Healing Time Correlates With the Quality of Scaring: Results From a Prospective Randomized Control Donor Site Trial

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BACKGROUND Scar formation remains a potential problem after surgery or trauma. Factors influencing scar tissue have been recognized, most notably healing time and wound depth.

OBJECTIVE To examine the association between healing time and the quality of scar tissue formation.

MATERIALS AND METHODS Scarring was assessed at 3 and 12 months after treatment in an RCT of 219 patients and consecutive 438 split-thickness skin graft donor sites. The primary end point of the study was healing time and the quality of scar tissue, which was scored by a validated scar scale evaluating scar height, surface, and color.

RESULTS The mean time of wound healing was 15.8 days, with a mean scar score of 6.89 at 3 months and 4.66 at 12 months. There was a significant ($p < .000001$) and linear correlation between healing time and scar quality. Of particular note, at 12 months, all subparameters of the score demonstrated worsening with prolonged time to heal.

CONCLUSION The authors could objectively demonstrate that epithelialization time is an important factor influencing scar quality. In contrast to previous assumptions, this correlation follows linearly. It is reasonable then to assume that treatment strategies expediting healing will also improve scar outcome.

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In humans and most animals, scar tissue formation remains an expected sequela after surgery, traumatic tissue injury, or loss, as well as complicating many other cutaneous dermatopathophysiologic and immunologic diseases. Hypertrophic scarring may lead to functional, aesthetic, and psychological problems. Tragically, even mild scarring may prove particularly disturbing for the patient, and the overall impact of scar formation globally and for the individual remains a widely discussed issue.[1] Many clinical studies and volumes of experimental work have focused on exploring the pathophysiology of hypertrophic scar tissue formation and factors influencing the quality of scar development.[2–15] The avoidance of excessive scarring remains a paramount treatment goal in nearly every surgical discipline.[1]

Numerous factors influencing problematic scar tissue formation have been recognized, most notably are depth of injury,[16–18] wound healing time,[9,10,13,14] patient age,[9,13] race,[7,10,13] and wound location.[15] A recent review has focused on molecular events

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related to inflammation and stem cell cytokine interaction.[19]

Time to complete wound closure is generally reflected by epithelialization, a function of migration, and proliferation of keratinocytes at the wound edge and skin adnexa. Epidermal–mesenchymal interaction may play a role in silencing fibrous tissue development.[20,21]

Depth of injury is traditionally characterized by dermal insult, and the loss of reticular dermis has been associated with an increased severity of scar formation.[16–18,22,23] Work by Dunkin and colleagues[16] suggests that scar formation is solely dependent on depth of dermal injury.

Deitch and colleagues[14] were among the first to formally postulate and explore the profound impact of wound healing time on hypertrophic scar tissue formation. Factors associated with an increased risk of the development of hypertrophic burn scars as evaluated in their 1983 clinical study established that the most important indicator of whether scar problems manifest was the time required for the wound to heal. They observed a significant increase of hypertrophic scar formation in wounds which healed after 14 or 21 days.[14] Interestingly and complementary to their previous results, McDonald postulated in 1987 that operations performed before 14 days postburn lead to a significant improvement in resultant scar quality.[13] These studies on burn injuries, however, did not specifically resolve the general question of whether depth of injury or time for complete reepithelialization is the dominant factor influencing scar formation, information that may prove critical in establishing future treatment algorithms and strategies. These studies also suggest that scar formation follows a stepwise function, with reepithelialization times of under 14 days leading to minimal or no scar formation.[13,14] Unfortunately to date, the authors could identify no definitive prospective randomized control trials in which a conclusion could be reached, establishing the relevant impact on scar development of these 2 individual risk factors. Burn injuries are heterogeneous in depth and pathophysiologic consequence resulting in different epithelialization rates and times. In an effort to differentiate and define the role of both epithelialization and time to wound closure on scaring in general, one requires a more standardized yet clinically relevant study design with a defined wound depth of sufficient size. Donor sites have been used in numerous studies as a defined wound model to answer questions on improvement of healing.[24,25] The aim of this study then was to evaluate the influence of time to wound closure on the development and quality of scar tissue.

Patients and Methods

This report describes the results of 2 open, blindly evaluated, prospective, controlled, randomized, clinical trials, both using the same protocol (study BSG-12: EudraCT no. 2012-003390-26 and study BSH-12: EudraCT no. 2012-000777-23).

