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QUALITY OF LIFE IN PATIENTS WITH EPIDERMOLYSIS BULLOSA

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Summary

Background: Epidermolysis bullosa (EB) is a rare, inherited group of disorders characterized by blistering of the skin following friction or mechanical trauma. EB has a clinical and socio-economic impact on patients and their families.

Objectives: To assess the Quality of Life (QoL) in patients with EB and to determine disease burden.

Methods: The study was an observational, cross-sectional postal survey. 185 patients were invited to participate. Different sets of questionnaires (SF-36, Skindex-29, GHQ-12, EQ-5D) were sent to patients according to age. The perceived severity of the disease was evaluated by patients or by the mothers of the younger EB children, using the Patient Global Assessment 5-point scale. Caregivers received the Family Strain Questionnaire (FSQ).

Results: 125 respondents were analysed. EB patients showed lower values in physical components of SF-36, while the mental ones were not significantly impaired. Among EB types, junctional EB and severe generalized recessive dystrophic EB patients reported lower values and their General Health scale was significantly different from EB simplex. There were no significant differences among EB types/subtypes for Skindex-29 values. Females had a worse QoL compared to males in each Skindex-29 and SF-36 scales ($p < 0.05$). GHQpositive cases were 48% among females, 16% among males ($p = 0.003$); GHQpositive cases had a worse QoL compared to GHQnegative. The patient QoL and the family burden increased with increasing patient's perceived disease severity and with increasing patient's body surface involved. No differences were seen among EB types for the family burden.

Conclusions: In EB patients mental components of SF-36 scores are similar to the normal population. The perceived disease severity and skin area involved are relevant for QoL in all EB types/subtypes. EB imposes a heavy burden on the caregiver and the family. Psychological support and close monitoring of QoL may help EB patients and their caregivers.

INTRODUCTION

Epidermolysis bullosa (EB) is a rare, inherited group of disorders clinically characterised by blistering of the skin following friction or mechanical trauma. Its prevalence in the population is reported to range from 1:20,000 in Scotland¹ to 1:100,000 in Italy² and 1:130,000 in the USA³. The mode of inheritance is either autosomal dominant or recessive. Four major EB types are currently distinguished based on the ultrastructural level of separation of the epidermis from the underlying dermis: intra-epidermal in EB simplex (EBS), intra-lamina lucida in junctional (JEB), sub-lamina densa in dystrophic EB (DEB), and mixed in Kindler Syndrome (KS)⁴. KS, which has only recently been included among EB types, is characterised by photosensitivity, poikiloderma and skin atrophy, in addition to trauma-induced blistering⁵. The clinical course of these major EB types is extremely variable, from fatal (severe forms involving various organs with early postnatal death or chronic progression) to relatively mild (skin fragility with local blistering with little or no impact on life expectancy). EB types are thus further subdivided into major and minor subtypes based on clinical and laboratory findings⁴.

EB has a significant clinical and socio-economic impact both on patients and their families. Even though chronic skin blistering affects the personal, physical, emotional, and professional aspects of patients' life, only a few published studies to date have tried to determine the specific impact of the different EB types and subtypes on patients' daily life and the strategies of coping with EB. Such studies have been performed mainly in the USA using the National EB Registry. They reported the assessment of mobility, activities, and pain in the different EB types and the impact on parental, interpersonal relationships, marital status, and family size^{6,7}. Quality of Life (QoL) in EB has been assessed in Scotland using the National EB Register⁸. Also several papers have described in a narrative manner how hard life is with this condition. Among them, some were patient/caregiver reports, usually from members of the Dystrophic Epidermolysis Bullosa Research Association (DebRA)⁹, a non-profit organisation constituted for charitable and educational purposes. In

addition, the main problems experienced by affected children and by their parents have been described in a number of qualitative studies^{10,11}.

The aims of the study were to assess the QoL in a group of Italian patients with EB, to compare its impact to that of other relevant dermatological conditions, and to assess the burden of the disease on patients' caregivers.

MATERIALS AND METHODS

For this observational, cross-sectional study, patients' names were obtained from the EB database of the IDI-IRCCS Institute in Rome, a reference centre for EB and other skin diseases in Central and Southern Italy, and from the database of DebRA Italy. Only patients with a diagnosis confirmed by immunofluorescence antigen mapping and/or transmission electron microscopy were included.

