Skin replacement therapies for diabetic foot ulcers: Systematic review and meta-analysis

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ABSTRACT

Diabetic ulcers complications are a leading cause of hospitalization and amputation. Ten to 15% of the 20 million individuals with diabetes are at risk of developing diabetic ulcers. Standard therapy involves the use of dressings to protect the wound bed from trauma and to absorb exudate, offloading of high pressure on the wound bed e.g. by prescribing protective footwear, and wound bed preparation to accelerate endogenous healing and to facilitate the effectiveness of topically applied substances. But these measures are often deficient to heal all diabetic ulcers when the patient’s own intrinsic wound healing system is insufficient. In this group of patients skin replacement therapies are second line treatment options. However, the evidence of skin replacement therapies in diabetic ulcers is unclear. The objective of this study is to assess their 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 key- and text-words plus a filter for controlled-clinical trials. The last update of searches was performed on Sept 30, 2007. We included trials if the allocation of participants was described as randomized with participants of any age and in any care setting with diabetic leg or foot ulceration. We included studies which compared the following types of grafts with any other intervention:

- autografts: pinch, split thickness, or full thickness skin grafts, cultured keratinocytes or fibroblasts,
- allografts: cultured keratinocytes or fibroblasts,
- xerografts,
- bioengineered skin.

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

The pre-specified primary end-point was complete healing rate at the end of the trial. Results are presented as odds ratios (OR) with 95% confidence intervals (CI). We used standard fixed effects meta-analysis and Cochran’s Q test for heterogeneity (4). Analyses were performed using Stata 9.2 (Stata Corporation, College Station, Tex).

RESULTS

We identified 1993 references in our literature search. Of those, 26 reports were retrieved for detailed evaluation. Eleven reports describing 7 randomized trials in diabetic foot ulcer patients were identified. One trial comparing an epidermal keratinocyte allograft versus standard care (1) and one 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 measured a 50% (6/12) complete healing rate in the experimental group, whereas 8% (1/13) ulcers in the control group were completely healed (3). Naughton reported rates of complete wound closure of 39% (42/109) for the treatment group and 32% (40/126) for the control group (6). In Marston’s study, 30% (39/130) of patients in the experimental group as compared to 18% (21/115) in the control group had complete wound closure (5). Veves compared bioengineered skin versus standard care and found 56% (63/112) in the treatment group and 38% (36/96) in the control group with complete ulcer closure (8). Caravaggi investigated a combined epidermal and dermal autograft consisting of cultured fibroblasts and keratinocytes. He reported complete ulcer healing of 60% (26/43) in the treatment group and 42% (15/36) in the control group (2). None of the studies identified safety concerns related to the treatment.

None of the reports provided detailed description of the setting in which the study was done and of the proportion of the eligible population which was finally included into the study. Inclusion and exclusion criteria were clearly listed in 3 trials (2, 5, 8). The trial duration was 11 (2) or 12 (3, 5, 6, 8) weeks.

The trials have severe methodological limitations. Trials 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, since there was no mention of drop outs. Two trials reported drop out rates in the intervention and control group and reported to perform 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 for 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 (Figure 1).

CONCLUSIONS

This systematic review identified a small number of randomized controlled trials investigating the effects of cultured skin equivalents for foot ulcers. No trials on surgical skin grafting, on xerografts and 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.

Problems with the quality of the trials included affect the strength of the conclusions and reduce the trust in the individual study results. Furthermore, the trials did not report the settings in which the therapies were applied and 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 high quality large-scale trials, especially those investigating surgical skin autografts and comparing the 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 (for example, the Consolidated Standards of Reporting Trials statement). They should include a clear description of recruitment strategy and reporting of baseline patient characteristics and setting.

Given the small number of the studies identified, their methodological flaws, and the different types of cultured skin equivalents they investigated, and in the absence of randomized trials investigating surgical autografts or xerografts, no conclusive recommendations for clinical practice can be made. However, cultured skin equivalents have a potential because, in contrast to surgical grafting, large wounds at the graft side 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, yet evidence is sparse and conclusive recommendations can not be made until good quality controlled studies are performed.

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REFERENCES

FIGURE 1. Forest plot of 5 trials comparing cultured skin equivalents with standard care

<table>
<thead>
<tr>
<th>Study, Year</th>
<th>Odds ratio (95% CI)</th>
<th>% Weight</th>
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<tbody>
<tr>
<td>Gentzkow 1996</td>
<td>3.86 (0.55, 27.09)</td>
<td>1.3</td>
</tr>
<tr>
<td>Naughton 1997</td>
<td>1.21 (0.86, 1.72)</td>
<td>32.0</td>
</tr>
<tr>
<td>Veves 2001</td>
<td>1.50 (1.11, 2.04)</td>
<td>33.4</td>
</tr>
<tr>
<td>Caravaggi 2003</td>
<td>1.45 (0.92, 2.29)</td>
<td>14.1</td>
</tr>
<tr>
<td>Marston 2003</td>
<td>1.64 (1.03, 2.62)</td>
<td>19.2</td>
</tr>
<tr>
<td>Overall (95% CI)</td>
<td>1.46 (1.21, 1.76)</td>
<td></td>
</tr>
</tbody>
</table>

Favors control  Favors intervention