Sunscreens in organ transplant patients

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Introduction

Non-melanoma skin cancer, specifically basal cell carcinoma and squamous cell carcinoma, is the most frequent type of cancers diagnosed in fair-skinned populations. Their respective incidence is increasing worldwide by 3–5% per year [1].

Ultraviolet radiation is a major environmental cause. Both the total cumulative lifetime exposure to UV radiation and sporadic patterns of sun exposure (i.e. chronic, during work versus intermittent, during leisure time) are determinants for the individual risk of skin cancer. Increased cumulative lifetime sun exposure is associated with an increased risk of squamous cell carcinoma and actinic keratosis, the latter representing possible precursors of invasive squamous cell carcinoma [2].

Epidemiology in organ transplant recipients

Organ transplant recipients have particularly high rates of squamous cell carcinoma with a relative risk ∼100-fold higher than that in the immunocompetent population [3].

In an Irish study of renal transplant recipients, 93.5% of all squamous cell carcinomas occurred on the traditional ‘sunny terraces’ of the body, mainly head, neck, dorsum of the hands and forearms (Figure 1) [4]. Basal cell carcinoma is increased ‘only’ by a factor of 10 in organ transplant recipients. The reason for this is that the preferential sites of basal cell carcinoma are infrequently exposed to UV radiation, which could explain their occurrence on areas like the trunk that are less frequently exposed to the sun [5]. While basal cell carcinomas are believed to develop de novo, the development of cutaneous squamous cell carcinomas is viewed as a multi-step process that is initiated by p53 mutations of single cells leading to p53-mutated clusters and patches in clinically nonsuspicious skin and gradually progressing via different stages of actinic keratosis to invasive squamous cell carcinoma. Whereas, in immunocompetent patients, only ∼10% of individual lesions of actinic keratosis advance to invasive squamous cell carcinoma during a 5- to 10-year time frame, in organ transplant recipients the rate of progression of actinic keratosis is apparently accelerated (months) and the incidence of progression higher (>20–30%) [6]. Unfortunately, standardized data on the progression of actinic keratosis in organ transplant recipients are still missing.

The role of immune suppression

Apart from the direct effect of UV radiation causing DNA damage in keratinocytes, increasing evidence supports the hypothesis that UV radiation has also a negative effect on
the local immunosurveillance of exposed skin and even on systemic immunity [7]. UV radiation inhibits the function of antigen-presenting cells (Langerhans cells) and T-cells with suppressor activities. This inhibition enables previous UV radiation-induced mutant clones to escape from local immunosurveillance and to proliferate [7]. Systemic immunosuppression is mainly supported by the induction and release of IL-10 by keratinocytes caused by UV radiation [7].

Is UV radiation-induced skin damage avoidable?

UV radiation is not only the major risk factor for non-melanoma skin cancer in organ transplant recipients, but it is also presumably the only factor that is ‘avoidable’ in the immunocompromised organ transplant recipients. Two studies from Australia have shown good evidence that sunscreen use reduces the prevalence of actinic keratosis and of recurrent squamous cell carcinoma in immunocompetent populations [8,9]. Sun avoidance and sun protection measures, including sunscreen application techniques, are usually cornerstones of dermatological education programmes designed for organ transplant recipients worldwide [10,11]. Indeed, >90% of 128 renal transplant recipients surveyed by the transplant centre in Swansea, UK, were aware of the dangers of the sun, and 77% knew that they were more susceptible since receiving their transplant. However, 31% were not taking any precautions to reduce exposure to the sun and only 39% of the interviewed organ transplant recipients used sunscreens [12]. In 90% of those who used sunscreen, the sun protection factor (SPF) (which reflects only the protection level against UVB, not UVA radiation) was <10. In the USA, similarly alarming figures have been found: in a telephone survey, 79% of all 200 interviewed organ transplant recipients believed that the appearance of a tan was attractive and only 35% reported regularly using sunscreens. Episodes of sunburning were reported by 35% of the organ transplant recipients [13]. A study of 270 renal transplant recipients from Ireland found that more than 25% of the patients never applied sunscreen on a sunny day, compared to 68% prior to transplantation. Eighty percent of organ transplant recipients who subsequently developed keratinocyte skin cancer (KSC) following transplantation reported taking no precautions against sun exposure ($P = 0.03$). Especially, organ transplant recipients in the very high risk group, i.e. older patients, males and patients who worked outdoors or enjoyed outdoor hobbies, were less likely to apply sunscreen. Interestingly, the study showed a decreased KSC risk associated with the pre-transplant use of sunscreen, highlighting the need for early education of all transplant candidates entering the organ transplant waiting list [4].

Sunscreens—could they be the solution?

Sunscreens are topical preparations that attenuate the effects of UV radiation on the skin. A perfectly balanced combination of medical as well as cosmetic requirements dictates that an ideal sunscreen should meet the following criteria: easy to apply in a uniform layer, effective in blocking close to 100% of incident UV radiation,
invisible on the skin (no-whitening effect), non-greasy and non-sticky. When evaluating the reasons given by those patients denying regular sunscreen use despite the knowledge of the deleterious effects of UV radiation, two main groups of ‘reasons’ usually arise. The largest group describes sunscreens as ‘cosmetically and socially unacceptable’. Indeed, the physical inorganic filters (titanium or zinc oxide), which are the protective compounds in most broad-spectrum sunscreens recommended to organ transplant recipients, require a more greasy formulation; they are difficult to rub in and are comedogenic. Cyclosporine induces sebaceous gland hyperplasia, leading to a seborrheic (oily) skin with folliculitis and acne. Steroids, and also newer immunosuppressive agents such as everolimus and sirolimus (mTOR-inhibitors), are also able to induce or promote acne. Patients therefore usually try to avoid or reduce application of any additional fatty emollients to the face, including sunscreens. The final result of this cosmetic drawback is that much smaller amounts of sunscreens are used. Consequently, the SPFs are way below those indicated on the bottle, giving the patient a false sense of security.

