The evidence for the use of growth factors and active skin substitutes for the treatment of non-infected diabetic foot ulcers (DFU): a health technology assessment (HTA)


CRD summary
This review concluded that add-on therapy with growth factors or active skin substitutes could be an alternative to standard wound care alone for treatment of diabetic foot ulcers, but their use could not be explicitly recommended without stronger evidence. These conclusions appropriately reflect the limitations of the evidence presented.

Authors' objectives
To assess the safety and effectiveness of growth factors alone or in combination with other technologies in the treatment of diabetic foot ulcers.

Searching
MEDLINE, EMBASE, The Cochrane Library and 32 other databases were searched from 1990; the latest search date was not reported. Search terms were not reported in the paper. The search was limited to publications in German and English. Websites of health technology assessment agencies and reference lists of included articles and relevant reviews were screened to identify additional studies.

Study selection
Randomised controlled trials (RCTs) that evaluated recombinant growth factors or metabolically active skin grafts secreting growth factors were eligible. Trials had to focus on the treatment of diabetic foot ulcers. Included trials evaluated becaplermin, recombinant human epidermal growth factor (rhEGF), basic fibroblast growth factor (BFGF), Dermagraft and Apligraf. Further details of these products were not reported in the paper. Most trials compared the growth factor products with placebo or standard wound care. Study duration ranged from 12 to 20 weeks. The main outcomes evaluated were complete healing and time to complete healing. Ulcer size and duration at baseline varied widely between trials. Some trials had statistically significant differences between groups at baseline.

Two reviewers independently selected studies for the review. Disagreements were resolved by discussion.

Assessment of study quality
Quality was assessed using a modified version of the checklist of the German Scientific Working Group Technology Assessment for Health Care. This covered randomisation, allocation concealment, sample size calculation, reporting of drop-outs and intention-to-treat (ITT) analysis.

Quality assessment was done by two reviewers independently; disagreements were resolved by discussion.

Data extraction
Data were extracted on outcomes for each group and whether differences between groups were statistically significant. For one comparison, data of numbers of patients and events in each group were used to calculate the odds ratio (OR) for complete wound closure and its 95% confidence interval.

Two reviewers independently extracted data. Disagreements were resolved by discussion. Authors were contacted to obtain missing data if necessary.

Methods of synthesis
A mostly narrative synthesis was presented. Meta-analysis was performed where trials were considered sufficiently similar. Statistical heterogeneity was assessed using the $X^2$ test and $I^2$ statistic and if present a random-effects model was used for meta-analysis.

Results of the review
Fourteen trials (1,646 participants, range 17 to 382) were included. Randomisation and allocation concealment were
unclear or absent in many trials. Only one trial had an adequate sample size calculation and none reported an adequate ITT analysis.

Most trials showed a statistically significant benefit of the growth factor product for complete healing, time to complete healing or both. There was no statistically significant benefit of becaplermin compared with the extracellular wound matrix OASIS or BFGF compared with placebo (results not shown). Rates of adverse events were similar between groups.

A meta-analysis of four trials indicated that Dermagraft significantly increased the odds of complete wound closure compared with standard wound care (OR 2.65, 95% CI 1.11 to 6.30). Statistical heterogeneity was significant ($\eta^2 = 67\%$, $p=0.03$).

Cost information
A separate review of economic evaluations identified nine studies, all of which found growth factor treatment to be cost effective or cost saving.

Authors’ conclusions
Add-on therapy with growth factors or active skin substitutes could be an alternative to standard wound care alone but could not be explicitly recommended without stronger evidence.

CRD commentary
The review question and inclusion criteria were generally clear, although it was unclear whether outcomes of interest were specified in advance. The search was thorough but restricted to published studies in English and German, which meant that publication and language biases could not be ruled out. Measures were taken to minimise reviewer errors or bias. Study quality was assessed appropriately and the results were used in the synthesis. Some relevant details of included trials were reported. The mostly narrative synthesis was appropriate in view of the heterogeneity of the included trials.

The authors’ cautious conclusions reflect the limitations of the evidence presented (generally small and poor quality trials) and seem appropriate.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that future studies should have an adequate sample size and should investigate patient-relevant outcomes such as quality of life, tolerance of and compliance with treatment as well as clinical outcomes.

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