Study Design

The primary objective of the precedent study was to examine the impact of wound healing time on the quality of scar tissue. The primary efficacy end point was time to wound closure (≥95% epithelialization) of split-thickness skin graft (STSG) donor sites. The authors subsequently assessed the quality of related scar tissue development at 3 and 12 months.

Split-thickness skin graft donor sites were harvested according to the study protocol (EudraCT no. 2012-003390-26 and EudraCT no. 2012-000777-23), generally with a dermatome using 0.2 to 0.4 mm thickness/wound depth. Afterward, the donor sites of each patient were divided into 2 equal wound halves (upper and lower). Randomization was established using an interactive web response system. The standard control group was treated with a moist wound dressing (most frequently used was Mepilex, Mölnlycke Health Care, Göteborg, Sweden) alone. The treatment group (topical betulin gel [TBG] group) was dressed with the standard moist wound dressing plus TBG (Oleogel-S10, Birken AG, Germany). Every 3 to 4 days (or more frequently if medically necessary), the wound dressing was changed and standardized photodocumentation was performed. Treatment continued up to complete closure of both halves of the wound or, if complete closure of both wound halves was not observed, until day 28. Additional investigations of the wound/scar were performed after 3 and 12 months.

Wound healing was defined as epithelialization of ≥95% of the wound area and was assessed and documented by experienced clinical investigators. If wound closure was not observed, it was assumed to have closed 1 day after the last observation.

The assessment of scar formation after 3 and 12 months was based on a photographic evaluation by a remote panel of 2 masked experts. The authors used the reliable scar scoring system described by Mecott and colleagues.[26] This modified scale consists of 3 parameters as follows: scar height, surface appearance, and color mismatch. Each parameter was assigned a score of 1 (best) to 4 (worst), generating a total score of 3 to 12.

Study protocols were approved by the local ethics committee, and the studies were performed in compliance with International Conference on Harmonization guidelines for Good Clinical Practice and the principles in the Declaration of Helsinki. All investigators and study team members received training in the study protocol and in the standardized acquisition of photographs. Informed consent was obtained from patients before inclusion in the study.

Patients

Adults with STSG donor site wounds ≥15 cm^2 and ≥3 cm wide from 32 hospitals across 10 European countries (France, Spain, Greece, Latvia, Germany, Czech Republic, Poland, Finland, Austria, and Bulgaria) were considered for enrollment. Between August 2012 and September 2013, 219 patients and consequent 438 wound halves were identified for inclusion in this study.

Of these 219 patients, 79 were women and 140 were men. The mean age of these patients was 53 years. One hundred twenty patients (54·8%) had Fitzpatrick skin Type I or II; 99 patients (45,2%) had Fitzpatrick skin Type III, IV, or V. Wound sizes were on average 81.5 ± 66.4 cm^2 and were predominantly (188 of 219) located on the leg.

Of the 219 patients who were treated, 183 patients attended clinical assessment at 3 months and 149 patients participated in assessment after 12 months.

Statistical Analysis

Statistical analysis was performed in cooperation with the Department of Applied Computer Science, University of Würzburg, Germany, using the data analysis toolkit "pandas" (0.18.0) and the scientific computing library "SciPy" (0.17.0) available for the Python programming language (3.5.1).

Of the evaluable photographs, the 2 raters assessed image quality predominantly as good. Only 10 images were rated as poor and unfeasible. Accordingly, scores were calculated for 356 wounds (3-month assessment) and 298 wounds (12-month assessment). Afterward, the interrater correlation for the assessment of scar quality was calculated.

The time to wound closure is presented by both the mean value and range. The scar score was calculated as the mean value of both masked experts. The score is presented with the mean value, the SD, and range (R). Graphically, the scar score in relation to wound healing time is demonstrated by line plots with mean values and 95% confidence intervals. The statistical significance of differences was analyzed using the Wilcoxon signed-rank test. For calculation of the correlation between healing time and scar quality, the Pearson correlation coefficient was used. The significance of the correlation was analyzed with the 2-tailed *t*-test.

Results

The interrater correlation coefficient for the assessment of scar quality was 0.72 (Figure 1), demonstrating a good correlation. The overall mean time for wound healing was 15.8 days (R: 6–29). Wounds treated additionally with TBG healed significantly ($p < .05$) faster (15.3 days) than the intraindividual control wounds without TBG (= standard of care) (16.3 days).