The project was approved by IDI's Ethical Committee. The study was conducted in February - March 2008. One hundred eighty-five EB patients (adults and children) were invited by a telephone call to participate in a postal survey enquiring about their QoL and about caregiver burden due to EB. Those who agreed to participate were mailed the study questionnaires and written information with the details of the project and a form to be signed with their written informed consent. The signed consent forms and the completed questionnaires had to be returned using a self-addressed stamped envelope. For children <8 years old the mothers were asked to participate and to fill in the appropriate questionnaires. The main family caregiver was also asked to fill in a questionnaire. A reminder telephone call was made to patients who had not returned the questionnaire after a month.

Information about the clinical EB type and subtypes was obtained from the above mentioned databases. Inheritance pattern was based on family pedigrees and on molecular genetic findings. In particular for sporadic DEB cases dominant pattern of inheritance was established by comparison of the pathogenic sequence variant detected in the proband with previously identified mutations.

Whenever required, data were completed through phone interviews or patients' direct examination performed by a dermatologist with specific expertise in EB diagnosis. Different sets of

questionnaires were sent to patients according to three age groups: 0-7 years old, 8-14 years old, and adults.

Adult patients were sent the Medical Outcome Study 36-item short-form questionnaire (SF-36), the Skindex-29, and the 12-item General Health Questionnaire (GHQ-12), and the EuroQol 5 dimensions questionnaire (EQ-5D). Participants aged 8-14 years received only the EQ-5D(child). The perceived severity of the disease was evaluated by patients or by the mothers of the EB children using the Patient Global Assessment (PGA) 5-point scale. Adult caregivers were given the Family Strain Questionnaire (FSQ); children caregivers were also asked to fill in the GHQ-12.

Study measurement tools

SF-36

Although designed as a generic health status indicator for use in population surveys and health policy evaluation studies, the SF-36¹² can also be used as an outcome measure. The SF-36 includes 36 items in a Likert-type or forced-choice format, intended to measure the following eight dimensions: physical functioning (PF, limitations in performing physical activities such as bathing or dressing), role-physical (RP, limitations in work and other daily activities as a result of physical health), bodily pain (BP, how severe and limiting is pain), general health (GH, how general personal health is perceived by the patient), vitality (VT, feeling tired and worn out vs. feeling energetic), social functioning (SF, interference with normal social activities due to physical or emotional problems), role-emotional (RE, limitations in work and other daily activities as a result of emotional problems), mental health (MH, feeling nervous and depressed vs. peaceful, happy and calm). Scores for each domain range from 0 to 100, with higher scores indicating better health. Two additional summary measures, the physical (PCS) and mental component scores (MCS), cross-culturally validated in the framework of the International Quality of Life Assessment (IQOLA) project for the Italian version of the SF-36¹³, were also obtained.

For some analyses, MCS and PCS scores were dichotomised using as a cut-off the median value of the distribution, i.e., 46 and 43, respectively.

Skindex-29

The Skindex-29 is a valuable and reliable tool specifically designed to measure health-related QoL in dermatological patients¹⁴. It is constituted by three scales: symptom burden, functioning, and emotional state. The Italian version of this self-administered questionnaire has been validated at IDI-IRCCS¹⁵ and has proved valuable in assessing QoL in several skin diseases, including psoriasis¹⁶, nail disorders¹⁷ and vitiligo¹⁸. Patients are required to answer 29 questions referring to the previous 4-week period, using a five-point scale, from “never” (= 0) to “all the time” (= 4). The score for each scale ranges from 0 to 100 (as a percentage of the maximum score that can be obtained on the scale). Higher values reflect a worse QoL.

Skindex-29 scale scores were dichotomised using as cut-offs the median value of the distribution, i.e., 50 for symptoms, 33 for emotions, and 29 for functioning.

In the present study, this questionnaire has been used also for single-item analysis, in particular evaluating the percentage of the “often”, “all the time” answers to each item.

GHQ-12

The GHQ-12¹⁹ is a self-administered 12-item questionnaire designed to measure psychological distress and to detect current non-psychotic psychiatric disorders, such as depression and anxiety. The reliability and validity of the Italian version have been tested in several diseases, including dermatological conditions²⁰. Answers are given on a four-point scale; for instance, the item “in the last weeks, did you feel under strain?” envisages the following answers: “no”, “not more than usual”, “more than usual” and “much more than usual”. When scored with the binary method (0-0-1-1) the GHQ-12 can be used as a screening tool to detect minor non-psychotic psychiatric

disorders, yielding final scores that range from 0 to 12. Operationally, patients scoring 4 or more were considered as “GHQ-positive” (GHQ+).

