Original paper

Epidermal barrier function in patients after allogeneic hematopoietic stem cell transplantation – a pilot study

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Adv Dermatol Allergol 2022; XXXIX (6): 1083–1087
DOI: https://doi.org/10.5114/ada.2022.116778

Abstract

Introduction: The skin is the typically and predominantly affected organ in patients after allogeneic hematopoietic stem cell transplantation (alloHSCT). The supportive therapy in patients after alloHSCT includes especially ultraviolet protection and the use of emollients.

Aim: Due to the lack of studies regarding epidermal barrier function in patients with alloHSCT, our aims were to monitor dermatologically patients 1 year after the procedure with special emphasis on epidermal barrier function and to evaluate the properties of epidermal barrier function in patients with confirmed chronic GvHD (cGvHD).

Material and methods: Our pilot study included 30 patients after alloHSCT and 20 healthy controls. In the group of patients after alloHSCT there were 10 individuals who were monitored dermatologically (including evaluation of skin, mucosae, nails and hair) within 1 year after the procedure (subgroup 1) and 20 patients with previously confirmed cGvHD (subgroup 2). We evaluated transepidermal water loss (TEWL), skin hydration and skin color. The clinical assessment and all noninvasive evaluations in patients included in subgroup 1 were performed before (at baseline) and 3, 6, 9 and 12 months after the procedure, while in subgroup 2 they were performed once.

Results: In subgroup 1 we did not observe significant differences between baseline results and periods of assessments in TEWL values or corneometry, erythema and melanin measurements. In subgroup 2 the highest TEWL values and the lowest corneometry results were observed in patients with sclerodermoid chronic cutaneous GvHD in comparison to patients with lichenoid chronic cutaneous GvHD and patients with cGvHD but without skin lesions. TEWL values and melanin level were significantly higher in patients with cGvHD than in controls.

Conclusions: Our pioneer observations proved the disturbed epidermal barrier function among patients after alloHSCT. Therefore it seems that proper skin care, including photoprotection, should be recognized as a crucial component in long-term management of these patients.

Key words: allogeneic hematopoietic stem cell transplantation, epidermal barrier function, transepidermal water loss, transepidermal water loss, corneometry, graft versus host disease.

Introduction

The long-term complications after allogeneic hematopoietic stem cell transplantation (alloHSCT), including graft versus host disease (GvHD), are the most common causes of morbidity and mortality in these patients. Incidence of chronic GvHD (cGvHD) is approximately 50% among all patients following alloHSCT [1]. GvHD is induced by replacement of the host's immune system with donor cells and may lead to functional, physical and social disability with poor quality of life. Although chronic cGvHD may be a multiorgan disease, the skin and oral mucosa are the most commonly affected organs (81% and 89%, respectively) and usually are the first to become involved [1, 2].

Although the beneficial effects of emollients and photoprotection on the skin are well known, and according to the many publications they are recommended as a mandatory element of topical therapy in patients after HSCT, still there is a lack of studies assessing the epidermal barrier function in hematologic patients including patients with cGvHD [3–5].

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Received: 15.02.2022, **accepted**: 23.02.2022.

Aim

The aim of our pilot study was to (1) prospectively monitor skin in patients 1 year after alloHSCT with special emphasis on epidermal barrier function, (2) evaluate the epidermal barrier function in patients with confirmed cGvHD, both with and without skin lesions, and compare the results between these groups and healthy controls.

Material and methods

The study group consisted of 30 patients after alloHSCT and 20 healthy controls. In the group of patients after alloHSCT there were 10 individuals who were monitored dermatologically (including evaluation of skin, mucosae, nails and hair) within 1 year after the procedure (subgroup 1) and 20 patients who were diagnosed at least 6 months previously with cGvHD (subgroup 2). Patients in subgroup 1 were included independently of skin lesions. Patients' characteristics are summarized in Table 1.

Clinical evaluation

The diagnosis and evaluation of disease severity in patients with GvHD were obtained on the basis of NIH consensus criteria [6–8].

Table 1. Patient characteristics at the time of alloHSCT

Variable	Subgroup 1 (monitored patients)	Subgroup 2 (cGvHD patients)
Number of patients	10	20
Age – median/range	37 (18–64)	47 (25–67)
Gender:		
Male	6	12
Female	4	8
Disease:		
AML	8	9
CML, MF		6
CLL, NHL, HD		3
Aplastic anemia	2	2
Donor:		
Unrelated	8	13
Sibling	1	7
Haploidentical	1	
Conditioning regimen:		
Myeloablative	5	8
Nonmyeloablative	5	12

AML – acute myelogenous leukemia, CML – chronic myeloid leukemia, MF – primary myelofibrosis, CLL – chronic lymphocytic leukemia, NHL – non-Hodgkin lymphoma, HD – Hodgkin disease, cGvHD – chronic Graft versus Host Disease.

