, via induction of DNA photoproducts, is thought to inhibit cell proliferation transiently. It has therefore been speculated that the therapeutic effectiveness of phototherapy mainly relates to its antiproliferative properties.[73,82] Additionally, UVB phototherapy is effective for psoriasis by inhibiting cutaneous immune functions.[74] Recently, vitamin D has been brought in focus.[76,83–85] The beneficial effect of UVB exposure in patients with psoriasis may be explained, at least in part, by the induction of vitamin D, as topical vitamin D derivatives are also effective.[76,83–85] Heliotherapy, broadband and narrowband UVB phototherapy all increase serum 25-hydroxyvitamin D (25(OH)D) levels.[83–85]

Vitiligo. Vitiligo is a depigmentation skin disorder with an incidence rate of between 0.1% and 2% in the general population.[86,87] The cause of vitiligo appears to be a combination of genetic effects in both the immune system and in the melanocytes, both resulting in melanocyte destruction.[88] Due to the complexity of the disorder a lot of different treatments are recommended, including phototherapy with narrowband UVB radiation and excimer laser (308 nm) with or without topical application of calcineurin antagonists (tacrolimus and pimecrolimus).[86,87] Phototherapy for vitiligo was initiated by the observation that sun-exposed lesions tend to show follicular repigmentation during the summer months in many patients.[89] This effect is transient but repeatable.[89] The mechanism of action of phototherapy on patients with vitiligo has not been completely elucidated. The melanocytes are destroyed in the epidermis of patients with vitiligo, while the melanocytes in the outer root sheaths of hair follicles are not affected. Repigmentation after phototherapy may be initiated by activation, proliferation, and migration of these melanocytes to the epidermis, where they form perifollicular pigmentation islands.[86] Furthermore, the immunosuppressive action of UVB phototherapy may also contribute to the mecanisms of action.

Atopic dermatitis. Atopic dermatitis is a chronic inflammatory skin disease. The estimated prevalence in the United States is around 17%.[90] Narrowband UVB und UVA-1 are the most frequently applied treatment regimens in atopic dermatitis and in other T cell mediated inflammatory skin diseases. UV radiation

induces direct phototoxic effects on T-lymphocytes. Thereby, it causes a gradual reduction of the inflammatory infiltrate and a concomitant improvement of patients' skin.[73,91]

Localized scleroderma. UVA-1 phototherapy is used to treat localized scleroderma, also known as morphoea.[92] The precise action of UVA-1 phototherapy remains obscure. UVA-1 phototherapy may reduce the number of Langerhans cells and mast cells.[92]

Pain Relief

Sunbathing or tanning beds seem to have a potential to reduce pain in patients with fibromyalgia.[54] Patients with the chronic pain condition fibromyalgia have reported a greater short-term decrease in pain after exposure to UV compared with non-UV radiation exposure.[54]

UV Effects on Skin Barrier Functions

Skin exposed to UVB and UVA is more resistant to primary irritants, which may indicate the improvement of skin barrier functions.[30,93,94] Such an improvement is not due to epidermal hyperplasia, which does not appear after UVA exposure, and neither is it due to increase in lipids in the stratum corneum as has been believed earlier.[30,93,94]

UV Effects on Other Diseases

The risk and/or mortality of autoimmune diseases (multiple sclerosis, asthma and type 1 diabetes mellitus), cardiovascular diseases (hypertension and myocardial infarction), several cancers (bladder, breast, cervical, colon, endometrial, esophageal, gastric, lung, ovarian, pancreatic, rectal, renal and vulvar cancer) and other conditions increases with latitude (decreasing UV dose) of residence.[95,96] Generally, it is believed that the increased risk of these diseases is due to lack of UVB radiation which leads to vitamin D deficiency. No mechanism other than vitamin D production has been proposed to explain the effects of UVB exposure on reducing these disease risk.[96] A growing amount of molecular data demonstrates the involvement of vitamin D in cell proliferation, differentiation, apoptosis, angiogenesis, immune and inflammatory responses.[97,98] These findings provide a strong basis for epidemiological evidences documenting that vitamin D deficiency may be a risk factor for development and progression of some types of cancer. Other molecular mechanisms may explain the role of vitamin D in cardiovascular diseases, diabetes mellitus, cancer, multiple sclerosis, allergy, asthma, infection, muscle weakness, depression, etc.[99,100] Several studies found association between low vitamin D levels and hypertension, coronary artery calcification, heart disease and several cancers.[101–106] Recent meta-analyses have demonstrated reduction in mortality and cardiovascular risk associated with vitamin D.[101–107] Zitterman et al. have performed the meta meta-analysis of prospective cohort studies and found a nonlinear decrease in mortality risk as circulating 25(OH)D increases, with optimal concentrations 75–87.5 nmol/.[106] Some studies do not support any association between 25(OH)D and cancer risk nor total cancer mortality, except colorectal cancer, breast cancer risk or mortality.[108–111] The evidences of whether vitamin D supplementation may prevent cancer, cardiovascular diseases, and mortality are contradictory.[112–114] Vitamin D has been associated with increased survival rates for several types of cancer.[115,116] Additionally, there is no trend in serum 25-hydroxyvitamin D (25(OH)D) level with latitude.[117] This may be due to imprecise and unreliable vitamin D measurements.[118] It is possible that the reported protective effect of sunlight on the mentioned types of cancer and other diseases are not mediated only through vitamin D but also through other and as yet unknown mechanisms.[110,119,120] A few years ago Becklund et al.[120] demonstrated that vitamin D supplementation is less efficient than UV radiation in suppressing multiple sclerosis in animals. Lukas et al.[121] found in a multicenter case-control study that multiple sclerosis risk decreased with increasing serum 25(OH)D levels, measured at the time of the first demyelinating events, and with increasing UV exposure, estimated by questionnaires or by the degree of actinic damage. Lukas et al.[121] suggested that sun exposure and vitamin D status may play independent roles for development of central nervous system demyelination. A recent population-based case-control from Sweden[122] suggested that UVR exposure may also exert a protective effect against developing multiple sclerosis via other pathways than those involving vitamin D. The role of UV and vitamin D should be evaluated in clinical trials for multiple sclerosis prevention.

African Americans at higher latitudes have a higher rate of vitamin D deficiency than Caucasians have.[119,123,124] However, Caucasians have about two times higher rates of multiple sclerosis than African Americans have.[119] (At the same time, the course of disease is more aggressive among African Americans.)[125] Therefore, the involvement of additional mechanisms, rather than only vitamin D synthesis, has been proposed.[119,120] Other mediators than vitamin D that are induced by UV radiation may be more important for UV-mediated immunomodulation and may be involved in the prevention and progression of immunopathological diseases (psoriasis, multiple sclerosis and asthma), non-immunopathological diseases (cancer) and during infection.[119,126,127] It is clear that exposure to UV radiation is an important environmental interference with immune functions[126,127] which may play important roles in prevention, initiation or progression of several diseases.