EQ-5D and EQ-5D(child)

The EQ-5D is a standardised measure of health status developed by the EuroQoL Group to provide a simple, generic measure of health for clinical and economic appraisal²¹. The EQ-5D consists of two parts, the EQ-5D descriptive system and EQ-5D Visual Analogue Scale (EQ VAS). The former comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 3 levels: no problems, some problems, severe problems. The EQ VAS records the respondent’s self-rated health on a vertical visual analogue scale where the end points are “best imaginable health state” and “worst imaginable health state”. A validated Italian version of EQ-5D(child) was used in children aged 8 years or more.²²⁻²⁴

PGA

The PGA index consists of a 5-point scale, with scores from 0 to 4, corresponding to “very mild”, “mild”, “moderate”, “severe”, and “very severe” disease²⁵. The first two and last two categories were pooled in data analysis because of small numbers.

FSQ

The FSQ consists of a brief semi-structured questionnaire and 44 self-completed dichotomic items²⁶. This is a validated instrument for the general screening of caregiving-related problems. It makes it possible to optimise administration and data analysis time, and also to make comparisons between the extent of problems experienced by caregivers of patients with different diseases. The semi-structured interview collects information concerning the socio-economic status of caregivers and their beliefs/interpretations concerning the disease of their patients. Five areas are investigated: Emotional burden (Eb); Problems in social involvement (Si); Need for knowledge about the disease

(Kd); Satisfaction with family relationships (Sfr); and Thoughts about death (Td). “Yes” answers are attributed a score of 1, so the higher the score for each area, the greater the problems experienced, with the exception of Sfr, where a high score indicates good relationships.

The information collected from patients included personal data (e.g., age, gender, disease duration, days of hospitalisation due to the disease, etc.) and skin lesion distribution evaluated by the patient or the child’s caregiver (to be marked on a silhouette of the human body). A senior dermatologist then evaluated the patient’s representation of skin involvement, and coded it into three categories: < 10%; 10 to 30% or >30%.

Statistical analysis

Mean values and standard deviation (SD) were calculated for all QoL scores and compared using the t-test and ANOVA. The χ^2 test was applied to compare frequencies between groups for categorical variables. A *P*-value <0.05 was considered significant.

All statistical analyses were performed with the STATA statistical package, release 9 (STATA, College Station, TX, USA)²⁷.

RESULTS

Among 185 patients contacted, 134 filled in the questionnaires and sent them back. Nine incomplete questionnaires were discarded and were not included in the analysis. Thus, overall 125 questionnaires were included in the analysis (68% of those contacted by phone). The characteristics of the sample are reported in Table 1.

The distribution of EB types and subtypes in our patients, according to the last revision of EB classification⁴ was the following:

EBS (9 cases with EBS, Dowling-Meara ,[EBS-DM] 4 cases EBS localized, and 5 cases affected with other generalized EBS subtypes); JEB (15 cases - all non-Herlitz generalized subtype); DEB 83 cases, of which 5 dominant DEB (DDEB) generalized and 8 DDEB other subtypes, 27 recessive DEB (RDEB) severe generalized, 37 RDEB generalized other, 6 RDEB other subtypes; and KS (9 cases).

Fifty percent of EBS, 71% of JEB, 69% of DDEB, 46% of RDEB and 50% of KS patients had an involvement of skin between 10 and 30% of their body surface while 11% of EBS, 7% of JEB and 16% of RDEB had an involvement > 30%. The correlation between the skin area involved and the disease severity as perceived by patients (PGA) was 0.64 (Spearman Rho $p < 0.001$) for RDEB, 0.89 ($p < 0.026$) for DDEB and 0.74 ($p < 0.001$) for EBS, while no correlation was found for non-Herlitz JEB and KS.

Table 2 shows the QoL scores (Skindex-29) for different levels of several variables of interest.

Patients with higher perceived disease severity had significantly higher scores in all Skindex-29 scales. Adult female patients had higher scores in each Skindex-29 scale, with significantly higher mean values than male patients for the Symptoms and Emotions scales. Skindex-29 values were not significantly different among the various EB types and subtypes; however the highest values were consistently observed in patients with JEB. The analysis of the single Skindex-29 items addressing symptoms showed that 58% of adult patients answered “often” or “all the time” to the item “My skin is sensitive”, 51% to “My skin itches”, and 40% to “My skin condition burns or stings”. As regards emotions, 45% of adult patients answered “often” or “all the time” to the item “I am annoyed by my skin condition”, 34% to “I am angry about my skin condition”, and 34% to “I worry that my skin condition may get worse”. Among to the items addressing functioning, 43% of patients answered “often” or “all the time” to “My skin condition makes it hard to work or do hobbies”, 31% to “My skin condition makes me tired”, and 27% to “My skin condition interferes with my sex life”.