Test procedure

The clinical assessment and all noninvasive evaluations in patients included in subgroup 1 were performed before (at baseline) and 3, 6, 9 and 12 months after the procedure, while in subgroup 2 they were performed once. For ethical reasons all patients during the test procedure were advised to use emollients at least twice per day and to use sunscreens (against UVA/UVB) every 2–3 h, +except the day of performing the measurements. Due to the severe clinical state of patients before the procedure of alloHSCT, the evaluation before alloHSCT was performed only in 6 patients. For the same reasons after 12 months the evaluations were performed in 5 patients.

Biophysical measurements

Biophysical assessments were performed similarly to our previous studies [9]. Transepidermal water loss (TEWL) was measured with the Tewameter TM 300 (Courage-Khazaka, Köln, Germany) according to the guidelines [10, 11]. At least 20 measurements given as a mean value and expressed in SI units (g/m^2/h) were carried out.

To assess hydration of the stratum corneum (corneometry) the Corneometr CM 825 (Courage-Khazaka, Köln, Germany) was used, which is able to determine the electrical capacitance moisture. Its principle is based on the fact that the dielectric constant of water is 81 and that of dry skin is below this. A normal value of stratum corneum hydration was accepted as higher than 40 u. Five measurements given as a mean value in arbitrary units (range: 0–130) were obtained in accordance with guidelines [11].

Erythema and melanin measurements were assessed with Color Meter II (Cortex Technology, Hadsund, Denmark). The device is equipped with different color systems. For this study the erythema and melanin indexes were determined by skin reflectance spectroscopy, where the redness is calculated by subtracting the absorbance due to melanin from the absorbance of the green filter. Three independent measurements were performed at an interval of 30 s, on the basis of which the average value was determined.

The biophysical measurements were always conducted in the same order: TEWL, corneometry, the measurement of erythema and melanin. All measurements were performed in the same room conditions (temperature 20–22°C, humidity 20–40%) after 15–30 min acclimatization by the same trained physician.

The institutional review board approved the study and all patients signed the consent to participate in the study.

Statistical analysis

The calculations were carried out with Microsoft Excel 2010 and Statistica version 25 software (StatSoft Inc.). Patients' demographic data were analyzed using descriptive statistics. The contiguous data were tested for normal distribution using the Kolmogorov-Smirnov test. In the case of normally distributed data, the results

are presented as mean values. Depending on the number of analyzed groups, the differences between them were tested using the Wilcoxon test. The differences were considered to be statistically significant at $p < 0.05$.

Results

Demographic and clinical results

During 1-year follow-up we included 10 patients in subgroup 1 with mean age of 39.8 years (range: 18–64 years). Acute cutaneous GvHD (acGvHD) developed in 2 (15.4%) patients from this group in the form of mild exanthematous macular and maculo-pustular lesions (score 1), which disappeared before the first visit at the Department of Dermatology. These patients progressed to chronic cutaneous GvHD (ccGvHD) in the form of eczema-like lesions and were observed during the first visit (both assessed as score 1). One patient had onset of ccGvHD without prior history of acGvHD after a period of 3 months and developed dyspigmentation of the whole body and eczema-like lesions (body surface area, BSA > 50%).

In subgroup 2, which consisted of 20 patients (mean age: 47.3 years; range: 25–67 years), ccGvHD was observed in 13 (65%) patients. All these patients had classic ccGvHD (8 lichen planus-like ccGvHD and 5 scleroderma-like ccGvHD) and none presented an overlap syndrome. In all patients with lichenoid ccGvHD the scoring according to NIH criteria was 2, while in patients with scleroderma-like ccGvHD the scoring was 3. Mucosal and nail involvement was not detected.

The systemic manifestations of GvHD were observed in 3 patients from subgroup 1 (these were the same patients who presented with acGvHD) and in 12 patients from subgroup 2 (11 also manifested skin changes and in 7 of them lichen- or scleroderma-like ccGvHD was confirmed). Five patients presented symptoms of acute GvHD (aGvHD), followed by chronic symptoms, and the rest only cGvHD. The most commonly involved organs besides skin were the liver and gastrointestinal tract. Fourteen patients required systemic treatment, 3 in subgroup 1 and 11 in subgroup 2.