Beneficial Roles of UVA-Induced Nitric Oxide ($NO^{\cdot}$) on Human Health

A few years ago it was demonstrated that nitric oxide ($NO^{\cdot}$), a gaseous free radical, is non-enzymatically induced in skin by UVA.[128–130] However, UVA-induced $NO^{\cdot}$ and its influence on human physiology and pathophysiology are not so well studied as the influence of $NO^{\cdot}$ produced enzymatically by NO synthases.[131] $NO^{\cdot}$ is able to diffuse rapidly across cell membranes, and, depending on the conditions, is able to diffuse more than several hundred microns. The biological half-life of $NO^{\cdot}$ is in the range from 1 ms to 2 sec, depending on superoxide ($O_2^{\cdot-}$), antioxidants

and oxygen concentrations.[2] The biological effects of $NO^{\bullet}$ are mediated through the reaction of $NO^{\bullet}$ with a number of targets, such as haem groups, cysteine residues and iron and zinc clusters. This wide range of targets for $NO^{\bullet}$ helps to explain the multiple roles it plays, including vasodilatation, immune defense, neurotransmission, regulation of cell death (apoptosis) and cell motility. Due to the importance of $NO^{\bullet}$, abnormal regulation of the concentration of UV-induced $NO^{\bullet}$ may affect a number of important biological processes.

The rapid release of $NO^{\bullet}$ following UVA exposure suggests the existence of latent stores. It is well known that part of the endogenously produced $NO^{\bullet}$ is converted into nitrite (NO_2^-), nitrate or nitrosothiols. Earlier it was thought that these compounds are inert end products of endogenous $NO^{\bullet}$ metabolism. In 2003 Rodriguez et al.[132] demonstrated that in rat vascular tissue NO_2^- and nitrosothiols, but not nitrate, are converted back to $NO^{\bullet}$ under UVA exposure: $NO_2^- + h\nu \rightarrow NO^{\bullet} + O^{\bullet-}$.

The action spectra for $NO^{\bullet}$ release from nitrite and from nitrosothiols have a peak at around 335 nm and lie in the range from 310 to 400 nm.[132] Human skin and dermal vasculature contains high quantities of NO_2^- (8.4 μM) and nitrosothiols (2.9 μM), which can be recycled by environmental stimuli, such as UVA radiation, to form $NO^{\bullet}$.[128–130,133] The skin of a human weighs approximately 4 kg and can be considered the largest human storage organ for NO derivatives such nitrite and nitrosothiols.[133] Thus, they represent an important alternative non-enzymatic physiological source of biologically active $NO^{\bullet}$. Healthy human skin contains 25-fold higher concentrations of NO_2^- than plasma of healthy volunteers.[130] It has been demonstrated in human keratinocytes in vitro and in healthy volunteers that UVA exposure induces $NO^{\bullet}$ in concentrations comparable to, or even higher than, those produced enzymatically by NO synthases.[129]

Protective effects of UV-induced $NO^{\bullet}$. Low concentrations of $NO^{\bullet}$ protect cultured keratinocytes and skin from oxidative stress and UVA-induced apoptosis.[130,131,134] The mechanism and the required concentrations for this protective action in skin are still unknown. Induction of Bcl-2 expression and inhibition of caspase activation have been suggested in some studies,[130] but this fails to explain the rapid timescale of the response. It is possible that UVA-induced $NO^{\bullet}$ may protect skin against solar radiation induced damages within 20–30 min, depending on UVA dose. Two independent studies have demonstrated that UVA exposure of human skin specimens leads to non-enzymatic $NO^{\bullet}$ formation which reaches a maximum after 20 min (320–400 nm, 40 J/cm^2) or after 30 min (350–400 nm, 30 J/cm^2).[128,133]

In 2009 Oplander et al. demonstrated that irradiation of healthy individuals with biologically relevant doses of UVA lead to a sustained reduction in blood pressure.[129] In 2010 it was proposed that many of the beneficial effects of sunlight related to cardiovascular health may be mediated by mechanisms that are independent of vitamin D and exposure to UV alone, but through UVA-induced $NO^{\bullet}$ and nitrite.[135] NO_2^-, for a long time considered biologically inert at low concentrations, is now known, not only to dilate blood vessels in its own right, but also to protect organs against ischemia/reperfusion damage.[136] Hemoglobin, myoglobin, xanthine oxidoreductase, cytochrome P-450, and mitochondrial enzymes can all generate $NO^{\bullet}$ from NO_2^- under hypoxic conditions.[135,137] In adults, skin and blood are of comparable weight and volume. The total amount of NO_2^- in the epidermis is around 135 μM, while the total amount of NO_2^- in blood rarely exceeds 13–15 μM.[133,135] Thus, mobilization of only a fraction of the relatively large epidermal pool of NO_2^- by sunlight is likely to be sufficient to increase plasma NO_2^- concentrations transiently. Thus, Feelisch et al. suggested that NO_2^- can be delivered to the systemic circulation and exert coronary vasodilator and cardioprotective as well as antihypertensive effects.[135] NO-containing gas is effective in tissue disinfection and regulating inflammatory processes associated with acute and chronic wounds.[138–140] It has been proposed that UVA-induced $NO^{\bullet}$ may also have antimicrobial effects, be involved in cutaneous wound healing as well as have antitumor activity.[130,141]

UVA-exposure of human skin releases $NO^{\bullet}$ into the circulation. In the bloodstream, $NO^{\bullet}$ can reach the nervous system.[129] In this way, UVA can influence transmission of nerve signals indirectly.[38]

However, $NO^{\bullet}$ can represent, not only beneficial effects, but also toxicity, and, due to this, it is known as a Janus molecule.[130] Many of the local and systemic UV-induced responses, including erythema and edema formation, inflammation, premature aging and immune suppression, can be influenced by UVA-produced $NO^{\bullet}$. Its role in the induction and in the progression of skin cancer remains uncertain. The direct toxicity of $NO^{\bullet}$ is modest, but is greatly enhanced by reactions with superoxide ($O_2^{\bullet-}$) to form the powerful oxidant peroxynitrite ($ONOO^-$), which can promote oxidative damage to blood vessels and skin. Under normal conditions $O_2^{\bullet-}$ is rapidly removed by superoxide dismutases (SOD). $NO^{\bullet}$ is quickly removed by its rapid diffusion through tissues into red blood cells where it is converted to nitrate and nitrite by a reaction with oxyhemoglobin. This limits the biological half-life of $NO^{\bullet}$ in vivo to less than a second.

Conclusions

UV radiation may affect many processes in the human body independent of vitamin D production. However, it is very difficult or even impossible, to understand which of the processes are mediated by UV alone and which via vitamin D. Even in situations where it has been doubtlessly assumed that only UV radiation is responsible for the effect (i.e., skin tanning and photoprotection), vitamin D may play an important role.[142–144] More studies similar to those of Becklund et al.[120] must be performed with the laboratory animals and all precautions must be taken to distinguish the influence of vitamin D and UV radiation in the development and progression of different disorders. Another approach might be to identify the responses that are due to vitamin D, and those independent of vitamin D, would be to study the effects of UV radiation in laboratory animals which are unable to make calcitriol or which have a mutated vitamin D receptor (VDR).

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References

1. Banerjee SC, Greene K, Bagdasarov Z, Campo S. 'My friends love to tan': examining sensation seeking and the mediating role of association with friends who use tanning beds on tanning bed use intentions. Health Educ Res 2009; 24:989-98; PMID:19574406; http://dx.doi.org/10.1093/her/cyp035
2. Ladizinski B, Mistry N, Kundu RV. Widespread use of toxic skin lightening compounds: medical and psychosocial aspects. Dermatol Clin 2011; 29:111-23; PMID:21095535; http://dx.doi.org/10.1016/j.det.2010.08.010
3. Harrington CR, Beswick TC, Leitenberger J, Minhajuddin A, Jacobe HT, Adinoff B. Addictive-like behaviours to ultraviolet light among frequent indoor tanners. Clin Exp Dermatol 2011; 36:33-8; PMID:20545951; http://dx.doi.org/10.1111/j.1365-2230.2010.03882.x
4. Agar N, Young AR. Melanogenesis: a photoprotective response to DNA damage? Mutat Res 2005; 571:121-32; PMID:15748643; http://dx.doi.org/10.1016/j.mrfmmm.2004.11.016
5. Tran TT, Schulman J, Fisher DE. UV and pigmentation: molecular mechanisms and social controversies. Pigment Cell Melanoma Res 2008; 21:509-16; PMID:18821855; http://dx.doi.org/10.1111/j.1755-148X.2008.00498.x
6. Miyamura Y, Coelho SG, Wolber R, Miller SA, Wakamatsu K, Zmudzka BZ, et al. Regulation of human skin pigmentation and responses to ultraviolet radiation. Pigment Cell Res 2007; 20:2-13; PMID:17250543; http://dx.doi.org/10.1111/j.1600-0749.2006.00358.x
7. Wolber R, Schlenz K, Wakamatsu K, Smuda C, Nakanishi Y, Hearing VJ, et al. Pigmentation effects of solar-simulated radiation as compared with UVA and UVB radiation. Pigment Cell Melanoma Res 2008; 21:487-91; PMID:18627527; http://dx.doi.org/10.1111/j.1755-148X.2008.00470.x
8. Routaboul C, Denis A, Vinche A. Immediate pigment darkening: description, kinetic and biological function. Eur J Dermatol 1999; 9:95-9; PMID:10066954
9. Suh KS, Roh HJ, Choi SY, Jeon YS, Doh KS, Bae JH, et al. Long-term evaluation of erythema and pigmentation induced by ultraviolet radiations of different wavelengths. Skin Res Technol 2007; 13:154-61; PMID:17374056; http://dx.doi.org/10.1111/j.1600-0846.2007.00213.x
10. Coelho SG, Choi W, Brenner M, Miyamura Y, Yamaguchi Y, Wolber R, et al. Short- and long-term effects of UV radiation on the pigmentation of human skin. J Investig Dermatol Symp Proc 2009; 14:32-5; PMID:19675550; http://dx.doi.org/10.1038/jidsymp.2009.10
11. Hönigsmann H. Erythema and pigmentation. Photodermatol Photoimmunol Photomed 2002; 18:75-81; PMID:12147040; http://dx.doi.org/10.1034/j.1600-0781.2002.180204.x
12. Auletta M, Gange RW, Tan OT, Matzinger E. Effect of cutaneous hypoxia upon erythema and pigment responses to UVA, UVB, and PUVA (8-MOP + UVA) in human skin. J Invest Dermatol 1986; 86:649-52; PMID:3711678; http://dx.doi.org/10.1111/1523-1747.ep12275683
13. Yamashita T, Akita H, Astner S, Miyakawa M, Lerner EA, González S. In vivo assessment of pigmentary and vascular compartments changes in UVA exposed skin by reflectance-mode confocal microscopy. Exp Dermatol 2007; 16:905-11; PMID:17927573; http://dx.doi.org/10.1111/j.1600-0625.2007.00604.x
14. Agin PP, Desrochers DL, Sayre RM. The relationship of immediate pigment darkening to minimal erythemal dose, skin type, and eye color. Photodermatol 1985; 2:288-94; PMID:4070027
15. Mahmoud BH, Ruvolo E, Hexsel CL, Liu Y, Owen MR, Kollias N, et al. Impact of long-wavelength UVA and visible light on melanocompetent skin. J Invest Dermatol 2010; 130:2092-7; PMID:20410914; http://dx.doi.org/10.1038/jid.2010.95
16. Bataille V, Boniol M, De Vries E, Severi G, Brandberg Y, Sasieni P, et al. A multicentre epidemiological study on sunbed use and cutaneous melanoma in Europe. Eur J Cancer 2005; 41:2141-9; PMID:16125927; http://dx.doi.org/10.1016/j.ejca.2005.04.038
17. Gandini S, Autier P, Boniol M. Reviews on sun exposure and artificial light and melanoma. Prog Biophys Mol Biol 2011; 107:362-6; PMID:21958910; http://dx.doi.org/10.1016/j.pbiomolbio.2011.09.011
18. Gordon L, Hirst NG, Green AC, Neale RE. Tanning Behaviors and Determinants of Solarium use Among Indoor Office Workers in Queensland, Australia. J Health Psychol 2011; PMID:22131168; http://dx.doi.org/10.1177/1359105311427476
19. Gies P, Javorniczky J, Henderson S, McLennan A, Roy C, Lock J, et al. UVR emissions from solaria in Australia and implications for the regulation process. Photochem Photobiol 2011; 87:184-90; PMID:21091485; http://dx.doi.org/10.1111/j.1751-1097.2010.00835.x
20. Nilsen LT, Aalerud TN, Hannevik M, Veierød MB. UVB and UVA irradiances from indoor tanning devices. Photochem Photobiol Sci 2011; 10:1129-36; PMID:21445424; http://dx.doi.org/10.1039/c1pp05029j
21. Matsumura Y, Ananthaswamy HN. Toxic effects of ultraviolet radiation on the skin. Toxicol Appl Pharmacol 2004; 195:298-308; PMID:15020192; http://dx.doi.org/10.1016/j.taap.2003.08.019
22. Doré JF, Chignol MC. Tanning salons and skin cancer. Photochem Photobiol Sci 2012; 11:30-7; PMID:21845253; http://dx.doi.org/10.1039/c1pp05186e
23. Rigel DS. Cutaneous ultraviolet exposure and its relationship to the development of skin cancer. J Am Acad Dermatol 2008; 58(Suppl 2):S129-32; PMID:18410798; http://dx.doi.org/10.1016/j.jaad.2007.04.034
24. Schulman JM, Fisher DE. Indoor ultraviolet tanning and skin cancer: health risks and opportunities. Curr Opin Oncol 2009; 21:144-9; PMID:19532016; http://dx.doi.org/10.1097/CCO.0b013e3283252fc5
25. Young C. Solar ultraviolet radiation and skin cancer. Occup Med (Lond) 2009; 59:82-8; PMID:19233827; http://dx.doi.org/10.1093/occmed/kqn170
26. Barysch MJ, Hofbauer GF, Dummer R. Vitamin D, ultraviolet exposure, and skin cancer in the elderly. Gerontology 2010; 56:410-3; PMID:20502035; http://dx.doi.org/10.1159/000315119
27. Narayanan DL, Saladi RN, Fox JL. Ultraviolet radiation and skin cancer. Int J Dermatol 2010; 49:978-86; PMID:20883261; http://dx.doi.org/10.1111/j.1365-4632.2010.04474.x
28. Trautinger F, Kindås-Mügge I, Knobler RM, Hönigsmann H. Stress proteins in the cellular response to ultraviolet radiation. J Photochem Photobiol B 1996; 35:141-8; PMID:8933720; http://dx.doi.org/10.1016/S1011-1344(96)07344-7
29. Shindo Y, Hashimoto T. Ultraviolet B-induced cell death in four cutaneous cell lines exhibiting different enzymatic antioxidant defences: involvement of apoptosis. J Dermatol Sci 1998; 17:140-50; PMID:9673896; http://dx.doi.org/10.1016/S0923-1811(98)00008-5
30. Agache P, Humbert P. Measuring the Skin: Non-invasive Investigations, Physiology, Normal Constants. In: Agache P, Humbert P, eds. Berlin and Heidelberg GmbH & Co. KG: Springer-Verlag, 2004: 1-807.
31. Meinhardt M, Krebs R, Anders A, Heinrich U, Tronnier H. Effect of ultraviolet adaptation on the ultraviolet absorption spectra of human skin in vivo. Photodermatol Photoimmunol Photomed 2008; 24:76-82; PMID:18353087; http://dx.doi.org/10.1111/j.1600-0781.2008.00342.x
32. Fisher DE, James WD. Indoor tanning–science, behavior, and policy. N Engl J Med 2010; 363:901-3; PMID:20818900; http://dx.doi.org/10.1056/NEJMp1005999
33. Oren M, Bartek J. The sunny side of p53. Cell 2007; 128:826-8; PMID:17350568; http://dx.doi.org/10.1016/j.cell.2007.02.027
34. Catania A, Lonati C, Sordi A, Carlin A, Leonardi P, Gatti S. The melanocortin system in control of inflammation. ScientificWorldJournal 2010; 10:1840-53; PMID:20852827; http://dx.doi.org/10.1100/tsw.2010.173
35. Gange RW, Blackett AD, Matzinger EA, Sutherland BM, Kochevar IE. Comparative protection efficiency of UVA- and UVB-induced tans against erythema and formation of endonuclease-sensitive sites in DNA by UVB in human skin. J Invest Dermatol 1985; 85:362-4; PMID:3840189; http://dx.doi.org/10.1111/1523-1747.ep12276983
36. Miyamura Y, Coelho SG, Schlenz K, Batzer J, Smuda C, Choi W, et al. The deceptive nature of UVA tanning versus the modest protective effects of UVB tanning on human skin. Pigment Cell Melanoma Res 2011; 24:136-47; PMID:20979596; http://dx.doi.org/10.1111/j.1755-148X.2010.00764.x
37. Moan J, Nielsen KP, Juzeniene A. Immediate pigment darkening: its evolutionary roles may include protection against folate photosensitization. FASEB J 2012; 26:971-5; PMID:22159146; http://dx.doi.org/10.1096/fj.11-195859
38. Juzeniene A, Brekke P, Dahlback A, Andersson-Engels S, Reichrath J, Moan K, et al. Solar radiation and human health. Rep Prog Phys 2011; 74:1-56; http://dx.doi.org/10.1088/0034-4885/74/6/066701
39. Gambichler T, Boms S, Stücker M, Moussa G, Kreuter A, Sand M, et al. Acute skin alterations following ultraviolet radiation investigated by optical coherence tomography and histology. Arch Dermatol Res 2005; 297:218-25; PMID:16215762; http://dx.doi.org/10.1007/s00403-005-0604-6
40. Xiang YC, Liu G, Yang L, Zhong JL. UVA-induced protection of skin through the induction of heme oxygenase-1. Biosci Trends 2011; 5:239-44; PMID:22281537; http://dx.doi.org/10.5582/bst.2011.v5.6.239
41. Gruber F, Oskolkova O, Leitner A, Mildner M, Mlitz V, Lengauer B, et al. Photooxidation generates biologically active phospholipids that induce heme oxygenase-1 in skin cells. J Biol Chem 2007; 282:16934-41; PMID:17449870; http://dx.doi.org/10.1074/jbc.M702523200
42. Thomas NE, Kricker A, From L, Busam K, Millikan RC, Ritchey ME, et al. Genes, Environment, and Melanoma Study Group. Associations of cumulative sun exposure and phenotypic characteristics with histologic solar elastosis. Cancer Epidemiol Biomarkers Prev 2010; 19:2932-41; PMID:20802019; http://dx.doi.org/10.1158/1055-9965.EPI-10-0686
43. Walther U, Kron M, Sander S, Sebastian G, Sander R, Peter RU, et al. Risk and protective factors for sporadic basal cell carcinoma: results of a two-centre case-control study in southern Germany. Clinical actinic elastosis may be a protective factor. Br J Dermatol 2004; 151:170-8; PMID:15270887; http://dx.doi.org/10.1111/j.1365-2133.2004.06030.x