The EB patients health status as measured by SF-36 (Fig. 1) was also found to be worse in women than in men on all SF-36 scales, reaching a statistically significant difference for PF, VT, and MH. It was worse in GHQ positive patients and in patients with a larger skin involvement especially in physical scales. The SF-36 mean values of our adult patients, categorised according to the EB types, are reported and compared with the Italian normative values (Fig. 2). Patients with EB reported low physical scale scores, statistically lower than normal population, while mental health scores were only slightly below the normal population. No significant differences were observed among EB types, except for GH with lower values in patients with non-Herlitz JEB and severe generalized RDEB, the SF-36 values are similar in JEB and severe generalized RDEB.

GHQ+ cases were particularly frequent among women (48%) compared to men (16%, $p=0.003$). GHQ+ cases had a worse QoL and health status compared to GHQ- cases, both for Skindex-29 (Table 2) and SF-36 scores (Fig.1 -b-) in all scales ($p<0.001$).

The EQ-5D and EQ-5D(child) showed different median values of the 5-digit codes in adults ($n.=66$) and children ($n.=13$), i.e., 11222 and 22222, respectively. Different percentages of problem presence were reported for “Mobility” (33% vs 59%), “Self care” (29% vs 82%), “Usual activities” (52% vs 76%), “Pain discomfort” (76% vs 82%), and “Anxiety/Depression” (52% vs 41%). Pain was present in 92% of JEB. The EQ VAS was lower in children (mean \pm SD: 59 \pm 19), albeit not significantly different from adults (62 \pm 23), and showed no association with EB type: patients with EBS had mean \pm SD of 69 \pm 25; DDEB 68 \pm 24; RDEB 61 \pm 23, JEB 59 \pm 18; KS 61 \pm 29.

Results concerning the Family Strain Questionnaire, completed by parents for their children and by the principal caregiver for adults are shown in Table 3. Although no significant differences were seen among EB types, the family burden was particularly high in patients with KS and RDEB. The family burden increases with increasing patient’s perceived disease severity and increasing patient’s body surface involved, on all the scales and especially in the “Emotional burden”, the “Problems in social involvement” and “Thoughts about death” scales. Family burden was greater among GHQ+ patients. In particular it was greater in patients with a worse health status as measured by the SF-36

physical summary scale, and even greater on overall Skindex-29 scales for patients whose Skindex-29 values are above the median value used as cut-off.

DISCUSSION

To our knowledge, this is the study with the largest sample of EB patients in Southern Europe assessing the impact of the disease on their QoL, and evaluating the burden of the disease on caregivers.

The QoL of the EB patients was measured using two well-known and validated tools, one dermatology-specific and one generic, the latter allowing comparisons with other dermatological diseases.

In EB patients the physical components of SF-36 were more impaired than the mental ones. Compared to other dermatological diseases, values on the GH scale were low while the mental components were not statistically different from those of normal subjects. Women reported a worse QoL, and 48% of them were GHQ+ patients indicating the probable presence of anxiety and/or depression. These results have been observed also in other dermatological conditions^{18,20}. Due to the cross-sectional nature of the study, it is not possible to establish a causal relationship between QoL and psychological problems. This means that psychological problems could be either a cause or a consequence of worse QoL.

As recently suggested by Hagedoorn et al.²⁸, the lower level of health status and the higher impact on QoL of the dermatological disease observed in the women with EB could be in part due to the specific gender variable. The higher percentage of GHQ+ EB women supports this observation and underlines how EB burden may be greater in women.

Since EB commonly presents at birth and lasts throughout the patient's lifetime, the development of depression/anxiety may be a chance event or a reactive response to the disease or to other unknown

situations. Independently from the causal relationship, this observation should lead health providers to give appropriate support.

The stratification by EB types did not highlight major differences in health status or in the impact on QoL. However, the subgroups were not large, especially those of EBS and KS patients. The adult RDEB severe generalized cases and JED non-Herlitz were the most serious cases with lower physical health status and higher impact on QoL of the dermatological disease.

In the Pain dimension of the EQ-5D and EQ-5D(child), the proportion of individuals with pain was higher among children than adults. Particularly elevated was the percentage of JEB patients which reported pain presence. Pain was not included among the most frequently reported symptoms by adults on the Skindex-29 single items analysis.

