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Organ transplant recipients express enhanced skin autofluorescence and pigmentation at skin cancer sites

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ABSTRACT

Background: Skin autofluorescence and pigmentation can estimate photodamage and sun exposure. These techniques may quantify differences in actinic damage between high-risk organ transplant recipients (OTRs) and immunocompetent patients.

Methods: Age and gender-matched OTRs (n = 15) and immunocompetent controls (n = 15) with a new keratinocyte carcinoma (KC) were included. We measured skin autofluorescence (370 nm excitation, *F370*) and skin pigmentation at five standardized body sites; and determined black light-evaluated solar lentigines on the shoulders and photosensitivity to UVA and simulated solar radiation (SSR) as minimal erythema doses (MED).

Results: *F*370 autofluorescence values were enhanced at KC site versus other body sites in OTRs (2208 vs. 1458–1898 AU, $p < 0.05$). Compared with non-OTRs, OTRs expressed higher *F370* autofluorescence at KC site (2208 vs. 1385 arbitrary units AU, $p = 0.01$) and the shoulder (1898 vs. 1525, $p = 0.05$). Likewise, OTRs had increased skin pigmentation (25.0 vs. 20.8 pigment%, p = 0.05) and solar lentigines (3.5 vs. 3.0, $p = 0.048$) on the shoulders. MED tests showed increased UVA photosensitivity in OTRs (2.4 vs. 1.7 times higher than expected, $p = 0.03$), whereas SSR photosensitivity was similar.

Conclusion: Quantified *F*370 autofluorescence, skin pigmentation, and density of solar lentigines could serve to assess photodamage in OTR. Increased UVA photosensitivity may account for higher skin photodamage.

1. Introduction

Immunosuppressed organ transplant recipients (OTRs) are at high risk of developing keratinocyte skin cancers (KC) with incidence rates 65–100 times increased for squamous cell carcinomas (SCC) and 5–10-fold higher for basal cell carcinoma (BCC) than the background population [1, 2]. As the OTR population is rapidly growing, there is a need for intensified skin cancer surveillance regimens. To optimize resources, non-invasive objective measurements may assist clinicians to identify patients with severely photodamaged skin and high-risk features for developing skin cancer.

Exposure to ultraviolet radiation (UVR) is the major environmental risk factor for KC development in both immunosuppressed and immunocompetent patients. The harmful effects of UVR in human skin include direct and indirect damage to epidermal and dermal structures such as DNA, collagen, and elastin [3]. In addition to photocarcinogenesis, the chronic consequence of UVR is photodamage including increased and mottled pigmentation, density of solar lentigines, and photoaging [3]. The severity of photodamage in each patient however, depends on individual UVR sensitivity and accumulated UVR exposure. While Fitzpatrick's skin phototype is a useful clinical scale, a person's UVR sensitivity can be measured by determining the amount of UVR needed to induce just perceptible erythema, the minimal erythemal dose (MED). More conveniently, reflectance measurements can determine the objective phototype, expressed as pigment protection factor (PPF), which predicts the UVR dose required to produce a MED in healthy individuals [4]. In OTRs, immunosuppressive drugs accelerate photocarcinogenesis through decreased repair of UVR-induced DNA damage, reduced immunologic surveillance of dysplastic keratinocytes and increased UVA photosensitivity in patients undergoing azathioprine treatment [5, 6]. Hence, transplant recipient's risk of KC development varies considerably and represents a complex interaction between lifetime accumulated UVR exposure, UVR sensitivity and transplant immunosuppressive regimen [7].

As a number of UVR chromophores in the skin also possess natural fluorescent qualities, each with characteristic excitation and emission spectra, attempts have been made to correlate skin photodamage with skin autofluorescence intensities [8–11] These studies have shown a positive correlation between skin photodamage and fluorescence from fragmented elastin fibres as well as UVR-induced cross-links of