The control group consisted of 20 healthy individuals with a mean age of 42.4 years (range: 20–66 years).

Results of biophysical measurements

In subgroup 1 we did not observe significant differences between baseline results and periods of assessments in TEWL values or corneometry, erythema and melanin measurements (all, $p > 0.05$). The lowest corneometry results were observed after 9 (36.7 units) and 12 months (35.65 units), while due to the small sample size in evaluation after 12 months a statistical analysis was not performed. Consistently the highest TEWL value was observed after 12 months.

In subgroup 2 the highest TEWL values and the lowest corneometry results were observed in patients with sclerodermoid ccGvHD. However, the results were not statistically significant in comparison to patients with lichenoid ccGvHD and patients with cGvHD but without skin lesions (all, $p > 0.05$).

TEWL value was higher in cGvHD patients than in subgroup 1 evaluated in the 3rd month ($p = 0.031$). There was also a significantly higher mean TEWL value in sclerodermoid ccGvHD when compared to subgroup 1 assessed at 6 months ($p = 0.024$). We also compared other biophysical results (corneometry, erythema and melanin) between the two groups in other periods of assessment and found no differences (all, $p > 0.05$).

Significantly higher mean TEWL and melanin values were observed in cGvHD patients than in controls ($p < 0.0005$; $p < 0.014$, respectively). What is more, the mean TEWL and melanin values were significantly lower in the control group (9.99 g/m^2/h; 37.4 units) than in the "hematological group", which was created from the combination of patients with cGvHD and patients from the group undergoing monitoring for 6 months (14.27 g/m^2/h; 44.4 units) ($p = 0.001$; $p = 0.003$, respectively). There were no differences between the above-mentioned groups in corneometry and erythema results.

The biophysical results in both subgroups are summarized in Tables 2–4.

Discussion

The risk of moderate-to-severe aGvHD accounts for 40–60% of patients after alloHSCT and regards the epithelia of the skin, gastrointestinal tract, and small intrahepatic bile ducts [1, 12]. The cutaneous manifestations of aGvHD are usually observed after 2 to 8 weeks after HSCT and are related to the presence of itching and burning eruptions of the palms, soles, neck, auricle and upper back [1, 2]. In our study in subgroup 1 acute GvHD was observed in 2 individuals (15% of cases). Both presented cutaneous and extracutaneous manifestations (grading 1 according to NIH criteria). The skin lesions presented as erythematous patches and subtle papules. All lesions disappeared after therapy. However, both patients progressed to ccGvHD and after 3 months presented eczema-like lesions. The third patients from our study group (subgroup 1) who presented with ccGvHD, without a prior history of acGvHD, also developed eczematous lesions and dyspigmentation along with extracutaneous manifestations. According to the literature, cutaneous disease in patients with cGvHD is observed in 90% to 100% of patients and its characteristic forms include scleroderma-like or lichen-planus-like lesions [12]. However, none of the patients from our group who were followed up after 1 year presented these variants. The most common variant of ccGvHD in our group of patients was eczema-like ccGvHD. Other rare forms described in the literature of

Table 2. Mean values of TEWL as well as corneometry, erythema and melanin evaluations in subgroup 1

Period of assessment (*n*)		TEWL [g/m²/h]	Corneometry	Erythema	Melanin
Before/baseline (6)		9.95	43.95	10.61	37.75
After	3 months (13)	9.93	46.85	12.08	40.63
	6 months (13)	8.17	48.69	10.37	39.53
	9 months (13)	8.23	36.7	10.33	37.5
	12 months (5)	10.95	35.65	10.42	37.10

TEWL – transepidermal water loss.

Table 3. Mean values of TEWL as well as corneometry, erythema and melanin results in subgroup 2 including types of skin involvement

cGvHD (*n*)	TEWL [g/m²/h]	Corneometry	Erythema	Melanin
All group (20)	15.37	38.47	11.2	46.13
Lichenoid ccGvHD (8)	13.88	35.7	13.27	46.56
Sclerodermoid ccGvHD (5)	18.74	34.75	9.9	45.82
Without skin lesions (7)	14.65	44.48	10.21	45.98

TEWL – transepidermal water loss, cGvHD – chronic graft versus host disease, ccGvHD – chronic cutaneous graft versus host disease.