An important aspect of our study is the evaluation of the burden of EB on caregivers. Family members play a major role in providing care and in giving assistance to the elderly and the sick²⁹. The effect of stressors on family members caring for a physically or mentally ill relative has been referred to as the caregiver burden. The scientific literature is rich in reports, particularly concerning persons involved in caring for patients affected by cancer or schizophrenia³⁰, or by other diseases^{31,32}, however not many reports compare the family burden in different diseases²⁶. Our study of caregivers of EB patients highlights the need to provide these families with support interventions, including management of relatives' psychological reaction to patient illness; provision of information on the nature, course and outcome of the patient's disease; training for relatives in the management of patient symptoms, and reinforcement of relatives' social networks. EB imposes a heavy burden on the caregiver and of course on the family, where most patients live. The emotional burden of caregivers is similar to that observed in other major diseases, and similarly it is associated with the disease severity. Our study highlights that the Emotional burden in EBS patients' caregivers is high, and that only RDEB patients' caregivers show higher values.

Although this finding can be partly due to the fact that the most severe EBS variants (i.e. EBS-DM and other generalized EBS forms) are highly represented in our study population, it also underlines how reductive it is to consider EBS as a very mild variant of EB.

The patient's body surface involved by blisters, the GHQ status and the lower quality of life increased the caregiver burden and the FSQ scores were a bit lower than those observed in caregivers of oncological patients²⁶ and of patients with leg ulcers³³. Since EB usually arises at birth and lasts throughout the patient's lifetime, the use of coping strategies might explain the level of family burden observed in EB compared to other diseases, and also why in patients the mental domain appears to be less impaired than the physical one. It has been previously reported that these patients are capable of accepting their disease and coping with the consequences with a conscious commitment, so that it was suggested that EB patients are able to achieve normal and often even high levels of personal development, as well as social integration and affirmation³⁴.

Administration of the EQ-5D in the adult and child versions enabled the two groups to be compared and highlighted differences in Mobility and Self-care. The proportions of adults and children with problems were different, and Anxiety/Depression were higher among adult patients. It is possible that also in this case coping strategies are involved. Affected children are more dependent, their self-care is limited, and they are most likely to experience more mobility limitations than healthy children. The proportion of GHQ+ caregivers (mothers of younger and older children) warrants further investigation. In fact, despite being lower than expected (19% and 24% for caregiver of patients in the 0-7 and 8-14 age group, respectively), such percentages were higher than those commonly observed in the general population (i.e., approx. 12%).

We have to consider that no specific treatment, nor any sort of protection from trauma, is currently available for patients with any form of EB. Thus, what we observe is the natural history of the disease, whose evolution is essentially related to the traumas and the skin damage each patient experienced.

The present study has some limitations. First of all, the IDI-IRCCS Institute is a National reference centre for skin diseases and in particular for EB laboratory diagnosis, thus our sample is not completely representative of the general EB population. Severe and rare forms of EB are over-represented, because serious or unusual cases are often referred to the Institute from Central and Southern Italy. This is confirmed also by the fact that we observed a great number of KS, a rare and still often underdiagnosed EB type. An additional selection bias is related to the fact that all participants, including those contacted through the DebRA Italy support group, volunteered. Thus the study may have selected people with a more conscious commitment to deal with the disease. The study was conducted in winter which is the best period of the year for patients with EB variants (especially for localised EBS) who are characterized by significant seasonal variation. Furthermore, the clinical assessment of the amount of skin involved was based exclusively on self-reported data. Our study however remains the largest and most comprehensive investigation on QoL in EB and particularly in the most severe EB subtypes in Southern Europe.

CONCLUSIONS

EB has a severe impact on QoL and impairs the health status in the majority of patients. On average female patients have a worse QoL, and among them a high proportion is GHQ+, reflecting the possible presence of anxiety and depression. The impact of this genodermatosis on QoL is more severe than that of other dermatological conditions. The mental component is less impaired than the physical one and the family burden is high. The main determinants of the caregivers burden are the severity and extension of the disease, and the poor QoL of the patient. Children suffer more than adults and those with problems in any of the five areas depicted by the EQ-5D are in a high proportion. Psychological support and close monitoring with QoL measurements may help EB patients and their care providers.

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Figure and legends

Fig. 1

Mean SF-36 scores in EB adult patients according to gender (a), GHQ status (b) and percentage of body area involved (c).

SF-36 Scales:

PF= Physical Functioning (limitations in performing physical activities such as bathing or dressing)

RP= Role-Physical (limitations with work and other daily activities as a result of physical health)

BP= Bodily Pain (how severe and limiting is pain)

GH= General Health (how general personal health is evaluated by the patient)

VT= Vitality (feeling tired and worn out vs. feeling full of energy),

SF= Social Functioning (interference with normal social activities due to physical or emotional problems)

RE= Role-Emotional (limitations with work and other daily activities as a result of emotional problems)

MH= Mental Health (feeling nervous and depressed vs. peaceful, happy and calm)

PCS= Physical Component Score, MCS= Mental Component Score.