The second most frequently heard reason for not using sunscreens on a regular basis is the cost of high-quality sunscreens. In Germany, as well as in most other Western countries, health insurance companies still consider sunscreens to be ‘cosmetic’ products. Consequently, they are not reimbursed even for patients at high risk of skin cancer such as organ transplant recipients.

Nevertheless, the compliance of patients will hopefully be increased by new sunscreen formulations: gel, spray or newer filters embedded in liposomes and delivered into the upper level of the epidermis [14].

**Is there evidence of benefit?**

In a single-centre, matched pairs observational study, a group of 60 organ transplant recipients (20 heart, 20 kidney, 20 liver-grafted patients) with daily application of a highly protective, liposomal sunscreen (2 mg/cm²) as part of their rigorous sun protection behaviour were compared with a control group matched for age, sex, skin type, transplant duration, previous post-transplant skin malignancies and type of graft. These controls received the identical written and oral information on sun protection as did the sunscreen group, but free sunscreen was not provided to these patients. Patients documented all sun protection measures including sunscreen product dosing (frequency, amount) in a study diary. The amount of sunscreen product applied was monitored by counting the sunscreen bottles distributed and used. After 24 months of follow-up, the following endpoints were evaluated: the incidence of new actinic keratoses, invasive squamous cell carcinoma and basal cell carcinoma. Analysis of the effect of sunscreen was based on skin cancers that developed at the sites of daily application.

In order to obtain the highest patient compliance by providing a highly protective and yet cosmetically favourable sunscreen, a preliminary study was performed with five different sunscreen products (SPF > 50, high-UVA absorption). Nine out of 12 randomly recruited organ transplant recipients (four kidney, four heart, four liver transplant patients) expressed a preference for a liposomal sunscreen product. Due to their unique properties, liposomes are frequently used for drug delivery of otherwise poorly penetrating agents into the skin. Within the duration of the study of 24 months, 42 of the 120 patients developed 82 new lesions of actinic keratosis (all in the control group). In contrast, in the sunscreen group, 102 lesions of actinic keratosis went into spontaneous remission ($P < 0.01$). Eight patients of the control group developed new invasive squamous cell carcinomas versus none in the sunscreen group ($P < 0.01$). A total of 15 new basal cell carcinomas occurred, 6 in the sunscreen group and 9 in the control group (n.s.). With an average of 5.6 applications per week, year round, for a total of 24 months, the compliance and acceptance of the selected liposomal sunscreen was excellent. In spite of equal numbers of lesions of actinic keratosis at baseline, a marked difference in favour of the intention-to-treat sunscreen group was recorded after 24 months [89 versus 273; $P < 0.01$, mean difference 3.07 (1.76–4.36)]. The lesion count was significantly lower as compared to the initial visit [89 versus 191; $P < 0.01$, mean difference 1.7 (0.68–2.72)], indicating even remission of actinic keratosis when the patients received sunscreen. There were no statistically significant differences in the incidence of basal cell carcinoma, but the proportion of patients who developed a squamous cell carcinoma was markedly reduced in the intent-to-treat group.

This study, like others showing similar results in immunocompetent populations before, documents that sun protection measures also have a positive impact on the high-risk group of organ transplant recipients [15].

Previous publications have speculated that the reason for the early post-transplant development of skin cancer in organ transplant recipients, particularly in elderly patients, is the fact that ‘dormant’ precursor cells of squamous cell carcinoma and lesions (including subclinical actinic keratosis) are frequent, even in the middle-aged population. [16] As long as these earliest steps towards invasive squamous cell carcinoma are well controlled by the local cutaneous immune system, they remain clinically invisible. In contrast, in individuals who are chronically or repetitively exposed to UV radiation, and in systemically immuno-compromised patients such as organ transplant recipients, haemodialysis patients, etc., as well as the elderly with impaired immunosurveillance, progression to an invasive squamous cell carcinoma occurs in a relatively short time frame. This fact highlights the need to protect the remaining cutaneous immunity against the UV hazard. This provides the rationale that such primary and even secondary prevention should be part and parcel of the management of organ transplant recipients.

The fact that sun protection can influence pre-vitamin D3 synthesis in skin and the question about the importance of optimal vitamin D levels for general health are a current hot topic both in popular press and in the scientific literature, although this still remains currently controversial. In all patients with regular sun protection, we believe that vitamin D levels should be monitored regularly and should be substituted *per os* to prevent vitamin D deficiency [17]. On the other hand, excessive sun exposure may also have unwanted side effects on vitamin D metabolism: vitamin D
synthesis is maximal at suberythemal UV doses and further UV exposure only increases the conversion of pre-vitamin D3 to lumisterol and tachysterol, both biologically inert compounds [18]. Furthermore, continued sun exposure degrades the active form of the photolabile vitamin D3 [19].

Conclusion

For individuals with an increased risk of skin cancer development, such as dialysis patients and organ transplant recipients, sun protective measures must be employed throughout the life of the patient. Sunscreens, as part of a conclusive sun protection strategy, are an important pillar of preventive healthcare. Since posttransplantation skin cancer becomes an increasingly important cause of morbidity and mortality in organ transplant recipients, the cost for sunscreens with medically proven efficacy should be covered by healthcare providers.

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References


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