Skin Replacement Therapies for Diabetic Foot Ulcers

Systematic review and meta-analysis

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Diabetic ulcer complications are a leading cause of hospitalization and amputation. Of the 20 million individuals with diabetes, 10–15% are at risk for developing diabetic ulcers. Standard therapy involves the use of dressings to protect the wound bed from trauma and to absorb exsudate; offloading high pressure from the wound bed, e.g., by prescribing protective footwear; and wound bed preparation to accelerate endogenous healing and facilitate the effectiveness of topically applied substances. But these measures are often deficient in healing all diabetic ulcers when the patient's own intrinsic wound-healing system is insufficient. In such patients, skin replacement therapies are second-line treatment options; however, the effectiveness of skin replacement therapies in treatment of diabetic ulcers is unclear. The objective of this study is to assess their effectiveness using evidence from randomized trials in diabetic leg and foot ulceration.

RESEARCH DESIGN AND METHODS — We searched the Cochrane Controlled Trials Register (1970–2006), MEDLINE (1966–2006), EMBASE (1980–2006), and CINAHL (1982–2006) using a combination of text and keywords in addition to a filter for controlled clinical trials. The last update of searches was performed on 30 September 2007. We included trials if the allocation of participants was described as randomized, with participants of any age and in any care setting having diabetic leg or foot ulceration. We included studies that compared the following types of grafts with any other intervention: *1*) autografts (pinch, split or full-thickness skin grafts, cultured keratinocytes, or fibroblasts), *2*) allografts (cultured keratinocytes or fibroblasts), *3*) xerografts, and *4*) bioengineered skin.

Two reviewers independently evaluated reports for eligibility and assessed methodological details and results of the studies. Disagreements were resolved by discussion.

The prespecified primary end point was complete healing rate at the end of the trial. Results are presented as odds ratios (ORs 95% CI). We used standard fixed-effects meta-analysis and Cochran's *Q* test for heterogeneity (4). Analyses were performed using Stata (version 9.2; Stata, College Station, TX).

RESULTS — We identified 1,993 references in our literature search, of which 26 reports were retrieved for detailed evaluation. Eleven reports describing seven randomized trials in diabetic foot ulcer patients were identified. One trial comparing an epidermal keratinocyte allograft versus standard care (1) and another trial evaluating meshed skin autograft against split thickness autograft (7) reported continuous outcomes only. Five trials (817 patients) met all inclusion criteria and were included in the meta-analysis.

Three trials compared dermal allografts to standard care (3,5,6). Gentzkow et al. (3) measured a 50% (6 of 12) complete healing rate in the experimental group, whereas 8% (1 of 13) of the ulcers in the control group were completely healed. Naughton et al. (6) reported rates of complete wound closure of 39% (42 of 109) for the treatment group and 32% (40 of 126) for the control group. In the study by Marston et al. (5), 30% (39 of 130) of patients in the experimental group, compared with 18% (21 of 115) in the control group, had complete wound closure.

Veves et al. (8) compared bioengineered skin versus standard care and found 56% (63 of 112) of patients in the treatment group and 38% (36 of 96) in the control group with complete ulcer closure. Caravaggi et al. (2) investigated a combined epidermal and dermal autograft consisting of cultured fibroblasts and keratinocytes. They reported complete ulcer healing of 60% (26 of 43) in the treatment group and 42% (15 of 36) in the control group.

None of the studies identified safety concerns related to the treatment, provided a detailed description of the setting in which the study was done, or noted the proportion of the eligible population that was finally included into the study. Inclusion and exclusion criteria were clearly listed in three trials (2,5,8). The trial duration was 11 (2) or 12 (3,5,6,8) weeks.

The trials have severe methodological limitations. They did not adequately report their recruitment strategy; little information is given on how study participants were randomized and whether trialists concealed allocation of treatment from the person recruiting a patient into the study. None of the trials reported blinded outcome assessment, and none used covariates to account for any differences in the distribution of covariates at randomization. Only two studies reported a priori sample size calculation (2,5). All five studies were funded by biotechnological companies. One trial performed a per-protocol analysis (6). In two trials, it is unclear whether intention-to-treat analysis was performed (3,5). In these trials, we assume that all randomized patients have finally been included in the analysis because there is no mention of dropouts. Two trials reported dropout

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Received for publication 30 October 2007 and accepted in revised form 16 December 2007.

Published ahead of print at http://care.diabetesjournals.org on 27 December 2007. DOI: 10.2337/dc07-2081.