Higher scores denote better health.

* $p < 0.05$ *t test* and ANOVA.

Fig. 2

Mean SF-36 scores in EB adult patients according to EB type and subtypes. Italian normative Sf-36 mean values are reported for comparison.

Table 1 Characteristics of EB patients participating in the study by age group.

		Age groups					
		0-7		8-14		Adults	
Patients (n.)		28*		18*		79*	
Age (years) mean±SD		3 ±1.7		10.2 ± 2.3		33.5 ±13.1	
EB duration (years) mean±SD		3 ±1.7		9.3 ± 3.1		28.7 ± 14.9	
		n.	%	n.	%	n.	%
Gender	Male	12	42.9	13	72.2	38	48.1
	Female	16	57.1	5	27.8	41	51.9
Perceived disease severity (PGA)	Low	14	51.9	3	16.7	25	31.6
	Medium	8	29.6	8	44.4	33	41.8
	High	5	18.5	7	38.9	21	26.6
Area of body surface involved	<10%	12	42.9	4	22.2	29	37.7
	≥10%≤30%	14	50.0	10	55.6	40	51.9
	>30%	2	7.1	4	22.2	8	10.4
Days of hospitalization due to EB in the last year	0	14	50.0	10	62.5	37	53.6
	≤7	9	32.1	3	18.75	21	30.4
	>7	5	17.9	3	18.75	11	16.0
EB type/subtype ^o	EBS-DM	6	21.4	-	-	3	3.8
	EBS, localized	1	3.6	1	5.56	2	2.5
	EBS, other subtypes	3	10.7	-	-	2	2.5
	JEB n-H, generalized	1	3.6	1	5.56	13	16.5
	DDEB, generalized	1	3.6	-	-	4	5.1
	DDEB, other subtypes	-	-	-	-	8	10.1
	RDEB, severe generalized	3	10.7	10	55.56	14	17.7
	RDEB, generalized other	9	32.1	5	27.78	23	29.1
	RDEB, other subtypes	4	14.3	-	-	2	2.5
	KS	-	-	1	5.56	8	10.2

^o EBS = epidermolysis bullosa simplex; EBS, Dowling-Meara (EBS-DM); JEB = junctional epidermolysis bullosa, JEB non-Herlitz (JEB n-H); DEB = dystrophic epidermolysis bullosa, dominant DEB (DDEB), recessive DEB (RDEB); KS = Kindler syndrome. EB types and subtypes are according the last revision of the EB classification. (ref.4)

*Totals may vary because of missing values.

Table 2 Mean Skindex-29 values in EB adult patients by gender, disease severity, body area involved, GHQ status, and EB types

	n.	Skindex-29		
		Sympt	Emot	Funct
All	75	49 ± 25	35 ± 26	31 ± 24
Gender				
Males	36	41 ± 26*	27 ± 26*	26 ± 26
Females	39	56 ± 23	42 ± 25	36 ± 22
Disease severity (PGA)				
Low	24	25 ± 21*	14 ± 18*	11 ± 14*
Medium	32	56 ± 19	42 ± 25	38 ± 24
High	19	65 ± 18	51 ± 22	44 ± 19
Body area involved				
<10%	27	35 ± 25*	28 ± 30	23 ± 26
≥10 ≤30%	39	55 ± 22	40 ± 25	36 ± 23
>30 %	7	70 ± 12	35 ± 16	38 ± 13
GHQ status				
GHQ positive	23	66 ± 19*	60 ± 19*	53 ± 17*
GHQ negative	51	42 ± 24	25 ± 22	22 ± 20
EB types				
EBS	5	41 ± 32	35 ± 37	31 ± 31
JEB	13	53 ± 18	40 ± 23	38 ± 22
DDEB	12	52 ± 32	37 ± 31	29 ± 26
RDEB	38	50 ± 25	35 ± 26	31 ± 24
KS	7	34 ± 22	23 ± 24	20 ± 25

Skindex-29: Sympt= Symptoms, Emot= Emotions, Funct= Social functioning.

* P<0.05 *t test* for dichotomised variables, ANOVA for more than two groups.

EBS = Epidermolysis Bullosa Simplex, DDEB = Dominant Dystrophic Epidermolysis Bullosa,

RDEB Recessive Dystrophic Epidermolysis Bullosa, JEB = Junctional Epidermolysis Bullosa, KS = Kindler Syndrome.

Totals may vary because of missing values.

