Burden of Keloid Disease: A Cross-sectional Health-related Quality of Life Assessment

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Keloid scars may be painful, itch severely and be cosmetically disturbing. The burden of keloid disease, however, has not yet been determined. This study evaluated the association of keloid disease with health-related quality of life (HRQL) and identified indicators of burden using a cross-sectional survey study, with one disease-specific HRQL measure (Skindex-29) and 2 generic HRQL measures (SF-36 and EQ-5D-5L). A total of 106 keloid patients with no other skin diseases participated in the study. Having keloid disease was associated with a considerable impairment of emotional wellbeing, with most impairment on the emotional and mental HRQL. Pain and itch were the strongest indicators of HRQL impairment in keloid patients. Having painful or itchy keloids was related to low mental and emotional HRQL, implying that patients with keloids require access to effective treatment aimed at alleviating physical symptoms.

Key words: keloid; health-related quality of life; POSAS; Skindex-29; SF-36; EQ-5D.

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Keloids are abnormal scars, which act like benign tumours growing beyond the margins of the original wound (1). Additional physical symptoms, such as itch and pain, occur in up to 80% of patients (1, 2). Keloid disease can lead to aesthetic, physical and psychological complaints in affected individuals (3, 4). Treatment has varying results and is associated with a high degree of resistance to treatment and recurrence (5).

The advent of health-related quality of life (HRQL) measures has greatly improved our insight into the burden of skin diseases. Skin diseases (e.g. psoriasis) may negatively affect HRQL to a degree comparable to or exceeding that of life-threatening illnesses, such as myocardial infarction and heart failure (6). Thus, the impact of skin diseases should not be underestimated, and HRQL research is warranted for all skin conditions.

The limited research available on HRQL of patients with scars shows negative effects on physical, psychological and social well-being (3, 4, 7–9). These studies, however, have substantial limitations, most importantly, a failure to differentiate between hypertrophic scars (HTS) and keloids, while these conditions are distinctly different from one another. HTS stay within the original wound margins, are self-limiting, and respond considerably better to treatment with lower recurrence rates (10). Preservation of HRQL is more likely with favourable symptoms, prognosis and duration of HTS compared with keloids. Research on these 2 conditions combined probably underestimates the burden of the more severe condition, keloid disease. In addition, none of these studies evaluated the effect of keloids on HRQL using both disease-specific and generic health measures. Generic health measures allow comparison of the burden of keloids with that of other major diseases. Thus, the degree of burden of keloids can be illustrated and the need for effective treatment can be formally prioritized. The combined use of different HRQL instruments provides such a broad and sensitive assessment of the burden of skin diseases (11).

METHODS

The present study was a multi-centre cross-sectional online survey.

Participants

All adults diagnosed with keloid disease by an experienced physician from the participating Departments of Plastic and Reconstructive Surgery and Dermatology at 2 university hospitals were eligible. Diagnosis of keloid disease was made on clinical presentation, most important continuous growth, beyond wound borders, without spontaneous regression after one year. Patients were excluded if there was any doubt about the diagnosis, or if the diagnosis differed between physicians. Patients, who were not proficient in Dutch, no longer had a keloid, or had additional skin diseases, were excluded. All respondents completed an online informed consent form and a series of self-administered questionnaires between February and May 2014. Non-responders were contacted by telephone after 3 weeks to invite them to participate.

Questionnaires

Patient and Observer Scar Assessment Scale (POSAS). Scar severity was subjectively assessed using the patient scale of this validated scar assessment tool (PSAS), consisting of 6 items on pain, itch, colour, stiffness, thickness, and irregularity, as well as an overall opinion on the scar. All items as well as overall opinion

were rated on a 10-point scale (13). Higher scores represent a more severe scar. A threshold of >3 on the pain and itch items was used to indicate substantial symptoms (14, 15).

SF-36. This widely used generic HRQL questionnaire contains 36 questions that provide scores on 8 different dimensions of functional health and well-being. Scores are given on a 100-point scale, with higher scores indicating better quality of life. Norm-based physical component summary scores (PCS) and mental component summary scores (MCS) (mean 50, SD 10) were calculated using pooled-age-matched norm scores from a Dutch urban (Amsterdam) reference population (16).

Besides the above-mentioned questionnaires, the Skindex-29 (17, 18) and EQ-5D-5L (19) were also used. These results have been reported previously (12).

Independent measures

Socio-demographic and clinical characteristics, including sex, age, skin colour as described by Fitzpatrick, location and visibility of the keloid, number of keloids (quantity), disease duration, origin of the keloid, previous treatments, and comorbidities, were collected.