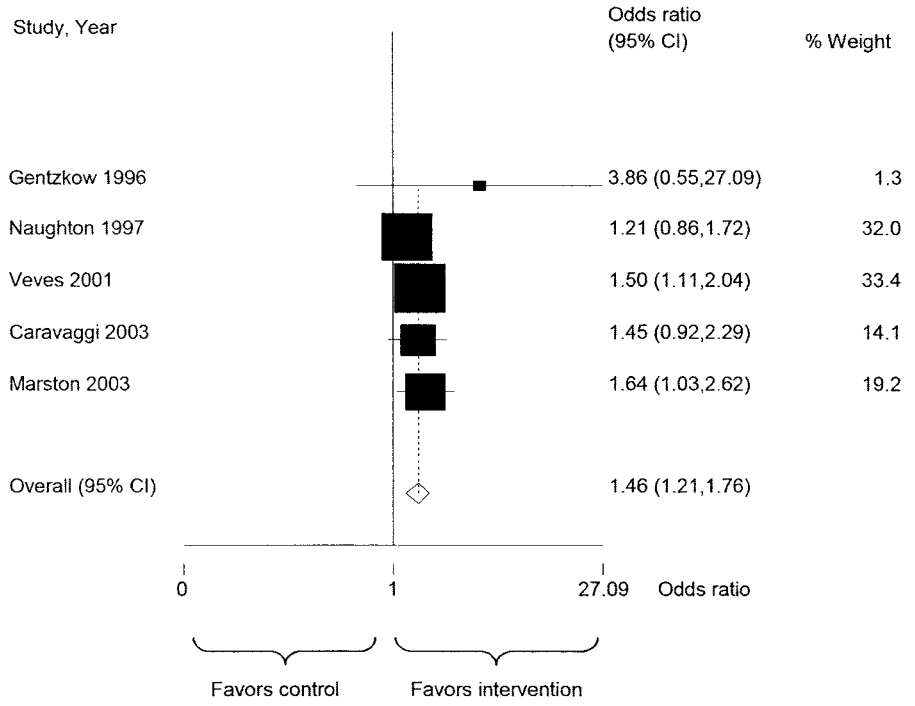

Figure 1—*Forest plot of five trials comparing cultured skin equivalents with standard care.*

rates in the intervention and control group and the performance of an intention-to-treat analysis (2,8).

All five trials showed effect estimates in favor of the intervention, with odds ratios ranging from 1.21 (6) to 3.86 (3). The 95% CI did not include the null effect in two trials (5,8), but results of three studies did not show a statistically significant effect (2,3,6). There was no evidence from statistical tests of heterogeneity between trials. The pooled estimate was 1.46 (95% CI 1.21–1.76), showing a significant effect in favor of cultured skin equivalents in comparison with standard care (Fig. 1).

CONCLUSIONS — This systematic review identified a small number of randomized controlled trials investigating the effect of cultured skin equivalents on foot ulcers. No trials on surgical skin grafting or xerografts or in patients with leg ulcers were identified. This study is based on a broad literature search, and it seems unlikely that relevant trials were missed.

The questionable quality of the included trials affects the strength of the conclusions and reduces our confidence in the individual study results. Furthermore, the trials did not report the settings in which the therapies were applied or how therapies were embedded in usual care processes. Most patients are managed in primary care and the generalizability of the results to real-world settings is unclear.

Therefore, we recommend further high-quality large-scale trials, especially those investigating surgical skin autografts and comparing different skin replacement methods. Future trials should adhere to methodological standards that reduce possible biases. Reports of trials should adhere to generally accepted standards of reporting of clinical trials (e.g., the Consolidated Standards of Reporting Trials Statement). They should include a clear description of recruitment strategy, baseline patient characteristics, and setting.

Given the small number of studies identified, their methodological flaws, the different types of cultured skin equivalents they investigated, and the absence of randomized trials investigating surgical autografts or xerografts, no conclusive recommendations for clinical practice can be made. However, cultured skin equivalents have potential because in contrast to surgical grafting, large wounds at the graft site and hospitalization for application can be avoided.

In conclusion, there are some hints that cultured skin equivalents may be promising treatment options for diabetic foot ulcers; however, evidence is sparse, and conclusive recommendations cannot be made until high-quality controlled studies are performed.

Acknowledgments— We thank Kerstin Heyde and Sophie Zitterbart from the Department of General Practice and Family Medicine, University of Göttingen, for their support in quality assessment and data extraction.

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