Table 3 Family Strain Questionnaire (FSQ) in EB patients: mean values for each FSQ scale with different patient characteristics and status.

	Family Strain					
	n.	Eb	Si	Kd	Td	Sfr
Overall EB	112	6.1±4.5	2.9±2.3	2.4±1.3	1.9±1.2	2.9±1.3
EB type						
EBS	15	6.0 ± 5.1	2.7 ± 1.75	2.2 ± 1.4	1.7 ± 1.0	2.9 ± 1.4
JEB	14	5.0 ± 4.5	1.9 ± 1.8	1.6 ± 1.45	1.7 ± 0.9	2.8 ± 1.5
DDEB	8	4.0 ± 5.0	1.9 ± 2.0	2.25 ± 1.5	1.9 ± 1.55	2.6 ± 1.2
RDEB	67	6.6 ± 4.1	3.15 ± 2.4	2.6 ± 1.2	1.9 ± 1.2	2.9 ± 1.3
KS	8	5.6 ± 5.3	3.5 ± 3.0	2.75 ± 1.2	2.25 ± 2.05	3.0 ± 1.2
Disease severity						
Low	34	3.6 ± 3.6*	1.3 ± 1.5*	1.9 ± 1.0*	1.15 ± 0.8*	2.9 ± 1.3
Medium	46	6.3 ± 4.4	3.1 ± 2.3	2.4 ± 1.4	2.0 ± 1.1	2.9 ± 1.3
High	31	8.6 ± 4.1	4.3 ± 2.0	3.0 ± 1.3	2.5 ± 1.4	2.8 ± 1.4
Body area involved						
<10%	37	4.3 ± 4.0*	1.9 ± 2.05*	2.0 ± 1.05	1.35 ± 1.0*	2.65 ± 1.3
≥10 ≤30%	60	6.9 ± 4.6	3.2 ± 2.2	2.5 ± 1.4	2.0 ± 1.2	2.9 ± 1.3
>30	14	8.1 ± 3.5	4.3 ± 2.2	2.9 ± 1.5	2.8 ± 1.3	3.4 ± 1.1
Adults						
GHQ status						
GHQ-negative	45	5.2 ± 4.6*	2.3 ± 2.2*	2.2 ± 1.3*	1.6 ± 1.2*	2.9 ± 1.2
GHQ-positive	21	8.7 ± 3.9	4.0 ± 2.05	3.1 ± 1.0	2.6 ± 1.2	2.4 ± 1.6
SF-36						
PCS≥43	26	3.4 ± 3.85*	1.4 ± 1.65*	2.5 ± 1.1	1.4 ± 1.2*	2.5 ± 1.4
PCS<43	29	8.3 ± 4.1	4.1 ± 2.1	2.5 ± 1.5	2.55 ± 1.3	3.2 ± 1.2
MCS≥46	29	4.9 ± 4.7	2.3 ± 2.2	2.0 ± 1.4*	1.7 ± 1.3	3.2 ± 1.25
MCS<46	26	7.15 ± 4.4	3.4 ± 2.35	3.1 ± 0.9	2.3 ± 1.5	2.6 ± 1.3
Skindex-29						
Sympt<50	27	3.9 ± 4.2*	1.7 ± 1.9*	2.1 ± 1.3*	1.3 ± 0.9*	2.8 ± 1.4
Sympt≥50	36	8.0 ± 4.25	3.5 ± 2.1	2.8 ± 1.2	2.4 ± 1.4	2.8 ± 1.3
Emot<33	30	4.6 ± 4.7*	2.1 ± 2.2*	1.9 ± 1.4*	1.6 ± 1.25*	3.0 ± 1.2
Emot≥33	32	7.9 ± 4.0	3.4 ± 2.1	3.0 ± 1.0	2.25 ± 1.3	2.6 ± 1.4
Funct<29	28	4.4 ± 4.8*	1.7 ± 1.8*	2.1 ± 1.3*	1.4 ± 1.1*	3.0 ± 1.2
Funct≥29	35	7.7 ± 4.1	3.6 ± 2.2	2.8 ± 1.2	2.4 ± 1.35	2.6 ± 1.4

FSQ: Eb= Emotional burden; Si= Problems in social involvement; Kd = Need for knowledge about the disease; Td= Thoughts about death; Sfr =Satisfaction with family relationships.

EBS = Epidermolysis Bullosa Simplex, DDEB = Dominant Dystrophic Epidermolysis Bullosa,

RDEB = Recessive Dystrophic Epidermolysis Bullosa, JEB = Junctional Epidermolysis Bullosa,

KS = Kindler Syndrome

SF-36: PCS=Physical Component Summary, MCS=Mental Component Summary (median values 43-46 respectively).

