SUN INDUCED SKIN DAMAGE AND IMMUNOSUPPRESSION
LEZIUNILE CUTANATE ACTINICE ȘI IMUNOSUPRESIA

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Abstract
Skin is the largest organ and has got not only aesthetic function, but lots of others such as: protection, thermoregulation, sensation, evaporation and absorption, water resistance and immune function. The skin is a major target for toxic insult by a broad spectrum of physical (i.e. UV radiation) and chemical (xenobiotic) agents that are capable of altering its structure and function. Excessive exposure to UV radiation of the skin increases the risk of various skin diseases and accelerates the aging process, so it is necessary to protect the skin. The article reviews sun induced morphological and clinical skin changes and immunosuppression.

Keywords:
ultraviolet radiation, oxidative stress, skin damage and immunosuppression

Rezumat
Pielea reprezintă cel mai mare organ și îndeplinește, pe lângă rolul estetic, și funcții precum: protecția, termoreglarea, sensibilitatea, absorbția și evaporarea, apărărea imună. Pielea constituie o țintă pentru agresiunile toxice ale numeroșilor agenți fizi (de exemplu radiația UV) și chimici, care îi pot altera structura și funcționalitatea. Expunerea excesivă a pielei la radiațiile UV crește riscul apariției diferitelor boli dermatologice și accelerează procesul de îmbătrânire cutanată, fapt ce impune protecția împotriva razelor UV. În acest articol facem un rezumat al modificărilor morfologice și clinice cutanate induse de soare în contextul imunosupresiei.
Introduction

The incidence and prevalence of melanoma and non-melanoma skin cancer is increasing rapidly at rate, such data is observed in Latvia especially during the last 15 years (table 1). Ultraviolet (UV) irradiation is harmful to human skin. UV-induced skin damage includes sunburn, premature skin aging (photoaging) and skin cancer (carcinogenesis). Most patients can observe sun "footmarks" after a period of sun exposure, called lentigo type pigmentation, hipo/hiper-melanosis. This phenomenon is conditioned due to UV cumulative properties, each sun exposure accumulates in the skin and becomes more pronounced. Melanoma is the most common form of cancer among young adults aged 25-29 years and the second most common cancer in those aged 15-29 years(1).

Ultraviolet radiation (UV) induced DNA damage(1,2,3)

In 2009, the World Health Organization categorized tanning beds as a carcinogenic to human beings. UV radiation is divided into three categories: UV - A (315 - 400 nm), UV - B (280 - 314 nm), UV - C (100 - 280 nm) radiation. The initial signaling event of exposure to UV radiation is damage to DNA within the epidermis. Both UVB and UVA radiation damage cell DNA, but in different pathways. UV radiation, whose wavelength is from 245 to 290 nm, is best absorbed by the DNA, so UVB radiation is mutagenic. UVB radiation induces DNA damage through its direct effect, resulting primarily formation of cyclobutane pyrimidine dimers. Aggregation of those inhibits cell replication and transcription, causing C>T and CC>TT mutations in DNA which can lead to carcinogenesis. DNA damage by UVA radiations occurs predominantly through the generation of reactive oxygen species and oxidative stress (table 2), those are mutagenic and lead to skin cancer. Sunbeds UVA and UVB radiation connection is different comparing with a natural sun.

There is recently showed that, p53, a protein that is the most commonly mutated suppressor gene in the body, recognizes DNA damage, which then stimulates the production of pro-opiomelanocortin. Pro-opiomelanocortin in turn generates release of melanocyte stimulating hormone, which results clinically as a tanning.

UVA radiation penetrates into the skin deeper than UVB, but UVB rays damage skin cells the most and promotes the carcinogenic effects such as: damage the cells DNA, molecules and structures, DNA repair mechanisms and suppresses cell-mediated immunity(6). DNA damage can lead to mutations, genetic instability and alter cell functions, resulting as increased risk of developing skin cancer. Any UV spectrum waves are able to cause damage in skin matrix, collagen fibers, contributing to its degradation and accelerating skin aging process(7).

