

# Review: In patients with chronic diabetic foot ulcers, hyperbaric oxygen reduces major amputations

Liu R, Li L, Yang M, Boden G, Yang G. Systematic review of the effectiveness of hyperbaric oxygenation therapy in the management of chronic diabetic foot ulcers. *Mayo Clin Proc.* 2013;88:166-75.

Clinical impact ratings: **GM** ★★★★★☆☆ **EP** ★★★★★☆☆ **PR** ★★★★★☆☆

## Question

In patients with chronic diabetic foot ulcers, what are the efficacy and safety of hyperbaric oxygen (HBO) therapy added to usual care?

## Review scope

Included studies compared usual care (e.g., control of glycemia, revascularization, debridement, off-loading, and metabolic and infection controls) plus HBO with usual care alone in patients with type 1 or type 2 diabetes and chronic lower-extremity ulcers attributable to diabetes. Outcomes included ulcer healing (complete epithelialization of the wound), major (above the ankle joint) or minor (below the ankle joint) amputation, and adverse events.

## Review methods

MEDLINE and EMBASE/Excerpta Medica (both to Apr 2012); Cochrane Library (2012); reference lists; abstracts of major diabetes, endocrinology, and plastic surgery meetings (2003 to Apr 2012); and trial Web sites (www.clinicaltrials.gov, www.novonordisk-trials.com, and www.clinicalstudyresults.org) were searched for randomized controlled trials (RCTs) and nonrandomized controlled trials. 13 trials ( $n = 624$ ), including 7 RCTs ( $n = 359$ , mean age range 53 to 72 y; follow-up range 2 to 92 wk), met selection criteria. No RCT reported allocation concealment, 2 had blinding, 3 used a random-number generator, and all reported loss to follow-up. Only the results of RCTs are presented here.

## Main results

Meta-analyses of RCTs show that adding HBO to usual care reduced major amputations compared with usual care alone (Table). Minor amputations and adverse events did not differ between groups (Table).

## Conclusion

In patients with chronic diabetic foot ulcers, adding hyperbaric oxygen to usual care reduces major amputations.

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## Commentary

The 7 RCTs summarized by Liu and colleagues show that HBO may increase healing of diabetic foot ulcers and reduce major amputations. Confidence in this evidence is low to moderate, balanced between the inconsistency of results across studies and the small number of events, and the very large (7-fold) effect found for healing rate. Despite the inconsistency, all point estimates for RCTs and observational studies are favorable for HBO and healing (Peto odds ratio 7.57, 95% CI 4.35 to 13.19; Peto odds ratio is a suitable estimate for meta-analyses that include studies with 0 events). Publication bias is a concern when all trials are small and positive. A recent large observational study, however, showed that HBO decreased healing and increased amputations (1), probably due to selection bias given that the worst, more recalcitrant ulcers are usually referred to HBO. The real effect should be derived from RCTs.

In practice, HBO sometimes works and sometimes not. There are several reasons for the varied responses observed in research and practice. First, a common misconception is that it works alone. HBO is an adjunctive therapy that should be delivered after an individualized approach with other wound care standards (e.g., debridement, revascularization, off-loading). In practice, once patients are referred to HBO, other wound care methods usually stop or decrease in intensity. Second, diabetic foot ulcers have multiple causes (e.g., ischemic, neuropathic, infectious) that affect how we should treat them and how they respond to HBO. Third, HBO is approved by society guidelines (2) and is funded by payers for Wagner III or higher ulcers that have failed 30-day standard therapy. In reality, only recalcitrant cases that have persisted for a much longer time are referred to HBO.

The results of the review by Liu and colleagues are consistent with a beneficial effect in some, but not all, diabetic foot ulcers. We recommend proper evaluation of the patient to establish an individualized diagnostic and treatment strategy that includes HBO. As wound care practitioners say, “Consider the whole patient, not just the hole in the patient.”

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### Usual care plus hyperbaric oxygen therapy (UC + HBO) vs UC alone in patients with chronic diabetic foot ulcers\*

Outcomes	Number of trials (n)	Weighted event rates		At 2 to 92 wk	
		UC + HBO	UC alone	RBI (95% CI)	NNT (CI)
Healed ulcers†	4 (233)	81%	11%	664% (-26 to 7793)	NS
				<b>RRR (CI)</b>	<b>NNT (CI)</b>
Major amputation‡	6 (331)	NR	NR	76% (52 to 88)	Not calculable
				<b>RRI (CI)</b>	<b>NNH (CI)</b>
Minor amputation§	4 (204)	28%	18%	55% (-3 to 147)	NS
Adverse events	4 (201)	12%	8.3%	41% (-34 to 198)	NS

\*NR = not reported; NS = not significant; RBI = relative benefit increase; other abbreviations defined in Glossary. Weighted event rates, RBI, RRR, RRI, NNT, NNH, and CI calculated from control event rates and relative risks in article.

†Complete epithelialization of the wound. Analysis based on a random-effects model since heterogeneity was 79%.

‡Amputation above the ankle joint. Analysis based on a fixed-effect model.

§Amputation below the ankle joint. Analysis based on a fixed-effect model.

## References

- Margolis DJ, Gupta J, Hoffstad O, et al. Lack of effectiveness of hyperbaric oxygen therapy for the treatment of diabetic foot ulcer and the prevention of amputation: a cohort study. *Diabetes Care.* 2013;36:1961-6.
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