44. Berwick M, Armstrong BK, Ben-Porat L, Fine J, Kricker A, Eberle C, et al. Sun exposure and mortality from melanoma. J Natl Cancer Inst 2005; 97:195-9; PMID:15687362; http://dx.doi.org/10.1093/jnci/dji019
45. Gillgren P, Brattström G, Frisell J, Persson JO, Ringborg U, Hansson J. Effect of primary site on prognosis in patients with cutaneous malignant melanoma. A study using a new model to analyse anatomical locations. Melanoma Res 2005; 15:125-32; PMID:15846146; http://dx.doi.org/10.1097/00008390-200504000-00007
46. Garbe C, Büttner P, Bertz J, Burg G, d'Hoedt B, Drepper H, et al. Primary cutaneous melanoma. Prognostic classification of anatomic location. Cancer 1995; 75:2492-8; PMID:7736393; http://dx.doi.org/10.1002/1097-0142(19950515)75:10<2492::AID-CNCR2820751015>3.0.CO;2-W
47. Grant WB. Skin aging from ultraviolet irradiance and smoking reduces risk of melanoma: epidemiological evidence. Anticancer Res 2008; 28(6B):4003-8; PMID:19192664
48. Vollmer RT. Solar elastosis in cutaneous melanoma. Am J Clin Pathol 2007; 128:260-4; PMID:17638660; http://dx.doi.org/10.1309/7MHX96XH3DTY32TQ
49. Pukkala E, Martinsen JI, Lynge E, Gunnarsdottir HK, Sparén P, Tryggvadottir L, et al. Occupation and cancer - follow-up of 15 million people in five Nordic countries. Acta Oncol 2009; 48:646-790; PMID:19925375; http://dx.doi.org/10.1080/02841860902913546
50. Newton-Bishop JA, Chang YM, Elliott F, Chan M, Leake S, Karpavicius B, et al. Relationship between sun exposure and melanoma risk for tumours in different body sites in a large case-control study in a temperate climate. Eur J Cancer 2011; 47:732-41; PMID:21084183; http://dx.doi.org/10.1016/j.ejca.2010.10.008
51. Kaskel P, Sander S, Kron M, Kind P, Peter RU, Krähn G. Outdoor activities in childhood: a protective factor for cutaneous melanoma? Results of a case-control study in 271 matched pairs. Br J Dermatol 2001; 145:602-9; PMID:11703287; http://dx.doi.org/10.1046/j.1365-2133.2001.04432.x
52. Field S, Newton-Bishop JA. Melanoma and vitamin D. Mol Oncol 2011; 5:197-214; PMID:21371954; http://dx.doi.org/10.1016/j.molonc.2011.01.007
53. Sivamani RK, Crane LA, Dellavalle RP. The benefits and risks of ultraviolet tanning and its alternatives: the role of prudent sun exposure. [vi.]. Dermatol Clin 2009; 27:149-54, vi; PMID:19254658; http://dx.doi.org/10.1016/j.det.2008.11.008
54. Feldman SR, Liguori A, Kucenic M, Rapp SR, Fleischer AB, Jr., Lang W, et al. Ultraviolet exposure is a reinforcing stimulus in frequent indoor tanners. J Am Acad Dermatol 2004; 51:45-51; PMID:15243523; http://dx.doi.org/10.1016/j.jaad.2004.01.053
55. Wintzen M, Yaar M, Burbach JP, Gilchrest BA. Proopiomelanocortin gene product regulation in keratinocytes. J Invest Dermatol 1996; 106:673-8; PMID:8618003; http://dx.doi.org/10.1111/1523-1747.ep12345496
56. Cui R, Widlund HR, Feige E, Lin JY, Wilensky DL, Igras VE, et al. Central role of p53 in the suntan response and pathologic hyperpigmentation. Cell 2007; 128:853-64; PMID:17350573; http://dx.doi.org/10.1016/j.cell.2006.12.045
57. Skobowiat C, Dowdy JC, Sayre RM, Tuckey RC, Slominski A. Cutaneous hypothalamic-pituitary-adrenal axis homolog: regulation by ultraviolet radiation. Am J Physiol Endocrinol Metab 2011; 301:E484-93; PMID:21673307; http://dx.doi.org/10.1152/ajpendo.00217.2011
58. Heckman CJ, Egleston BL, Wilson DB, Ingersoll KS. A preliminary investigation of the predictors of tanning dependence. Am J Health Behav 2008; 32:451-64; PMID:18241130; http://dx.doi.org/10.5993/AJHB.32.5.1
59. Levins PC, Carr DB, Fisher JE, Momtaz K, Parrish JA. Plasma beta-endorphin and beta-lipoprotein response to ultraviolet radiation. Lancet 1983; 2:166; PMID:6135011; http://dx.doi.org/10.1016/S0140-6736(83)90150-2
60. Wintzen M, Ostijn DM, Polderman MC, le Cessie S, Burbach JP, Vermeer BJ. Total body exposure to ultraviolet radiation does not influence plasma levels of immunoreactive beta-endorphin in man. Photodermatol Photoimmunol Photomed 2001; 17:256-60; PMID:11722750; http://dx.doi.org/10.1034/j.1600-0781.2001.170602.x
61. Gambichler T, Bader A, Vojvodic M, Avermaete A, Schenk M, Altmeyer P, et al. Plasma levels of opioid peptides after sunbed exposures. Br J Dermatol 2002; 147:1207-11; PMID:12452872; http://dx.doi.org/10.1046/j.1365-2133.2002.04859.x
62. Kaur M, Liguori A, Fleischer AB, Jr., Feldman SR. Plasma beta-endorphin levels in frequent and infrequent tanners before and after ultraviolet and non-ultraviolet stimuli. J Am Acad Dermatol 2006; 54:919-20; PMID:16635689; http://dx.doi.org/10.1016/j.jaad.2006.01.062
63. Kaur M, Liguori A, Lang W, Rapp SR, Fleischer AB, Jr., Feldman SR. Induction of withdrawal-like symptoms in a small randomized, controlled trial of opioid blockade in frequent tanners. J Am Acad Dermatol 2006; 54:709-11; PMID:16546596; http://dx.doi.org/10.1016/j.jaad.2005.11.1059
64. Nolan BV, Feldman SR. Ultraviolet tanning addiction. [v.]. Dermatol Clin 2009; 27:109-12, v; PMID:19254653; http://dx.doi.org/10.1016/j.det.2008.11.007
65. Nolan BV, Taylor SL, Liguori A, Feldman SR. Tanning as an addictive behavior: a literature review. Photodermatol Photoimmunol Photomed 2009; 25:12-9; PMID:19152511; http://dx.doi.org/10.1111/j.1600-0781.2009.00392.x