Human skin and oxidative stress

Ultraviolet radiation causes oxidative stress in the skin, oxidants or catalyze the production of reactive oxygen species (ROS) directly or indirectly. ROS are short-lived entities that are continuously generated at low levels during the course of normal aerobic metabolism. ROS include singlet oxygen (\(\cdot O_2\)), superoxide anion (\(\cdot O_2^-\) \(\cdot H_2O_2\), the hydroxyl radical (OH). ROS are believed to activate proliferative and cell survival signalling that can alter apoptotic pathways that may be involved in the pathogenesis of a number of skin disorders including photosensitivity diseases and some types of cutaneous malignancy. ROS act largely by driving several important molecular pathways that play important roles in diverse pathologic processes including ischemia-reperfusion injury, atheroscle-
rosis, and inflammatory responses\(^8\). Metabolic syndrome (MetS) due to oxidative stress supports chronic inflammatory process in the body including the skin. For protection against free radical damage neutrophils contain catalase and glutathione peroxidase (GP); these enzymes catalyse decomposition of hydroperoxides without formation of toxic side products. \(\text{H}_2\text{O}_2\) is eliminated by catalase (via reduction to \(\text{H}_2\text{O}\)). Skin is a major target of oxidative stress due to ROS that originate in the environment and in the skin itself\(^9\). ROS are generated during normal metabolism, are an integral part of normal cellular function, and are usually of little harm because of intracellular mechanisms that reduce their damaging effects. Antioxidants attenuate the damaging effects of ROS and can impair and/or reverse many of the events that contribute to epidermal toxicity and disease\(^10,11\). However, increased or prolonged free radical action can overwhelm ROS defence mechanisms, contributing to the development of cutaneous diseases and disorders.

Oxidative stress, which is thought to play a central pathogenic role in the pathogenesis of MetS, as a condition of oxidant/antioxidant imbalance, in which the net amount of reactive oxygen species (ROS) exceeds the antioxidant capacity of the body. Excessive ROS can react with cellular macromolecules and cause lipid peroxidation, protein oxidation and oxidative DNA damage\(^12\). Beside UV radiation, metabolic syndrome, as a 21 century pandemic reason for many diseases, impact skin as well. Metabolic syndrome causes oxidative stress and decreases body's antioxidant capacity may induce a clustering of risk factors for skin benign/ malignant neoplasms\(^13,14,15\).

The influence of overexposure of UV radiation, which may result as premature skin aging, flushing, carcinogenesis\(^16\).

In comparison, UV-non-exposed areas are mainly attributed to intrinsic factors such as genetics and changes in endocrine environment and reflects degradation processes of the entire organism. The clinical signs associated with photoaging are dyspigmentation, laxity, a yellow hue, telangiectasia etc.\(^17\).

Approximately 59% of cases after sun exposure have immediately at least one of the following symptoms: redness of the skin is the most common adverse reaction (44%), itching and/or burning, formation of hyperpigmentation, drought, polymorphic light eruption, the light-induced reaction of medication, skin fragility and blistering.

In later it is possible to develop solar/sunbed lentigines, new formations of atypical melanocytes, blurred vision, porphyria, systemic lupus erythematosus, worsening of subacute cutaneous lupus erythematosus, increasing developing risk of non-melanocytes skin cancer and melanoma\(^18\). Skin changes at the micro level are associated with decreasing of Langerhans cells, CD3 + and CD4 + (helper) cell count, induction of cytokine TNF-\(\alpha\), IL-10, CD3 + and CD4 + (helper)\(^19,20\).

### Morphological skin changes in sun-exposed areas

Morphological skin changes can be divided by layers - epidermis, dermis and hypodermis - which is described in table 2. In habitually sun-exposed skin, numerous sharply demarcated, irregular, thickenings of the horny layer are common, clinically we can reveal actinic or solar keratoses, with flattening of the
### UVB and UVA radiation mechanism of action, comparison of the skin (4,5)