Statistical analysis

Characteristics of the study population were analysed using descriptive statistics. Cohen's *d* effect sizes were calculated; values >0.20 were considered small effects, >0.50 medium effects, and >0.80 large effects (20).

Correlations were calculated between the independent variables and the 4 Skindex-29 scales, the SF-36 PCS and MCS scales, and EQ-5D-5L index scale. Previously-reported data from Skindex-29 and EQ-5D-5L instruments were also used to improve the validity of the correlation and regression analysis.

Pearson's correlation coefficients (r_p) were calculated for normally distributed data, and Spearman's correlation coefficients (r_s) for not normally distributed data.

Seven multiple linear regression models were made to assess the predictive value of the independent variables (sex, age, visibility of the keloid, number of keloids as well as all the PSAS variables: pain, itch, colour, stiffness, thickness, and irregularity) on HRQL outcomes. Non-normal dependent variables were root-transformed in order to obtain a normal distribution. Data were entered, followed by a backward procedure, in which non-significant effects ($p>0.10$) were removed from the models. Regression coefficients were standardized (betas) to allow for better comparison of different factors in the model, independent of the units of measurement of the variables. A beta of 0.1 indicates a small effect, 0.3 a medium effect, and 0.5 a large effect. R^2 represents the amount of variability in the outcome that is accounted for by indicators used in the model.

All analyses were executed using IBM® SPSS Statistics version 22 for Mac OSX. Two-sided *p*-values ≤0.05 were regarded as statistically significant.

Ethical considerations

The Ethics Board Committees of both participating academic hospitals concluded that this study was exempt from approval because of absence of any risk to participants.

RESULTS

Patient characteristics

Of the 280 eligible patients who were invited by post to participate in the study, 70 could not be reached after 3 attempts, 17 no longer had a keloid, 38 indicated they did not wish to participate, 8 had another skin disease besides keloids, and 41 did not complete the online survey, leaving 106 patients who successfully completed the questionnaires (36 from a dermatology department, and 70 from a plastic surgery department). The response rate was 57%. Socio-demographic and clinical characteristics of the responders are shown in **Table I**. Of the non-responders, 49% were male and the mean age was 39.1 years (SD 13.0, range 18–72 years), which was comparable to the responders (Table I).

Generic health-related quality of life of keloid patients

The outcomes for all the individual dimensions of the SF-36, as well as the PCSs and MCSs of the keloid patients were compared with an age-matched Dutch reference population, including healthy and unhealthy subjects with a living area and sex distribution comparable to our study population (**Table II**) (16). Compared with the reference population, keloid patients scored considerably lower on the SF-36 dimensions bodily pain, vitality, and social functioning as well as on the MCS, meaning that keloid patients reported a worse mental HRQL. The effect size for the MCS was –0.28, indicating a small effect (20). This is in contrast to the PCS, which was similar to that of the reference population (Table II).

Associated factors and predictors of health-related quality of life of keloid patients

The relationship between HRQL and the individual independent variables sex, age, skin colour, visibility of keloids, quantity of keloids, disease duration, hospital department, and all PSAS items were analysed. Pain and itch were correlated to all Skindex-29 scales (ranging from r_s 0.44 to 0.75, $p<0.001$), to both SF-36 component summary scores (ranging from r_s –0.24 to –0.29, $p<0.012$) and the EQ-5D-5L index (–0.54, $p<0.001$), meaning pain and itch were associated with nearly all HRQL measures. In addition, scar stiffness, thickness, and irregularity showed high correlations with HRQL outcomes. Duration of disease, skin colour, and department type (dermatology vs plastic surgery) showed no significant association with HRQL. Female sex correlated with worse outcomes on emotional, symptomatic, and sum scores of the Skindex-29 (r_p 0.23–0.24, $p<0.017$).

Regression analyses revealed that pain was a negative HRQL indicator in 6 (moderate effect on all Skindex-29 scales, small effect on PCS, and moderate effect on EQ-5D-5L index), and itch in 4 (large effect on symptomatic Skindex-29 and moderate effect on Skindex-29 sum, MCS and EQ-5D-5L) models, respectively, making these the most consistent and strongest indicators of HRQL. Besides pain and itch, other indicators were age (moderate effect on PCS), keloid visibility (small effect