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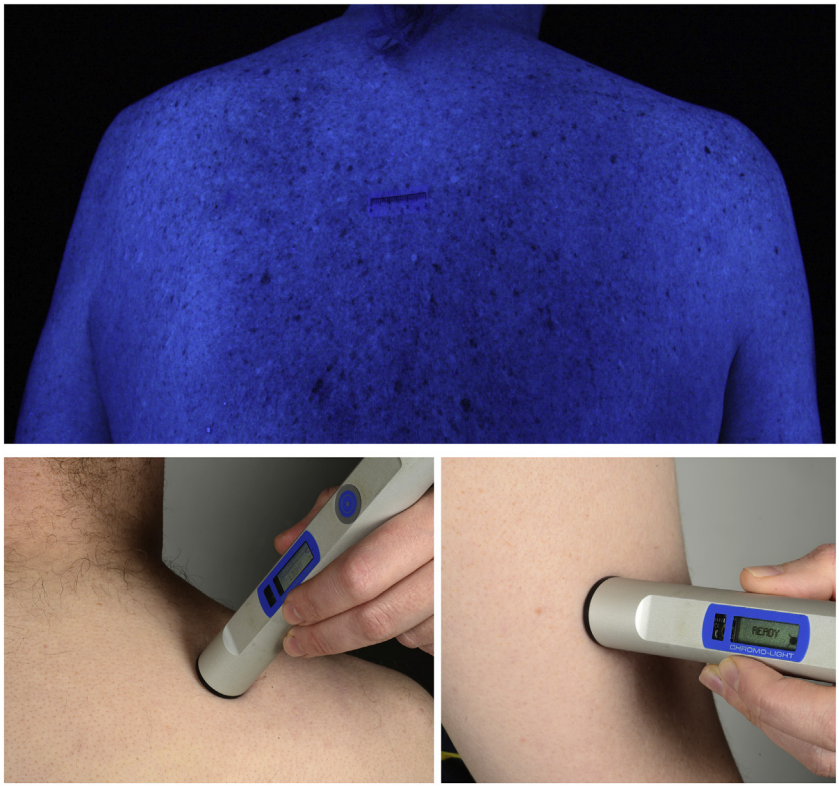

Fig. 1. Objective quantification of skin photodamage. Solar lentigines visualized in black—light UVA light showing moderate density of lentigines on the shoulders in an organ transplant recipient (top), and non—invasively quantification of skin autofluorescence and skin pigmentation on the shoulder and lateral arm (bottom).

degraded collagen fibres [10, 11]. Moreover, recent reports find enhanced skin pigmentation and density of solar lentigines related to higher UVR-exposure doses and skin cancer occurrence [12]. These findings suggest that non-invasive measurements potentially can estimate skin photodamage at different body locations.

To characterize skin photodamage in relation to KC development in high-risk patients, we aimed to compare non-invasive markers of photodamage in UVR-exposed skin and in unexposed skin between OTRs and immunocompetent patients. We quantified photodamage in terms of density of solar lentigines, skin autofluorescence and pigmentation, and determined individual MED for UVA and simulated solar radiation.

2. Materials and Methods

2.1. Patients

A total of 30 patients were included from the Department of Dermatology at Bispebjerg Hospital. Solid OTRs (n = 15) with newly diagnosed KC were consecutively recruited from the OTR clinic at Department of Dermatology at Bispebjerg Hospital and immuncompetent controls (n = 15), matched according to age and gender with OTRs, were recruited from the skin cancer clinic. Inclusion criteria for controls and OTRs were histology confirmed new BCC, SCC, or SCC in situ within 2 months of inclusion, minimum age 18 years and Fitzpatrick skin type I-III. Furthermore, OTRs should have stable immunosuppressive regimen at 12 months prior to inclusion. Exclusion criteria were pregnancy, breastfeeding, and skin disease with increased sensitivity to visible light or UVR. The study was conducted from March to June 2011 in accordance with the Helsinki Declaration and approved by the Ethics Committee of the Capital Region of Denmark (H-3-2010-037).

2.2. Interventions and End-Points

Skin autofluorescence, skin pigmentation, density of solar lentigines, and MED dose for UVA, and simulated solar radiation (SSR) were measured in all patients (Fig. 1). Skin autofluorescence and pigmentation were non-invasively measured using identical measurement sites at five standardized body sites, i) immediately adjacent to recent skin cancer sites and in normal skin at ii) right lateral upper arm, iii) back of right shoulder, iv) manubrium of the sternum, and v) right buttock. The median value of three consecutive measurements was applied for calculations.

Outcome measures were skin autofluorescence, skin pigmentation, density of solar lentigines on shoulders, and UVA and simulated solar radiation MED doses.

2.2.1. Skin Autofluorescence

Skin autofluorescence was measured by a *F*370 prototype (Chromolight, Espergaerde, Denmark) with maximum emission at 370 nm and a filtered detector (Wratten 2A LP-filter, Eastman Kodak Company, NY, USA), measuring wavelengths > 395 nm targeting fluorescence bands of collagen cross-links (8). Autofluorescence values (*fl370)* were corrected for pigmentation and redness in accordance with the method utilized by Sandby-Moller and colleagues (8):

$$F370 = \mathrm{Ln}(fl370_{\mathrm{corrected}}) = \mathrm{Ln}(fl370_{\mathrm{measured}}) + 0.060 \times \mathrm{pigment} + 0.024 \times \mathrm{redness}$$

2.2.2. Skin Reflectance Measurements

Skin reflectance measurements (Optimize Scientific Model, Chromolight, Espergærde, Denmark) were used to simultaneously quantify the content of pigment (percentage of melanin), and redness of the skin. In addition, the device determines the pigment protection factor (PPF), an