<table>
<thead>
<tr>
<th>UVB radiation</th>
<th>UVA radiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High activity in epidermis</td>
<td>Low photon activity with a deeper permeability (epidermis, dermis)</td>
</tr>
<tr>
<td>Cellular DNA absorbed directly an energy of photon</td>
<td>Indirect damage, through intermediation of free radicals</td>
</tr>
<tr>
<td>1 UVB photon energy is 1000 times stronger than UVA</td>
<td>Accumulating and causing skin damage gradually throughout the thickness of the skin</td>
</tr>
<tr>
<td>Intensity of sun ray depends directly on the height of the sun above the horizon</td>
<td>Cell genome inhibits collagen synthesis, activates matrix metalloproteinase (MMP), that destruct all components of dermal matrix</td>
</tr>
<tr>
<td>A person can experience UVB radiation dose (by erythema, edema, pain)</td>
<td>A person can not feel the pain caused by UVA reaction (solarium)</td>
</tr>
<tr>
<td>Causes local and systemic immunosuppression</td>
<td>Causes local immunosuppression</td>
</tr>
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</table>

**Skin defenses**

These safeguards are individual in every person and depend on human phototype (according to Fitzpatrick classification) (29), age, state of health, season, exposed body parts and other factors. Protection acting to some extent – every person has limited resources of photoprotection. To limit the photo-damage, skin has a spectrum of adaptive, protective systems and repair mechanisms. Endogenous skin defenses: increase of epidermal thickness, formation of pigment, DNA repair mechanisms, apoptosis, tissue metalloproteinase inhibitors, antioxidants, urocanic acid formation.

Skin tan. The body’s defense against UV radiation begins with production of brown pigment - melanin, whose increase depends on duration of UV exposure and skin type. Pigments are transported from melanocytes to keratinocytes, resulting in sunburn (30). The function of melanin is to absorb UV radiation and dissipate energy as harmless heat, and thus protect the epidermal stem cells and keratinocytes from UV damage. In society it is believed that artificial tan before the holiday protects from possible sunburns caused by natural sunlight, but actually it is a myth. As mentioned before, dominant radiation in sunbeds are UVA, and that’s why people who use a solarium, initially in the skin oxidate the melanin, which is already in the epidermal surface layer of keratinocytes, it is called an instant tan. This tan is of low persistence and fades quickly. More lasting tan can be obtained by the accumulation of radiation, depending on the tanning ability and the amount of UVB rays in lamp radiation.

Intervening skin lines are observed. Sun exposure has no effect on the hypoderm (21,22,23).

Dermal elastosis (accumulation of abnormal elastic tissue in dermis).

Increased MMP activity with collagen degradation.

Increased level of dysfunctional glycosaminoglycans and proteoglycans.

Increased number of inflammatory cytokines, neutrophiles and mast cells.

Flattening of dermo-epidermal junction.

Thickening of vascular walls, regression and disorganization of small blood vessels, impaired vessel function/ hyperpermeability.

Impaired proliferation, desquamation and apoptosis of keratinocytes.

Thickening of epidermis.

**Effects on dis-/hypopigmentation in sun affected skin and UV induced neoangiogenesis**

Sun exposure contributes to pigmentary changes. Sun tan occurs in two steps: immediate pigment darkening, occurring mostly in individuals with skin phenotype III-IV (Fitzpatrick’s classification) and delayed formation of new melanin (24,25).

Recent studies suggest that acute UV exposure may induce the formation of new leaky blood vessels through upregulation of the angiogenic inducer vascular endothelial growth factor and downregulation of the angiogenic inhibitor thrombospondin-1 signal regulated kinase. New immature, leaky vessels with hypermeability may be formed that are responsible for the initiation of local inflammation (26,27,28).

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Immediate tan type doesn’t have photo protective effect against UV-induced skin redness or burns. Permanent tan generated by UVA radiation provides very minimal photo protection. Solarium tan – is not a safe tan. Biological activity of solarium equipment is equal to or higher than the natural sun in Southern Europe, but UV intensity of the intense solarium can be 10 - 15 times higher than the sun in midday\textsuperscript{31}. In case of missing skin protection against UV rays, this can cause a variety of skin lesions from benign precursors even to the skin malignancies.

Skin antioxidants. Enzymatic and non-enzymatic antioxidants are found in the skin. Endogenous antioxidants: vitamin E, coenzyme Q10 (Co-Q10), ascorbate, carotenoids. Enzymatic antioxidants: superoxide dismutase, catalase, glutathione peroxidase. Endogenous antioxidative operating system acts in protecting radicals (ROS), which are naturally formed in the cell cycle.