Skindex-29: Sympt= Symptoms, Emot= emotions, Funct= Social functioning (median values 50-33-29 respectively)

As references for Family Strain

Oncological diseases =Eb 7.6±3.8, Si 3.5±2.1, Kd 2.3±1.4, Td 3.3±1.6 (**ref. 26**)

Vascular leg ulcers = Eb 7.0±3.7, Si 4.3±1.8, Kd 2.7±1.0, Td 2.2±1.5 (**ref. 33**)

P<0.05 *t* test for dichotomised variables, ANOVA for more than two groups.

Totals may vary because of missing values.

Fig.1

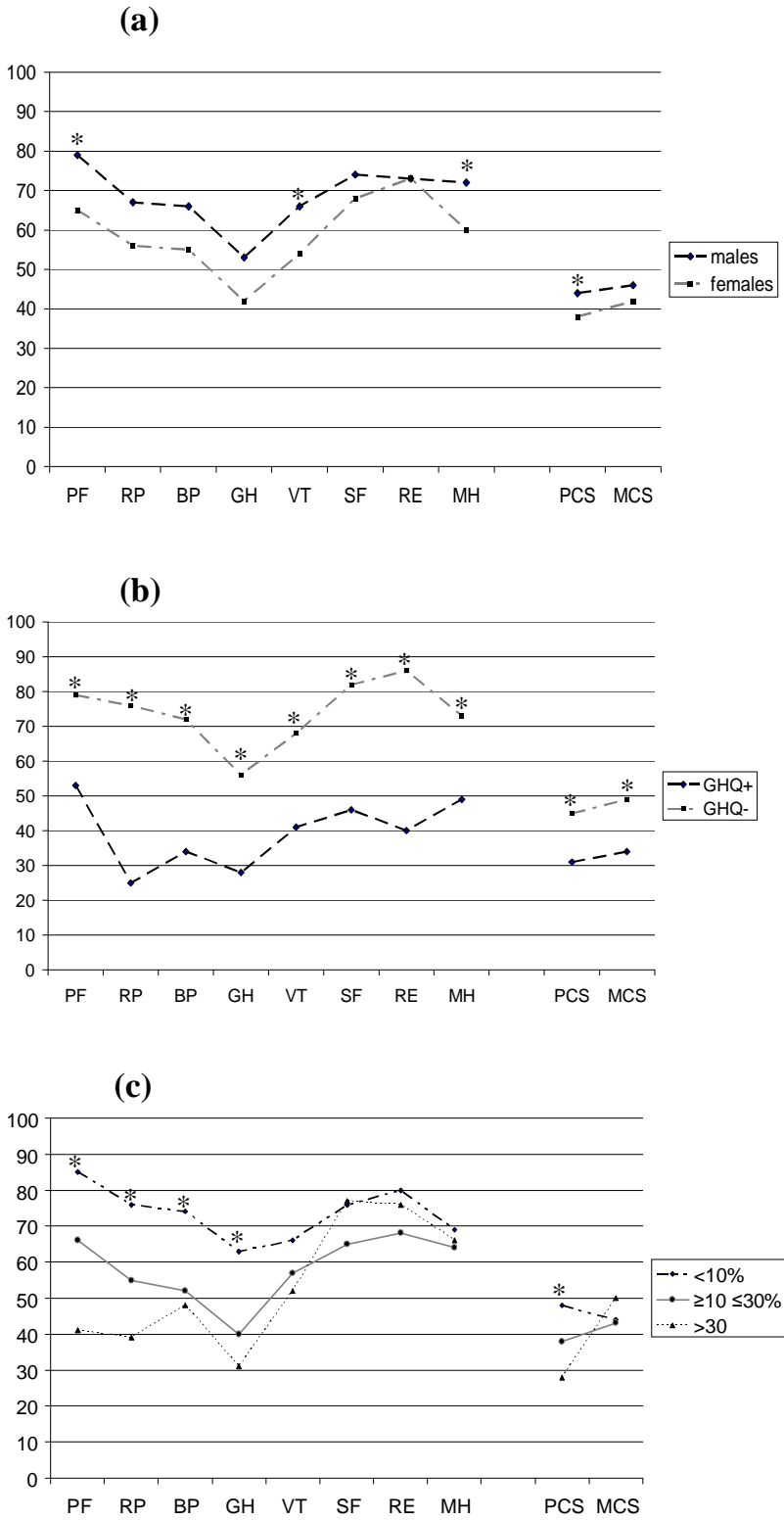


Fig. 2