Table I. Characteristics of the keloid patients (n = 106) analysed in this study

Characteristics	
Age, years, mean (SD) [range]	38.6 (11.9) [18–63]
Disease duration, years, mean (SD) [range]	13.8 (10.3) [1–40]
Sex, *n* (%)	
Male	51 (48.1)
Female	55 (51.9)
Skin colour (Fitzpatrick), *n* (%)	
1–2 Light	23 (21.7)
3–4 Coloured	44 (41.5)
5–6 Dark	38 (35.8)
Number of keloids, *n* (%)	
1	39 (36.8)
2–4	31 (29.2)
≥ 5	36 (34.0)
Secondary symptoms, *n* (%)	
Pain & itch ≤ 3	27 (25.5)
Pain > 3	3 (2.8)
Itch > 3	22 (20.8)
Pain & itch > 3	54 (50.9)
Location of keloids[a], *n* (%)	
Head	9 (8.5)
Ear	16 (15.1)
Neck	7 (6.6)
Shoulders	40 (37.7)
Chest	63 (59.4)
Back	11 (10.4)
Abdomen	17 (16.0)
Arm	9 (8.5)
Leg	7 (6.6)
Keloids visible (wearing normal clothing), *n* (%)	
No	40 (37.7)
Yes	66 (62.3)
Origin of keloid, *n* (%)	
Surgical procedure	36 (34.0)
Piercing	7 (6.6)
Vaccination	3 (2.8)
Acne	29 (27.4)
Traumatic injury	6 (5.7)
Unknown	25 (23.6)
Previous keloid treatment[a], *n* (%)	
None	4 (3.8)
Silicone sheets	56 (52.8)
Pressure therapy	4 (3.8)
Intralesional corticosteroid	82 (77.4)
Excision	25 (23.6)
Excision with additive	27 (25.5)
Radiation therapy	12 (11.3)
Cryotherapy	27 (25.5)
Laser	32 (30.2)
PSAS, mean (SD) [range]	
Pain	4.21 (2.82) [1–10]
Itch	5.84 (2.97) [1–10]
Colour	6.68 (2.52) [1–10]
Stiffness	7.00 (2.43) [1–10]
Thickness	7.73 (2.05) [1–10]
Irregularity	7.54 (2.21) [1–10]
Overall opinion	8.13 (2.05) [2–10]

[a]Multiple answers were possible, summed percentages exceed 100%.
SD: standard deviation; PSAS: patient part of the Patient and Observer Scar Assessment Scale.

on MCS), number of keloids (small effect on emotional, functional and sum Skindex-29), scar stiffness (moderate effect on PCS and EQ-5D-5L index) and irregularity (small effect on emotional, functional and sum Skindex-29). Keloid colour was present as indicator in 2 models, but a more aberrant scar colour improved the HRQL, while there was no proof of multi-collinearity. The Skindex-29 models could explain between 29% and 60% of the variability in outcome (R^2) and for the PCS, MCS, and EQ-5D-5L index it was 17%, 11%, and 34%, respectively (**Table III**).

Table II. Overview of SF-36 scores of the keloid patients compared with an age-matched reference population

	Keloid disease population *n* = 106 Mean (SD)	Reference population *n* = 3,800 Mean (SD)	Effect size Cohen's *d*	Student's *t*-test *p*-value
Physical function	90.4 (16.3)	88.6 (19.0)	0.12	0.17
Role physical	86.8 (29.1)	81.5 (33.4)	0.16	0.07
Bodily pain	72.8 (25.2)	81.7 (23.3)	−0.38	< 0.01
General health	73.4 (19.0)	72.6 (19.9)	0.04	0.67
Vitality	63.3 (21.2)	68.7 (18.9)	−0.28	0.01
Social function	80.1 (24.1)	85.9 (20.2)	−0.29	0.02
Role emotion	81.4 (36.0)	83.2 (32.5)	−0.05	0.63
Mental health	72.0 (20.7)	75.7 (17.5)	−0.21	0.07
PCS	50.4 (8.7)	50.0 (10.0)	0.05	0.60
MCS	47.2 (12.0)	50.0 (10.0)	−0.28	0.02

SF-36: the 36-item Short Form Health Survey; SD: standard deviation; PCS: physical component summary score; MCS: mental component summary score; pooled-SD: age-matched, urban (Amsterdam) reference population adapted from Aaronson et al. (16) with comparable proportions males (46%). PCSs and MCSs are norm transformed to the reference population with a mean 50 and SD 10. The study population is compared with the reference population; the effect size is given with Cohen's *d* (0.20 small effect, 0.50 moderate effect, 0.80 large effect).

DISCUSSION

In this study HRQL, specifically emotional wellbeing, of patients with keloid disease was considerably lower compared with a matched reference population on the generic instrument SF-36. This corresponds with the large proportion of keloid patients with severe impairment on the emotional scale of the Skindex-29, while the symptomatic and functional Skindex-29 scales were less affected, with 27% and 25% (12). Reinholz et al. (9) found similar results on HRQL of keloid patients using the Dermatology Life Quality Index (DLQI); specifically symptoms and feelings were affected.