66. Kourosh AS, Harrington CR, Adinoff B. Tanning as a behavioral addiction. Am J Drug Alcohol Abuse 2010; 36:284-90; PMID:20545604; http://dx.doi.org/10.3109/00952990.2010.491883
67. Roelandts R. The history of phototherapy: something new under the sun? J Am Acad Dermatol 2002; 46:926-30; PMID:12063493; http://dx.doi.org/10.1067/mjd.2002.121354
68. Møller KI, Kongshoj B, Philipsen PA, Thomsen VO, Wulf HC. How Finsen's light cured lupus vulgaris. Photodermatol Photoimmunol Photomed 2005; 21:118-24; PMID:15888127; http://dx.doi.org/10.1111/j.1600-0781.2005.00159.x
69. Lawrence G. Tools of the trade: the Finsen Light. Lancet 2002; 359:1784; PMID:12049905; http://dx.doi.org/10.1016/S0140-6736(02)08653-1
70. Van Der Lugt L, Rottier PB. Finsen therapy and vitamin D. Acta Derm Venereol 1958; 38:264-73; PMID:13594215
71. Wejse C. Tuberculosis and Vitamin D – What Is the Evidence for Interaction? European Infectious Disease 2008; 2:107-10.
72. Walker D, Jacobe H. Phototherapy in the age of biologics. Semin Cutan Med Surg 2011; 30:190-8; PMID:22123416; http://dx.doi.org/10.1016/j.sder.2011.08.004
73. Bulat V, Situm M, Dediol I, Ljubicić I, Bradić L. The mechanisms of action of phototherapy in the treatment of the most common dermatoses. Coll Antropol 2011; 35(Suppl 2):147-51; PMID:22220423
74. Mudigonda T, Dabade TS, Feldman SR. A review of targeted ultraviolet B phototherapy for psoriasis. J Am Acad Dermatol 2012; 66:664-72; PMID:22000769; http://dx.doi.org/10.1016/j.jaad.2011.07.011
75. Krutmann J, Morita A. Mechanisms of ultraviolet (UV) B and UVA phototherapy. J Investig Dermatol Symp Proc 1999; 4:70-2; PMID:10537012; http://dx.doi.org/10.1038/sj.jidsp.5640185
76. Sage RJ, Lim HW. UV-based therapy and vitamin D. Dermatol Ther 2010; 23:72-81; PMID:20136910; http://dx.doi.org/10.1111/j.1529-8019.2009.01292.x
77. Lapolla W, Yentzer BA, Bagel J, Halvorson CR, Feldman SR. A review of phototherapy protocols for psoriasis treatment. J Am Acad Dermatol 2011; 64:936-49; PMID:21429620; http://dx.doi.org/10.1016/j.jaad.2009.12.054
78. Trautinger F. Phototherapy of mycosis fungoides. Photodermatol Photoimmunol Photomed 2011; 27:68-74; PMID:21392108; http://dx.doi.org/10.1111/j.1600-0781.2011.00559.x
79. Grundmann SA, Beissert S. Modern aspects of phototherapy for atopic dermatitis. J Allergy (Cairo) 2012; 2012:121797.
80. Pavel S. Light therapy (with UVA-1) for SLE patients: is it a good or bad idea? Rheumatology (Oxford) 2006; 45:653-5; PMID:16522677; http://dx.doi.org/10.1093/rheumatology/kel063
81. Mang R, Krutmann J. UVA-1 Phototherapy. Photodermatol Photoimmunol Photomed 2005; 21:103-8; PMID:15752130; http://dx.doi.org/10.1111/j.1600-0781.2005.00146.x
82. Krutmann J. Therapeutic photoimmunology: photoimmunological mechanisms in photo(chemo)therapy. J Photochem Photobiol B 1998; 44:159-64; PMID:9757598; http://dx.doi.org/10.1016/S1011-1344(98)00139-0
83. Osmancevic A, Nilsen LT, Landin-Wilhelmsen K, Søyland E, Abusdal Torjesen P, Hagve TA, et al. Effect of climate therapy at Gran Canaria on vitamin D production, blood glucose and lipids in patients with psoriasis. J Eur Acad Dermatol Venereol 2009; 23:1133-40; PMID:19453805; http://dx.doi.org/10.1111/j.1468-3083.2009.03245.x
84. Cicarma E, Mørk C, Porojnicu AC, Juzeniene A, Tam TT, Dahlback A, et al. Influence of narrowband UVB phototherapy on vitamin D and folate status. Exp Dermatol 2010; 19:e67-72; PMID:19849714; http://dx.doi.org/10.1111/j.1600-0625.2009.00987.x
85. Osmancevic A, Landin-Wilhelmsen K, Larkö O, Krogstad AL. Vitamin D status in psoriasis patients during different treatments with phototherapy. J Photochem Photobiol B 2010; 101:117-23; PMID:20579901; http://dx.doi.org/10.1016/j.jphotobiol.2010.05.008
86. Nicolaidou E, Antoniou C, Stratigos A, Katsambas AD. Narrowband ultraviolet B phototherapy and 308-nm excimer laser in the treatment of vitiligo: a review. J Am Acad Dermatol 2009; 60:470-7; PMID:19157641; http://dx.doi.org/10.1016/j.jaad.2008.07.053
87. Yaghoobi R, Omidian M, Bagherani N. Vitiligo: a review of the published work. J Dermatol 2011; 38:419-31; PMID:21667529; http://dx.doi.org/10.1111/j.1346-8138.2010.01139.x
88. Boissy RE, Nordlund JJ. Vitiligo: current medical and scientific understanding. G Ital Dermatol Venereol 2011; 146:69-75; PMID:21317859
89. Krutmann J, Hönigsmann H, Elmets CA. Dermatological Phototherapy and Photodiagnostic Methods. In: Krutmann J, Honigsmann H, Elmets CA, eds. Second eds. Leipzig: Springer, 2009: 1-447.
90. Oyoshi MK, He R, Kumar L, Yoon J, Geha RS. Cellular and molecular mechanisms in atopic dermatitis. Adv Immunol 2009; 102:135-226; PMID:19477321; http://dx.doi.org/10.1016/S0065-2776(09)01203-6
91. Krutmann J. Phototherapy for atopic dermatitis. Clin Exp Dermatol 2000; 25:552-8; PMID:11122227; http://dx.doi.org/10.1046/j.1365-2230.2000.00700.x
92. Kroft EB, Berkhof NJ, van de Kerkhof PC, Gerritsen RM, de Jong EM. Ultraviolet A phototherapy for sclerotic skin diseases: a systematic review. J Am Acad Dermatol 2008; 59:1017-30; PMID:18835066; http://dx.doi.org/10.1016/j.jaad.2008.07.042

93. Lehmann P, Hölzle E, Melnik B, Plewig G. Effects of ultraviolet A and B on the skin barrier: a functional, electron microscopic and lipid biochemical study. Photodermatol Photoimmunol Photomed 1991; 8: 129-34; PMID:1804292
94. Jungersted JM, Høgh JK, Hellgren LI, Jemec GB, Agner T. The impact of ultraviolet therapy on stratum corneum ceramides and barrier function. Photodermatol Photoimmunol Photomed 2011; 27:331-3; PMID: 22092739; http://dx.doi.org/10.1111/j.1600-0781.2011.00618.x
95. Holick MF. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 2004; 80 (Suppl):1678S-88S; PMID:15585788
96. Grant WB. Ecological studies of the UVB-vitamin D-cancer hypothesis. Anticancer Res 2012; 32:223-36; PMID:22213311
97. Chakraborti CK. Vitamin D as a promising anticancer agent. Indian J Pharmacol 2011; 43:113-20; PMID: 21572642; http://dx.doi.org/10.4103/0253-7613.77335
98. Di Rosa M, Malaguarnera M, Nicoletti F, Malaguarnera L. Vitamin D3: a helpful immunomodulator. Immunology 2011; 134:123-39; PMID: 21896008; http://dx.doi.org/10.1111/j.1365-2567.2011.03482.x
99. Zhang R, Naughton DP. Vitamin D in health and disease: current perspectives. Nutr J 2010; 9:65; PMID:21143872; http://dx.doi.org/10.1186/1475-2891-9-65
100. Thacher TD, Clarke BL. Vitamin D insufficiency. Mayo Clin Proc 2011; 86:50-60; PMID:21193656; http://dx.doi.org/10.4065/mcp.2010.0567
101. Parker J, Hashmi O, Dutton D, Mavrodaris A, Stranges S, Kandala NB, et al. Levels of vitamin D and cardiometabolic disorders: systematic review and meta-analysis. Maturitas 2010; 65:225-36; PMID: 20031348; http://dx.doi.org/10.1016/j.maturitas.2009.12.013
102. Witham MD, Nadir MA, Struthers AD. Effect of vitamin D on blood pressure: a systematic review and meta-analysis. J Hypertens 2009; 27:1948-54; PMID:19587609; http://dx.doi.org/10.1097/HJH.0b013e32832f075b
103. Grandi NC, Breitling LP, Brenner H. Vitamin D and cardiovascular disease: systematic review and meta-analysis of prospective studies. Prev Med 2010; 51:228-33; PMID:20600257; http://dx.doi.org/10.1016/j.ypmed.2010.06.013
104. Elamin MB, Abu Elnour NO, Elamin KB, Fatourechi MM, Alkatib AA, Almandoz JP, et al. Vitamin D and cardiovascular outcomes: a systematic review and meta-analysis. J Clin Endocrinol Metab 2011; 96:1931-42; PMID:21677037; http://dx.doi.org/10.1210/jc.2011-0398
105. Sokol SI, Tsang P, Aggarwal V, Melamed ML, Srinivas VS. Vitamin D status and risk of cardiovascular events: lessons learned via systematic review and meta-analysis. Cardiol Rev 2011; 19:192-201; PMID:21646873; http://dx.doi.org/10.1097/CRD.0b013e31821da9a5
106. Zittermann A, Iodice S, Pilz S, Grant WB, Bagnardi V, Gandini S. Vitamin D deficiency and mortality risk in the general population: a meta-analysis of prospective cohort studies. Am J Clin Nutr 2012; 95:91-100; PMID:22170374; http://dx.doi.org/10.3945/ajcn.111.014779
107. Schöttker B, Ball D, Gellert C, Brenner H. Serum 25-hydroxyvitamin D levels and overall mortality. A systematic review and meta-analysis of prospective cohort studies. Ageing Res Rev 2012; PMID: 22343489; http://dx.doi.org/10.1016/j.arr.2012.02.004
108. Grant WB. Relation between prediagnostic serum 25-hydroxyvitamin D level and incidence of breast, colorectal, and other cancers. J Photochem Photobiol B 2010; 101:130-6; PMID:20570169; http://dx.doi.org/10.1016/j.jphotobiol.2010.04.008
109. Freedman DM, Looker AC, Chang SC, Graubard BI. Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst 2007; 99:1594-602; PMID:17971526; http://dx.doi.org/10.1093/jnci/djm204
110. van der Rhee H, Coebergh JW, de Vries E. Sunlight, vitamin D and the prevention of cancer: a systematic review of epidemiological studies. Eur J Cancer Prev 2009; http://dx.doi.org/10.1097/CEJ.0b013e32832f9bb1
111. Mohr SB, Gorham ED, Alcaraz JE, Kane CJ, Macera CA, Parsons JK, et al. Serum 25-hydroxyvitamin D and prevention of breast cancer: pooled analysis. Anticancer Res 2011; 31:2939-48; PMID:21868542
112. Bjelakovic G, Gluud LL, Nikolova D, Whitfield K, Wetterslev J, Simonetti RG, et al. Vitamin D supplementation for prevention of mortality in adults. Cochrane Database Syst Rev 2011; CD007470; PMID:21735411
113. Chung M, Lee J, Terasawa T, Lau J, Trikalinos TA. Vitamin D with or without calcium supplementation for prevention of cancer and fractures: an updated meta-analysis for the U.S. Preventive Services Task Force. Ann Intern Med 2011; 155:827-38; PMID: 22184690
114. Avenell A, MacLennan GS, Jenkinson DJ, McPherson GC, McDonald AM, Pant PR, et al. RECORD Trial Group. Long-term follow-up for mortality and cancer in a randomized placebo-controlled trial of vitamin D(3) and/or calcium (RECORD trial). J Clin Endocrinol Metab 2012; 97:614-22; PMID:22112804; http://dx.doi.org/10.1210/jc.2011-1309
115. Drake MT, Maurer MJ, Link BK, Habermann TM, Ansell SM, Micallef IN, et al. Vitamin D insufficiency and prognosis in non-Hodgkin's lymphoma. J Clin Oncol 2010; 28:4191-8; PMID:20713849; http://dx.doi.org/10.1200/JCO.2010.28.6674
116. Tretli S, Schwartz GG, Torjesen PA, Robsahm TE. Serum levels of 25-hydroxyvitamin D and survival in Norwegian patients with cancer of breast, colon, lung, and lymphoma: a population-based study. Cancer Causes Control 2012; 23:363-70; PMID:22193397; http://dx.doi.org/10.1007/s10552-011-9885-6
117. Hagenau T, Vest R, Gissel TN, Poulsen CS, Erlandsen M, Mosekilde L, et al. Global vitamin D levels in relation to age, gender, skin pigmentation and latitude: an ecologic meta-regression analysis. Osteoporos Int 2009; 20:133-40; PMID:18458986; http://dx.doi.org/10.1007/s00198-008-0626-y
118. Snellman G, Melhus H, Gedeborg R, Byberg L, Berglund L, Wernroth L, et al. Determining vitamin D status: a comparison between commercially available assays. PLoS One 2010; 5:e11555; PMID:20644628; http://dx.doi.org/10.1371/journal.pone.0011555
119. Ponsonby AL, McMichael A, van der Mei I. Ultraviolet radiation and autoimmune disease: insights from epidemiological research. Toxicology 2002; 181-182:71-8; PMID:12505287; http://dx.doi.org/10.1016/S0300-483X(02)00257-3
120. Becklund BR, Severson KS, Vang SV, DeLuca HF. UV radiation suppresses experimental autoimmune encephalomyelitis independent of vitamin D production. Proc Natl Acad Sci U S A 2010; 107:6418-23; PMID:20308557; http://dx.doi.org/10.1073/pnas.1001119107
121. Lucas RM, Ponsonby AL, Dear K, Valery PC, Pender MP, Taylor BV, et al. Sun exposure and vitamin D are independent risk factors for CNS demyelination. Neurology 2011; 76:540-8; PMID:21300969; http://dx.doi.org/10.1212/WNL.0b013e31820af93d
122. Bäärnhielm M, Hedström AK, Kockum I, Sundqvist E, Gustafsson SA, Hillert J, et al. Sunlight is associated with decreased multiple sclerosis risk: no interaction with human leukocyte antigen-DRB1*15. Eur J Neurol 2012; PMID:22289117; http://dx.doi.org/10.1111/j.1468-1331.2011.03650.x
123. Grant WB, Peiris AN. Possible role of serum 25-hydroxyvitamin D in black-white health disparities in the United States. J Am Med Dir Assoc 2010; 11:617-28; PMID:21029996; http://dx.doi.org/10.1016/j.jamda.2010.03.013
124. Signorello LB, Shi J, Cai Q, Zheng W, Williams SM, Long J, et al. Common variation in vitamin D pathway genes predicts circulating 25-hydroxyvitamin D Levels among African Americans. PLoS One 2011; 6:e28623; PMID:22205958; http://dx.doi.org/10.1371/journal.pone.0028623
125. Kaufman MD, Johnson SK, Moyer D, Bivens J, Norton HJ. Multiple sclerosis: severity and progression rate in African Americans compared with whites. Am J Phys Med Rehabil 2003; 82:582-90; PMID: 12872014; http://dx.doi.org/10.1097/01.PHM.0000078199.99484.E2
126. Hart PH, Gorman S, Finlay-Jones JJ. Modulation of the immune system by UV radiation: more than just the effects of vitamin D? Nat Rev Immunol 2011; 11:584-96; PMID:21852793; http://dx.doi.org/10.1038/nri3045
127. Norval M. The mechanisms and consequences of ultraviolet-induced immunosuppression in the skin and eye. Eye Contact Lens 2011; 37:176-84; PMID:21709488; http://dx.doi.org/10.1097/ICL.0b013e31821d7573
128. Paunel AN, Dejam A, Thelen S, Kirsch M, Horstjann M, Gharini P, et al. Enzyme-independent nitric oxide formation during UVA challenge of human skin: characterization, molecular sources, and mechanisms. Free Radic Biol Med 2005; 38:606-15; PMID: 15683717; http://dx.doi.org/10.1016/j.freeradbiomed.2004.11.018
129. Opländer C, Volkmar CM, Paunel-Görgülü A, van Faassen EE, Heiss C, Kelm M, et al. Whole body UVA irradiation lowers systemic blood pressure by release of nitric oxide from intracutaneous photolabile nitric oxide derivates. Circ Res 2009; 105:1031-40; PMID: 19797169; http://dx.doi.org/10.1161/CIRCRESAHA.109.207019
130. Suschek CV, Opländer C, van Faassen EE. Non-enzymatic NO production in human skin: effect of UVA on cutaneous NO stores. Nitric Oxide 2010; 22:120-35; PMID:19879370; http://dx.doi.org/10.1016/j.niox.2009.10.006
131. Weller R. Nitric oxide: a key mediator in cutaneous physiology. Clin Exp Dermatol 2003; 28:511-4; PMID:12950342; http://dx.doi.org/10.1046/j.1365-2230.2003.01365.x
132. Rodriguez J, Maloney RE, Rassaf T, Bryan NS, Feelisch M. Chemical nature of nitric oxide storage forms in rat vascular tissue. Proc Natl Acad Sci U S A 2003; 100:336-41; PMID:12502793; http://dx.doi.org/10.1073/pnas.0234600100
133. Mowbray M, McLintock S, Weerakoon R, Lomatschinsky N, Jones S, Rossi AG, et al. Enzyme-independent NO stores in human skin: quantification and influence of UV radiation. J Invest Dermatol 2009; 129:834-42; PMID:18818674; http://dx.doi.org/10.1038/jid.2008.296
134. Suschek CV, Schroeder P, Aust O, Sies H, Mahotka C, Horstjann M, et al. The presence of nitrite during UVA irradiation protects from apoptosis. FASEB J 2003; 17:2342-4; PMID:14525939
135. Feelisch M, Kolb-Bachofen V, Liu D, Lundberg JO, Revelo LP, Suschek CV, et al. Is sunlight good for our heart? Eur Heart J 2010; 31:1041-5; PMID:20215123; http://dx.doi.org/10.1093/eurheartj/ehq069
136. Lundberg JO, Weitzberg E. NO-synthase independent NO generation in mammals. Biochem Biophys Res Commun 2010; 396:39-45; PMID:20494108; http://dx.doi.org/10.1016/j.bbrc.2010.02.136