Table 4. Summary of statistically significant differences between study groups

Compared groups	Biophysical assessment	*P*-value
Haematological group 1 vs. control group	TEWL	0.024
Haematological group 1 vs. control group	Melanin	0.001
cGvHD vs. control	TEWL	< 0.01
cGvHD vs. control	Melanin	0.014
Sclerodermoid cGvHD vs. monitored patients after alloHSCT in 6th month of assessment	TEWL	0.024
cGVHD vs. monitored patients after alloHSCT in 3th	TEWL	0.031

Haematological group[1] – combination of patients with cGvHD and patients from the group undergoing monitoring for 6 months, cGVHD – chronic graft versus host disease, alloHSCT – allogeneic hematopoietic stem cell transplantation, TEWL – transepidermal water loss.

ccGvHD include psoriasiform, erythema multiforme-like, exfoliative dermatitis-like, and seborrheic dermatitis-like, and are mostly restricted to case reports or case series [13–20].

In this study our main aim was to analyze epidermal barrier function in patients after alloHSCT with and without GvHD. There is a lack of studies regarding TEWL and corneometry in that group of patients and there are no data available on the biophysical parameters of the skin in patients with ccGvHD. We carried out an assessment of the approved skin parameters defining the state of the epidermal barrier in 2 separate subgroup of patients: first – patients within 1 year after alloHSCT (independently from GvHD presence); second – patients with cGvHD (independently from the skin lesions' presence).

TEWL has been regarded as one of the most important parameters measuring the integrity of the skin barrier function. The values of this parameter depend on skin localization. According to the literature the 'normal' TEWL values are unknown, and it is considered that higher TEWL is often associated with skin barrier impairments [20]. In subgroup 1 we did not observe significant differences between baseline results and periods of assessments in TEWL values or corneometry, erythema and melanin. However, the lowest corneometry results (less than 40 u according to the producer means insufficient moisture) were observed after 9 (36.7 units) and 12 months (35.65 units). In subgroup 2 the highest TEWL values and the lowest corneometry results were observed in patients with sclerodermoid ccGvHD, which may be related to the extensive fibrosis and lack of hair follicles. Although there was no difference between patients without skin involvement in cGvHD and sclerodermoid as well as lichenoid forms in analyzed parameters, the skin involvement in all the cGvHD group manifested the most disturbed epidermal barrier function and presented significantly higher levels than healthy controls. What is more, we found some significant differences which support the hypothesis that the epidermal barrier function is disturbed in hematological patients (combined subgroups 1 and 2) more than in healthy controls and shows higher TEWL values (p = 0.001). Additionally, patients

with cGvHD more than patients after alloHSCT without skin lesions (in assessment after 3 and 6 months) present with higher TEWL values (Table 4).

The pigmentation in the form of melanin level was also the highest among ccGvHD patients (above 45) than in the group monitored after 1 year in the 6th month of assessment (range: 37–40.6) as well as in the control group. The hyperpigmentation could be the result of postinflammatory lesions but also may be related to the increased sensitivity to sunlight. Additionally, it should be noted that hyperpigmentation can also be induced by some chemotherapy agents (for example cyclophosphamide, doxorubicin, fluorouracil, busulfan) [21]. However, in such circumstances it typically disappears after 3 months without treatment [21].

The limitation of the study is the small sample size to perform reliable statistical results and further investigation in this field should be performed in the future. Regardless of this limitation, the results of this pilot study show that disturbed epidermal barrier function is observed among patients after alloHSCT, especially in patients with ccGvHD, which indicates the need for proper skin care [4]. What is more, the use of emollients should be introduced as early as possible together with appropriate topical and immunosuppressive therapy, as needed. In subgroup 1 we detected gradually decreasing corneometry results, which finally reached results below the expected ranges. The clinical benefits of emollients in dermatology are well established as they reduce TEWL and increase skin hydration and may present a low-potent anti-inflammatory effect together with an antipruritic one [5, 6, 9]. The enhanced pigmentation observed in hematological patients (especially in ccGvHD), in comparison to healthy skin, reflects the need for year-round photoprotection with UVA and UVB sunscreens.

Conclusions

This is, according to our knowledge, the first study which assesses the epidermal barrier function in patients after alloHSCT. We proved disturbed epidermal barrier function among patients after alloHSCT, especially among those suffering from sclerodermoid ccGvHD. Based on our results, we can conclude that due to the great importance of skin as a typically and predominantly affected organ, proper skin care and treatment seem to be crucial as a component in the long-term management of these patients.

Conflict of interest

The authors declare no conflict of interest.

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