Factors associated with worse HRQL of keloid patients were pain and itch symptoms that are more prominent in keloids than in other scar types (12). Remarkably, cosmetic issues correlated less, or even inconsistently with HRQL. These findings support priority setting, as surgery for cosmetic issues can be interpreted as "luxury healthcare", instead of a medical need, which relates to its current lower priority in health policy decision-making (21). The current study showed that HRQL can be considerably impaired in patients with keloid disease, causing reasonable doubt on current priority setting.

Skin colour, age, and disease duration did not interact with HRQL. Generally, pain and itch are frequently reported symptoms of keloid disease (1). Of the patients with pain and itch scores >3, 70% had severe emotional HRQL impairment (Skindex-29) compared with 16% in the group of patients that had low pain and itch scores. Moreover, we showed that pain and itch were consistently and strongly associated with HRQL impairment.

A previous study on HRQL in patients with scars found less pain (26%) and itch (44%) complaints and minimal

Table III. Summary of the multivariate regression analyses for the health-related quality of life outcomes as dependent variable and patient characteristics as dependent variables, in the total group and for males and females

	Skindex-29 ($n = 106$)				SF-36 ($n = 106$)		EQ-5D-5L ($n = 100$)
	Emotional scale	Functional scale	Symptomatic scale	Sum scale	PCS	MCS	Index value
Regression R^2	0.36	0.29	0.60	0.47	0.17	0.11	0.34
	β (p)	β (p)	β (p)	β (p)	β (p)	β (p)	β (p)
Age					−0.25 (0.008)		
Visibility						−0.19 (0.048)	
Number	0.19 (0.21)	0.18 (0.030)		0.16 (0.028)			
Pain	0.45 (<0.001)	0.35 (<0.001)	0.29 (0.002)	0.32 (0.004)	−0.18 (0.077)		−0.28 (0.027)
Itch			0.53 (<0.001)	0.26 (0.030)		−0.28 (0.004)	−0.26 (0.059)
Scar colour					0.31 (0.014)		0.40 (0.001)
Stiffness					−0.33 (0.013)		−0.30 (0.017)
Irregularity	0.19 (0.029)	0.23 (0.013)		0.17 (0.054)			

β: regression coefficient; R^2: proportion of variance explained by the model; SF-36: 36-item Short Form Health Survey; PCS: physical component summary score of SF-36; MCS: mental component summary score of SF-36; Number: number of keloids.

correlations of pain and itch with emotional HRQL (4). These discrepancies can be explained by the large differences between keloids and other scar types, which are less severe than keloids.

Furtado et al. (8) specifically studied keloid patients and similarly found that pain and itch correlated with worse HRQL. They showed non-visible keloids resulted in worse physical HRQL, while we could not find an effect of keloid visibility on physical HRQL. However, we did find impairment of mental HRQL in patients with a visible keloid. Visible keloids could affect HRQL because they are socially more disturbing. Furtado et al. (8) explained that in their population non-visible keloids were long-existing recalcitrant pre-sternal keloids, resulting in worse HRQL in this group.

High-profile reviews on pathological scarring focused mainly on the morphological and disfiguring aspects of keloid disease, and considered the accompanying symptoms of secondary concern (22–24). However, the results of our study challenge this view by clearly showing that itch and pain symptoms are the main indicators of HRQL impairment. Consequently, we believe that these symptoms should be of primary concern in the evaluation and treatment of keloid disease, as well as in scientific research on this topic.

Limitation

A limitation of the current study is that all patients were recruited from academic hospitals, possibly resulting in a selection bias towards patients with a relatively high burden of disease. This could limit the generalizability of the current results to the entire keloid patient population. On the other hand, the patients from the present study represent those who seek treatment from a medical specialist. The sample was evenly distributed on sex and contained a variety of skin types, disease durations, age groups, and other clinical characteristics and had similar composition to other population-samples described in the literature (9, 12). The incomplete response rate could also have introduced selection bias.

Another issue could be the cross-sectional design with online questionnaires for scar quality and HRQL assessment that completely relied on self-reports. Patients may think that exaggerating their burden may result in better treatment, a higher chance of insurance fees or sick leave. These disease induced benefits, or secondary gains, may have influenced their answers. However, a large part of our study group was not currently under treatment or clinically re-evaluated, and was probably less affected by secondary gains.

Conclusion

Our previous report (12) and the present report show that keloid disease is strongly associated with mental and emotional HRQL impairment, which suggests a high need for effective treatment and thus a priority in healthcare policymaking. HRQL is most severely affected in patients with an itching or painful keloid, suggesting that, in these patients, cosmetic appearance is less of a concern than physical symptoms.

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