The average scar score after 3 months was 6.89 (SD: 1.71; R: 3–11). The Pearson correlation coefficient (wound healing time/scar quality) was significantly positive ($p < .000001$) with 0.46. The average scar score after 12 months was 4.66 (SD: 1.4; R: 3–9.5). The Pearson correlation coefficient (wound healing time/scar quality) was significant positive ($p < .000001$) with 0.51 (Figure 2).

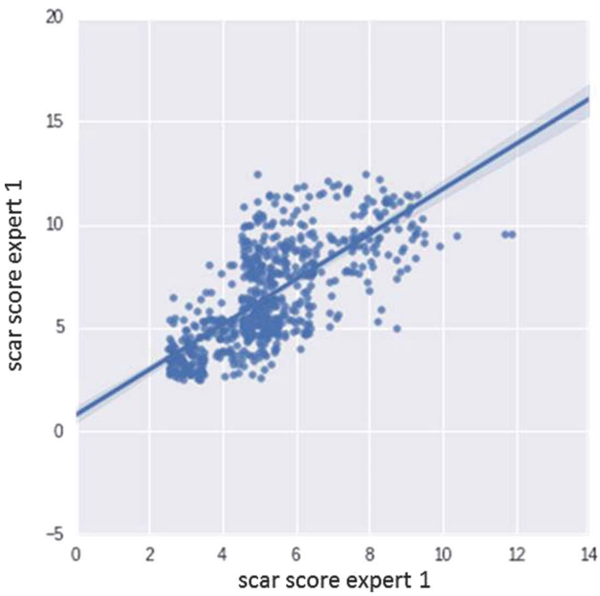

Figure 1. Interrater correlation. Presentation by scatter plot.

Each defined quality of the scar score was analyzed separately and presented in the following table (Table 1 and Figures 3–5).

The authors similarly evaluated patients according to their topical treatment. At 3 months, the mean scar score for the "TBG group" (faster wound healing) was 6.7 (SD: 1.7; R: 3–11) and 7.1 (SD: 1.7; R: 3–11) for the "standard group" (slower wound healing). At 12 months, the mean scar score for the TBG group was

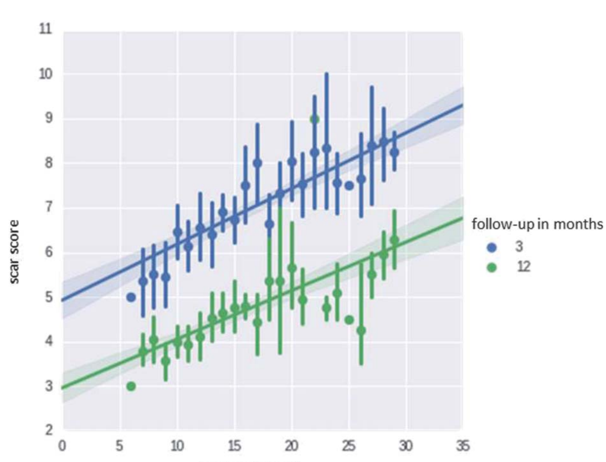

Figure 2. Overall correlation between scar score and time of wound healing after 3 months (n = 356 wounds) and 12 months (n = 298 wounds). Presentation with mean values (dots) and 95% confidence intervals (shaded areas). Significant correlation, $p < .00001$.

4.6 (SD: 1.4; R: 3–9.5) and 4.71 (SD: 1.4; R: 3–9.5) for the standard group. These intraindividual differences between both groups were significant ($p < .05$) at both time points.

Discussion

The formation of a scar after skin injury is a consequence of wound healing occurring through a predominantly reparative rather than regenerative mechanism.[27–29] In accordance with the authors' clinical expectations, the current literature postulates a correlation between healing time and scar tissue development. Most of the existent studies are clinical intervention trials of burn wounds.[9,10,13,14] In these clinical study settings, factors such as depth of the wound, remaining dermal structures in the wound bed, possible surgical intervention, topical dressings, and general conditions all potentially influence scar development and dilute the validity of the available results. Using a standardized accepted wound model, the authors were able to establish the correlation between healing time and scar quality. Using the STSG donor site model with a defined depth, the authors were able to exclude the contribution of different wound depths, a well-recognized factor for excessive scarring. Healing time in this study could therefore be determined by epithelialization, as each patient served as his/her control. The results revealed a strong correlation between the time to epithelialization and the quality of scar tissue development. As time to reepithelialization increases, the quality of the resultant scar decreases (Figure 2).

In contrast to nearly all other studies that the authors reviewed,[9,10,13,14] they were able to demonstrate a linear correlation between healing time and scar tissue at both, 3- and 12-month, end points.

Deitch and colleagues postulated a significant increase of hypertrophic scar development in burn wounds if healing time exceeds 14 days.[14] A very recent multicenter study on scarring by Goei and colleagues[10] evaluated and estimated healing potential as predicted using laser Doppler imaging. The study population was divided into 3 groups of estimated healing time, and the groups were classified as high (<14 days), intermediate (14–21 days), and low (>21 days).[10]

TABLE 1. Overview of the Scar Score and Its Correlation With Healing Time

Average Scar Score, 3 mo	*Pearson Correlation Coefficient, 3 mo*	*Average Scar Score, 12 mo*	*Pearson Correlation Coefficient, 12 mo*
6.89 (SD: 1.71; R: 3–11)	+ 0.46 ($p < .000001$)	4.66 (SD: 1.4; R: 3–9.5)	+ 0.51 ($p < .000001$)
Average Scar Height, 3 mo	*Pearson Correlation Coefficient, 3 mo*	*Average Scar Score, 12 mo*	*Pearson Correlation Coefficient, 12 mo*
1.81 (SD: 0.64; R: 1–3.5)	+0.39 ($p < .000001$)	1.17 (SD: 0.41; R: 1–3.5)	+0.31 ($p < .000001$)
Average Scar Surface, 3 mo	*Pearson Correlation Coefficient, 3 mo*	*Average Scar Surface, 12 mo*	*Pearson Correlation Coefficient, 12 mo*
2.47 (SD: 0.62; R: 1–3.5)	+0.46 ($p < .000001$)	1.67 (SD: 0.58; R: 1–3.5)	+0.49 ($p < .000001$)
Average Color Mismatch, 3 mo	*Pearson Correlation Coefficient, 3 mo*	*Average Color Mismatch, 12 mo*	*Pearson Correlation Coefficient, 12 mo*
2.61 (SD: 0.62; R: 1–4)	+0.42 ($p < .000001$)	1.81 (SD: 0.62; R: 1–3.5)	+0.49 ($p < .000001$)

R, range.

These results, though valuable, can lead to the speculation that scar development follows a stepwise rather than a linear fashion.

The observation of a linear correlation between epithelialization time and scar quality has significant implications for clinical practice. The authors show evidence that even small improvements in healing time have a significant positive impact on the quality of the scar, and every single improvement in expediting healing time will lead to an improvement of the resulting scar tissue.

As demonstrated in the clinical Phase III trials, TBG improves wound healing in different burn wounds and STSG donor sites.[29–31] The results demonstrate that a small decrease in healing results in a lower scar score. Although the TBG group showed only 1 day faster healing time, this slight difference resulted in a significant lower scar score.

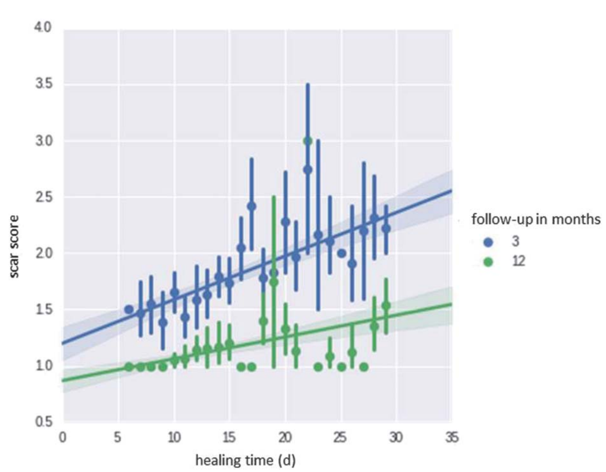

Figure 3. Correlation between "scar height" and time of wound healing after 3 months (n = 356 wounds) and 12 months (n = 298 wounds). Presentation with mean values (dots) and 95% confidence intervals (shaded areas). Significant correlation, $p < .000001$.

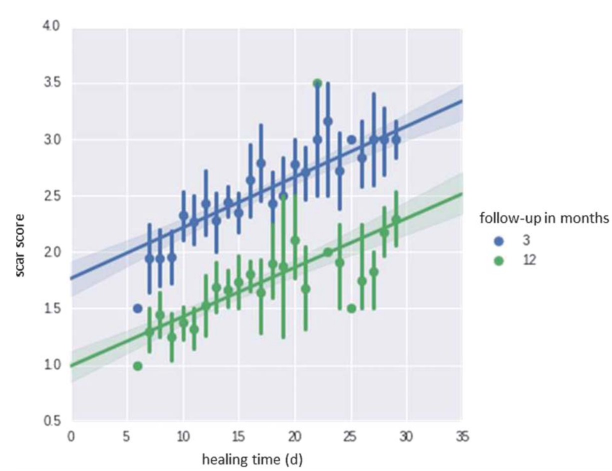

Figure 4. Correlation between "scar surface" and time of wound healing after 3 months (n = 356 wounds) and 12 months (n = 298 wounds). Presentation with mean values (dots) and 95% confidence intervals (shaded areas). Significant correlation, $p < .000001$.

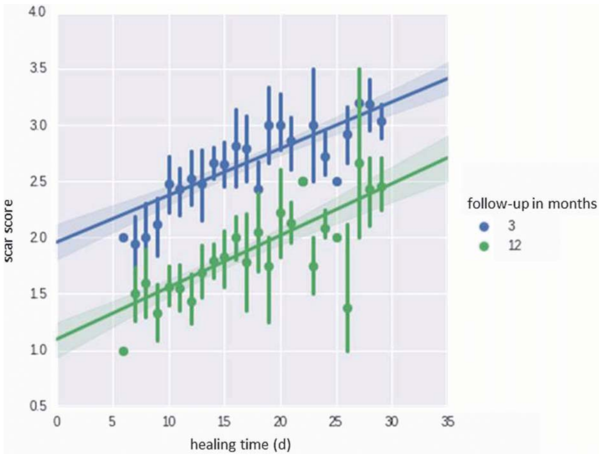

Figure 5. Correlation between "color mismatch" and time of wound healing after 3 months (n = 356 wounds) and 12 months (n = 298 wounds). Presentation with mean values (dots) and 95% confidence intervals (shaded areas). Significant correlation, $p < .000001$.

The results also reinforce the general notion that scar quality improves over time. The authors noted a significant improvement in a scar score as patients progressed from 3 to 12 months after injury. This observation correlates favorably with the results of van der Wal and colleagues.[17] They observed an increase in scar quality between each postoperative assessment performed at 3, 6, and 12 months.[17] Furthermore, the authors were able to demonstrate that the improvement in scar quality is evenly distributed to all 3 investigated scar parameters (height, surface, and color). Based on the observations with a photographic assessment of scars, the authors can conclude that STSG donor sites are still recognizable after 12 months.

It is interesting to note that at 12 months, the correlation coefficients for the parameter "color mismatch" and "surface appearance" were equally high (0.49), and yet, the value for the parameter "scar height" was significantly lower (0.31). It seems that the parameter scar height is less manipulable by wound healing time than the other parameters describing the scar quality.

The authors assessed scaring using remote photo-documentation. At least 10 different scar assessment scales and tools have been created in an attempt to qualify scar severity.[32,33] Although a gold standard scar scale does not yet exist, the patient and observer scar assessment scale (POSAS)[34] has become one of the most clinically applied scoring systems of late and requires a clinical assessment by at least 1 specialist and the patient themself. Although scoring scars through direct clinical examination such as the POSAS seems ideal, in multicenter trials, multiple raters may have an influence on the final result. Rating all scars from a multicenter trial in a remote fashion from photographs can exclude observational bias by multiple reviewers.[32] Reflecting this study design using a multicenter approach, a masked trial design and a very large number of patients, the authors decided to use a scar scoring system that assesses photographs of wounds as previously described by Mecott and colleagues[26] and established as both a valid and reliable tool. The interrater correlation coefficient was excellent, demonstrating the usefulness of this tool. Evaluating a scar based only on a photograph is clearly more challenging than clinical practice, as a single photograph shows only a single 2-dimensional view of the scar. Information on elasticity of the scar and the patient's subjective evaluation concerning its effect on quality of life however cannot be deemed from this methodology.

Conclusion

The results from this study in STSG donor sites verify the correlation between epithelialization time and scar tissue quality. The authors observed a linear correlation between these 2 factors, suggesting that treatment algorithms especially for burn patients, based on a stepwise healing and scarring pattern, have to be revisited. Moreover, treatment strategies or devices improving wound epithelialization even in small measures should be investigated for their potential impact on scar quality. The results revealed a small but positive influence of TBG on scar quality as compared to controls in this defined donor site model. The authors conclude that the speed of epithelialization, independently assessed from depth of cutaneous injury, has a direct influence on scar tissue.

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