In the absence of antioxidants, the cell gets into the condition of oxidative stress. The ability of this protection mechanism decreases by years\textsuperscript{32}.

DNA damage and p53 reparation. By UV proposed DNA molecule damage, p53 gene transcription is activated. p53 is a protein that regulates the cell cycle of cell activation. As a result of this activation, the cell life-cycle is stopped in the G1 phase of the cell cycle and the mechanisms of apoptosis are turned on. UV induced mutations, such as cyclobutane pyrimidine dimers and (6-4) photoproducts formation are separated by internal mechanisms – excision of nucleoids and repair systems\textsuperscript{33,34}.

Damage and apoptosis of DNA. In the process of keratinocytes apoptosis the following terms are used – “sunburn” cells -which are possible to be found 30 minutes after exposure to UV rays. Due to the inhibition of apoptosis mechanism by years, capacity of sunburn cell formation also decreases. The blockage of the mechanism of apoptosis offers the pathway of carcinogenesis, which increases the risk of developing skin malignancy\textsuperscript{35}.

The possibility of skin regeneration.

Skin recovery options are not dependent of the skin lesion. Skin healing process distinguishing between three mutually overlapping phases:
- inflammation
- proliferative
- reconstructive (remodeling)

Epidermal processes:
- the epidermal stem cell
- proliferation of epidermal cell

Dermal processes:
The main agent is updated with the derma matrix of fibroblasts and collagen synthesis (connective tissue protein elastin and glycosaminoglycans).

The extracellular matrix is the skeleton of the skin, where the main recovery, endurance and skin carcass functions are completed by the fibroblasts. Fibroblasts originate from the mesoderm and their main function is the synthesis of extracellular matrix, consisting of glycosaminoglycans, elastin, fibronectin, laminin, collagen (a major component). Fibroblasts also have secretory function, by producing: cytokines (IL-1, IL-6, IL-10, TNF-α), growth factors, chemokines and inflammatory mediators\textsuperscript{36}.

**Sun exposure induced skin immunosuppression, Langerhans cells**

A network composed of delicate physical, chemical and immunological barriers in the skin makes it a perfect organ to protect the integrity of the human body. Dendritic cells (DCs) are found in the epidermis and tend to migrate and drain into deeper layers of the lymphatic system\textsuperscript{37}.

DCs represent a heterogeneous cell population residing in most peripheral tissues, particularly at sites of interphase with the environment, e.g. skin and mucosa. They represent 1-3% of total cell numbers of these tissues (Banchereau & Steinman, 1998). In the skin, these cells are dedicated antigen-presenting cells (APCs) that play a key role in sensing danger and initiating both innate and adaptive responses, as well as protecting the skin from invading pathogens\textsuperscript{38,39,40}.

Langerhans cells (LCs) have different functions depending on location. In the periphery, immature LCs capture and process antigens. In afferent lymphatics, LCs present antigens and acquire the capacity to present antigens to native T-cells (described as maturation of LCs). Moreover, there is the T-cell activation and proliferation (T-cell priming), as well as polarization of T-cell reactivity toward type-1 and/or type-2 responses. In the epidermis and dermis, LCs participate in the recognition of invading pathogens (viral, bacterial, etc.), toxins and harmful irradiations (Elbe et al., 1989). An over-exposure to ultraviolet radiation (UV) from the sun might potentially affect skin immunosuppression\textsuperscript{41}.

Under UV radiation, direct (intrinsic) keratinocyte damage develops in the epidermis via apoptosis with clustering of death receptors on the cell surface (extrinsic), and generation of reactive oxygen species (ROS). When apoptotic keratinocytes are processed by adjacent immature Langerhans cells, the inappropriately activated LCs could result in immunosuppression. Furthermore, UV can deplete LCs
in the epidermis and impair migratory capacity (Schaerli, Willmann, Ebert, Walz, & Moser, 2005).

Skin aging and photo-aging

Chronological aging is a progressive physiological change in the body. By the years biological functions, adaptation mechanisms, endogenous antioxidants and the body’s ability to adapt the metabolic stress are running out. Aging is a genetically programmed defined process.

There are two basic theories of skin aging:

Genetically determined aging process, which is based on the length of telomere; terminal parts of chromosomes get shortened with each cell cycle. When the telomeres reach a critical size of brevity, cell cycle stoppes or switches on apoptosis mechanism.