137. Lundberg JO, Weitzberg E, Gladwin MT. The nitrate-nitrite-nitric oxide pathway in physiology and therapeutics. Nat Rev Drug Discov 2008; 7:156-67; PMID:18167491; http://dx.doi.org/10.1038/nrd2466

138. Shekhter AB, Serezhenkov VA, Rudenko TG, Pekshev AV, Vanin AF. Beneficial effect of gaseous nitric oxide on the healing of skin wounds. Nitric Oxide 2005; 12:210-9; PMID:15917214; http://dx.doi.org/10.1016/j.niox.2005.03.004

139. Ghaffari A, Miller CC, McMullin B, Ghahary A. Potential application of gaseous nitric oxide as a topical antimicrobial agent. Nitric Oxide 2006; 14:21-9; PMID:16188471; http://dx.doi.org/10.1016/j.niox.2005.08.003

140. Ghaffari A, Jalili R, Ghaffari M, Miller C, Ghahary A. Efficacy of gaseous nitric oxide in the treatment of skin and soft tissue infections. Wound Repair Regen 2007; 15:368-77; PMID:17537124; http://dx.doi.org/10.1111/j.1524-475X.2007.00239.x

141. Morcos E, Carlsson S, Weitzberg E, Wiklund NP, Lundberg JO. Inhibition of cancer cell replication by inorganic nitrite. Nutr Cancer 2010; 62:501-4; PMID:20432171; http://dx.doi.org/10.1080/01635580903441170

142. Slominski A, Tobin DJ, Shibahara S, Wortsman J. Melanin pigmentation in mammalian skin and its hormonal regulation. Physiol Rev 2004; 84:1155-228; PMID:15383650; http://dx.doi.org/10.1152/physrev.00044.2003

143. Kuritzky LA, Finlay-Jones JJ, Hart PH. The controversial role of vitamin D in the skin: immunosuppression vs. photoprotection. Clin Exp Dermatol 2008; 33:167-70; PMID:18205854; http://dx.doi.org/10.1111/j.1365-2230.2007.02632.x

144. Mason RS, Sequeira VB, Dixon KM, Gordon-Thomson C, Pobre K, Dilley A, et al. Photoprotection by 1alpha,25-dihydroxyvitamin D and analogs: further studies on mechanisms and implications for UV-damage. J Steroid Biochem Mol Biol 2010; 121:164-8; PMID:20399269; http://dx.doi.org/10.1016/j.jsbmb.2010.03.082