Environmental cumulative effects induced skin aging. Free radicals produced by normal metabolism of oxygen, contributing to the aging process. UV radiation damages the cells telomeres and accelerates aging. Aging is largely dependent on cumulative activity of environmental factors. The accelerated aging of the skin by UV radiation is called a „photo-aging“, “sun damaged skin”.

Clinical manifestations of skin aging:

Dyspigmentation
Skin flaccidity
Yellowish tinge
Wrinkles
Telangiectasies
Tough appearance
Skin benign formations – seborrheic keratosis
Skin malignant formations – basalioma
Actinic elastosis and Favre-Racouchot syndrome

Sun and Vitamin D synthesis

Synthesis of pre-vitamin D3 from 7-dehydrocholesterol occurs in the skin and involves UVB radiation that penetrates the epidermis. It is known that 7-dehydrocholesterol absorbs UV light most effectively at wavelengths between 270-290 nm and, thus, the production of vitamin D3 will occur at those wavelengths. “Calciol” - the product of the transformation of 7-dehydrocholesterol is an inactive, unhydroxylated form of vitamin D3.

The minimal daily concentration of vitamin D is well known and its amount for adults, who are not in the risk group, is 1000 IU per day. Those who are in a risk group (elderly, dark-skinned, live at certain latitude, work at certain time of day, don’t use sunscreens, have fat malabsorption, use anticonvulsant, have a chronic kidney disease, obese) need at least 2000 IU per day.

It has been reported that exposure of 6-10% of the body surface to one minimal erythema dose, which is defined as the minimum amount of UVB radiation that induces redness in 24 hours after exposure, is equivalent to ingesting about 600-1000 IU of vitamin D.

Vitamin D3 exerts pluripotent effects on adaptive immune function through:

- Adaptive T-cell immune reaction.
- Maturation and proliferation of LCs from immature dendritic cells (iDCs).
- Increasing innate immunity in skin and regulating antimicrobial defense at epithelial surfaces (cathelicidin expression).
- Regulation of keratinocyte differentiation and proliferation, as well as production of intact epidermal barrier.
- Changes in serum D vitamin level that may impact skin immunity, barrier functions, inflammatory reactions.

In the skin, the presence of vitamin D3 is essential for normal keratinocyte development, differentiation and function. Any alteration in the local vitamin D3 concentrations and/or activation will likely affect normal cutaneous immune function, barrier function, and inflammatory responses.

Prevention of UV radiation caused skin damage

Don’t visit sunbeds and avoid sunbathing.
Avoid direct sunlight (especially between 11:00 – 15:00).
Use a sunscreen with SPF 15 for adults, SPF 30 and more for children. The funds should be applied to the skin half an hour before going out in the sun, and applying should be repeated every 2-3 hours.
Suitable clothing provides protection from intense solar radiation, for example, cotton T-shirt, sunglasses, hats.

Some medicines and make-up reinforces the skin’s sensitivity to light. Cosmetics can cause unexpected reactions or long-term pigmentation. Their use must be strictly limited before sun exposure.

Conclusions

UV radiation induces various types of skin damage, like sunburn, dyspigmentation, telangiectasia, carcinogenesis and photoaging, characterized by fragmentation and reduced production of type I collagen fibrils, that provide strength to the skin (FrankWang MD, 2014). Each sun exposure accumulates in the skin and skin changes become more pronounced.

The initial signaling event of exposure to UV radiation is damage to DNA within the epidermis. Both UVB and UVA radiation damage cell DNA and cause skin cancer. DNA absorbs the most UV radiation of a wavelength of 245 to 290 nm, so, UVB ra-
radiation is a mutagen. Ultraviolet radiation causes oxidative stress in the skin. Oxidative stress is a condition of oxidant/antioxidant imbalance, in which the net amount of reactive oxygen species (ROS) exceeds the antioxidant capacity of the body. Excessive ROS can react with cellular macromolecules and cause lipid peroxidation, protein oxidation, and oxidative DNA damage. An important role in skin immunity to UV radiation-induced skin changes are Langerhans cells, Dendritic cells, antigen-presenting cells, T-cell and vitamin D.

References: