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Systematic Review of the Effectiveness of Hyperbaric Oxygenation Therapy in the Management of Chronic Diabetic Foot Ulcers

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Abstract

Objective: To assess the efficacy and safety of hyperbaric oxygenation (HBO) therapy as adjunctive treatment for diabetic foot ulcers with a systematic review and meta-analysis of the literature.

Methods: MEDLINE, EMBASE, and the Cochrane Library were searched to find relevant articles published up to April 20, 2012, without restriction as to language or publication status. All controlled trials that evaluated adjunctive treatment with HBO therapy compared with treatment without HBO for chronic diabetic foot ulcers were selected. A meta-analysis was performed to assess the efficacy and safety of hyperbaric oxygen in managing foot ulcers.

Results: Thirteen trials (a total of 624 patients), including 7 prospective randomized trials, performed between January 1, 1966, and April 20, 2012, were identified as eligible for inclusion in the study. Pooling analysis revealed that, compared with treatment without HBO, adjunctive treatment with HBO resulted in a significantly higher proportion of healed diabetic ulcers (relative risk, 2.33; 95% CI, 1.51-3.60). The analysis also revealed that treatment with HBO was associated with a significant reduction in the risk of major amputations (relative risk, 0.29; 95% CI, 0.19-0.44); however, the rate of minor amputations was not affected (P=.30). Adverse events associated with HBO treatment were rare and reversible and not more frequent than those occurring without HBO treatment (P=.37).

Conclusions: This meta-analysis reveals that treatment with HBO improved the rate of healing and reduced the risk of major amputations in patients with diabetic foot ulcers. On the basis of these effects, we believe that quality of life could be improved in selected patients treated with HBO.

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The worldwide epidemic of type 2 diabetes mellitus has brought increased attention to some of its common complications, such as foot ulcers, secondary infections, and limb amputations.[1,2] The development of diabetic foot ulcers is driven primarily by the effects of peripheral sensory neuropathy on foot biomechanics (foot deformity being associated with high pressures in specific weight-bearing areas).[3] Lower extremity ulcers are responsible for 20% of diabetes-related hospital admissions and are a major source of morbidity and loss of income for patients with diabetes mellitus.[4,5] Treatment is often prolonged and is sometimes unsuccessful, and the patients are prone to serious complications. Traditional management is based on cleansing, debridement, and eliminating infections.[6-9] Many different interventions have been proposed to accelerate the healing process, but few have been subjected to strict evaluation.

Hyperbaric oxygenation (HBO) has been proposed as an adjunctive treatment for diabetic foot ulcers[9-11] and has been reported to reduce the incidence of major amputations in diabetic patients with ischemic foot ulcers.[12] The value of HBO therapy, however, remains controversial because of conflicting data in the literature.[13-18] We believe that a systematic review of the literature, comparing treatment of chronic diabetic foot ulcers with and without HBO, would help clinicians and policymakers decide whether HBO therapy should be more widely used. Therefore, this review analyzes peer-reviewed medical publications that have reported results of HBO as an adjunctive treatment for diabetic foot ulcers.

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METHODS

Data Sources and Search

We conducted a systematic literature search of MEDLINE (1966 to April 20, 2012), EMBASE (1974 to April 20, 2012), and the Cochrane Library (2012) for studies reporting on HBO therapy of diabetic foot ulcers. In addition, we searched the reference lists of relevant publications, reviewed the abstracts of selected scientific meetings (American Diabetes Association, the Society for Research on HBO, and other major diabetes and endocrinology or plastic surgery scientific meetings) from 2003 to April 20, 2012. Other completed but still unpublished trials were identified and retrieved from the www.clinicaltrials.gov, www.novonordisk-trials.com, and www.clinicalstudyresults.org websites. For these electronic searches, we used versions of Medical Subject Headings and main keywords (*diabetic foot, diabetic lower extremity ulcers, diabetic leg ulcers, diabetic wounds, diabetes and chronic foot ulcer,* and *hyperbaric oxygenation* OR *hyperbar** OR *oxygen*) but limited them to *clinical trial* and *human*.

Study Selection

The identification of relevant abstracts and the selection of studies on the basis of the criteria described in this article were performed independently by 2 of the authors (R.L. and M.Y.), and any discrepancy was resolved by a third investigator (G.Y.).

Clinical trials were included if they met all the following criteria: (1) randomized controlled trials (RCTs) or unrandomized controlled trials using either crossover or parallel designs, conducted in humans and published in any language; (2) inclusion of patients with type 1 or type 2 diabetes with chronic lower extremity ulcers; (3) regular interventions performed for control of glycemia, revascularization, debridement, off-loading, and metabolic and infection controls assessed as outcome; (4) full-text articles of controlled trials examining HBO plus traditional therapy vs therapy without HBO; (5) reporting of proportion of healed ulcers, major or minor amputations, adverse events, quality of life, and cost-effectiveness from baseline to end of trial and the corresponding variances; and (6) inclusion of both prospective and retrospective studies. Studies that assessed the efficacy and safety of HBO therapy in managing foot ulcers attributable to causes other than diabetes, that did not report the outcomes of interest, in which it was impossible to assess the outcomes from the published results, or that lacked a control group were excluded.

Data Extraction and Quality Assessment

The primary clinical outcome of interest was the effect of HBO therapy on ulcer healing defined as complete epithelialization of the wound. Secondary outcomes included major or minor amputations. Furthermore, data on adverse events, quality of life, and cost-effectiveness were evaluated and tabulated along with death from any cause. Two reviewers independently extracted data from each study, including study title, first author, publication year, institution, population demographics, study design, follow-up period, inclusion and exclusion criteria, and main outcomes (healing percentages, major or minor amputations, adverse events, quality of life, and cost-effectiveness). Duplicate reports were merged. If outcomes from the same patients were published in multiple articles with different follow-up periods, we extracted the outcomes from the first study and the outcomes of the follow-up studies from the later reports. When studies from the same institution reported the same outcomes at similar follow-up periods, either the better quality or the most informative reports were selected.

The quality of the included RCTs was assessed by 3 categories, ranging from A (high quality) to C (low quality).[18] These categories included the randomization procedure, the use of intention-to-treat analysis, dropout rate, allocation concealment, and the extent to which valid outcomes were described (Table 1). Any disagreement regarding study quality was resolved by discussion among the authors.

Statistical Analyses

The RCTs in this meta-analysis were included according to the QUOROM guidelines.[24,25] For categorical variables, the relative risk (RR) was used to compare the event ratio between the study group (HBO therapy) and the control group (no HBO therapy). In the case of adverse events, an RR of less than 1 favored the study group. Statistical significance was assumed at the $P<.05$ level. A fixed-effects model was chosen on the presumption that variation in the individual trial results occurred around

TABLE 1. Quality Assessment of Randomized Clinical Studies

Reference	Allocation concealment	Blinding	Randomized generator	Lost to follow-up	Score
Löndahl et al,[19] 2011	No	Yes	Yes	Yes	4
Duzgun et al,[20] 2008	No	No	Yes	Yes	2
Abidia et al,[21] 2003	No	Yes	Yes	Yes	3
Kessler et al,[22] 2003	No	No	No	Yes	1
Faglia et al,[12] 1996	No	No	No	Yes	1
Doctor et al,[13] 1992	No	No	No	Yes	1
Leslie et al,[23] 1988	No	No	No	Yes	1

a true mean. Otherwise, the random-effects model was adopted. The heterogeneity of effects was calculated using χ^2 and I^2 tests. An I^2 of more than 50% was considered to indicate heterogeneity, and the random-effects model was adopted. All statistical analyses were performed with Stata statistical software, version 10 (StataCorp).

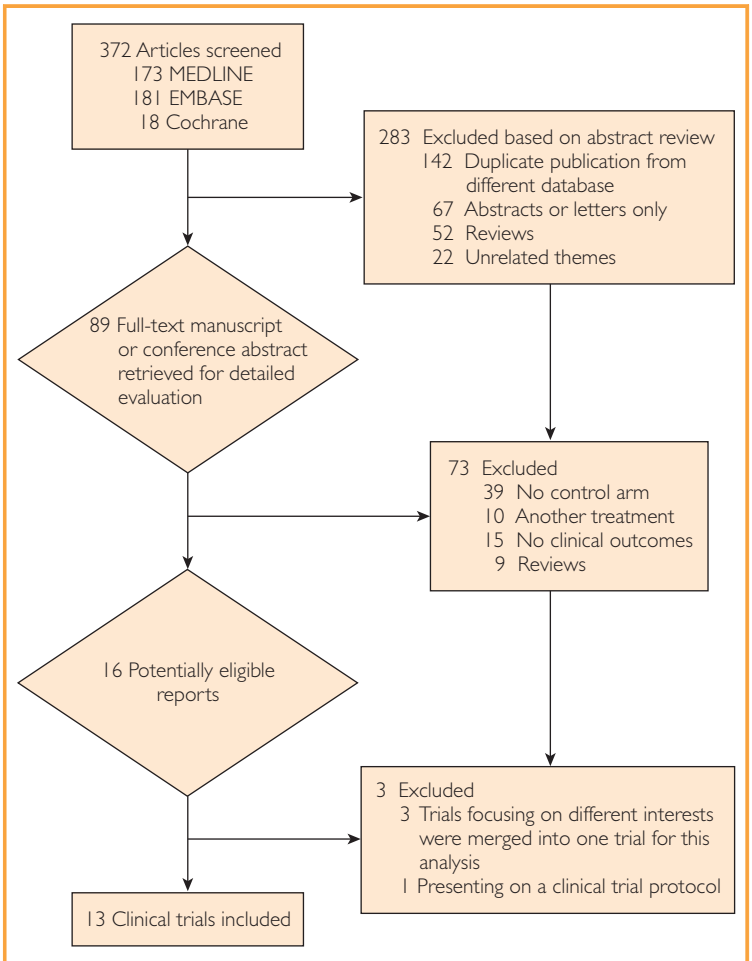

FIGURE 1. Study flow diagram.

We examined each study for potential selection, attrition, and detection bias. To verify possible bias associated with inadequate allocation or randomization, the quality of studies was evaluated. A funnel plot of primary end point outcomes or important secondary outcomes was examined to assess potential publication bias. In addition, the association between variance and effect size was analyzed by the Begg adjusted rank correlation test. Sensitivity analyses were conducted to estimate the strength of outcomes and to explore the influence of trial design and methods on the effect size.

RESULTS

Trial Flow and Characteristics

We identified a total of 89 relevant articles comparing adjunctive HBO therapy and conventional therapy for treatment of chronic diabetic foot ulcers. Sixteen articles[12,13,15,19-21,23,26-34] met our inclusion criteria. Three of these articles,[19,26,28] reporting different aspects of the same trial, were combined into one trial. However, the article by O'Reilly et al[27] was a study protocol without experimental results and was excluded. Results from 13 trials that included 624 participants (published between 1966 and April 20, 2012) were reviewed (Table 2). The flowchart listing reports screened and those included in this review is shown in Figure 1.

The study design was prospective and randomized in 7 studies,[12,13,19-23] prospective and nonrandomized in 4 studies,[15,16,18,26] and case-control in 2 studies[29,31] (Table 2). The overall quality was assessed on a 3-point scale according to the Cochrane handbook. All included articles scored B (moderate quality). In addition, because of the various trial designs and follow-up periods (from 30 days to 3 years), we compared subgroups with various follow-up periods to reduce heterogeneity.

Proportion of Ulcers Healing

Short-term Follow-up (≤6 Months). Ten studies[14,15,19-22,29-31,33] reported healing rates at final follow-up. Healing was defined as ulcers that were completely covered by epithelial regeneration. Although the overall pooled data revealed a statistically significant beneficial

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TABLE 2. Characteristics of 13 Clinical Controlled Trials of Diabetic Foot Ulcers Treated With or Without Hyperbaric Oxygenation

Reference	Study design	Inclusion criteria	Follow-up	Patients undergoing HBO therapy/therapy without HBO		
				No. of patients	Age (y), mean ± SD	No. with IUDM
Löndahl et al,[19] 2011	Randomized prospective	Chronic DFU >3 mo	12 mo	38/37	67±8.5/71±7	26/32
Blackman et al,[33] 2010	Nonrandomized prospective	Chronic DFU	24 mo	17/11	62.4±9.7/63.4±9.6	NA
Duzgun et al,[20] 2008	Randomized prospective	DFU >4 wk	92±12 wk	50/50	58.1±11.03/63.3±9.15	NA
Albuquerque and Sousa,[29] 2005	Retrospective	DFU >6 mo	55 mo	55/41	61.1±12.9/64.2±13.7	18/17.1
Abidia et al,[21] 2003	Randomized prospective	Ischemic DFU >6 wk	12 mo	8/8	72±12.6/70±6.6	NA
Kessler et al,[22] 2003	Randomized prospective	Nonischemic DFU >3 mo	1 mo	14/13	60.2±9.7/67.6±10.5	14/15
Kalani et al,[30] 2002	Nonrandomized prospective	Chronic DFU >2 mo	3 y	17/21	54±14/65±11	65/43
Zamboni et al,[15] 1997	Nonrandomized prospective	Nonhealing DFU	4-6 mo	5/5	63.6±3.96/53.8±3.50	NA
Faglia et al,[12] 1996	Randomized prospective	Ischemic DFU >1 mo	3 mo	35/33	61.7±10.4/65.6±9.1	60/66.7
Doctor et al,[13] 1992	Randomized prospective	Chronic DFU	2 mo	15/15	56.2/59.8	15/20
Oriani et al,[14] 1992	Nonrandomized prospective	Diabetic foot gangrene	3 mo	62/18	52.7±12.4/58.2±8.2	NA
Leslie et al,[23] 1988	Randomized prospective	DFU	2 wk	12/16	52.8±8.6/46.2±8.5	0/33
Baroni et al,[31] 1987	Retrospective	Diabetic foot gangrene	NA	18/10	67±8.5/71±7	NA

DFU = diabetic foot ulcer; HBO = hyperbaric oxygenation; IUDM = insulin-using diabetes mellitus; NA = not available.

effect in HBO-treated cases (RR, 2.33; 95% CI, 1.51-3.6), there was a great deal of heterogeneity (I^2=50.4%) (Figure 2, A). Because healing of diabetic ulcers might be influenced by the length of treatment, a random-effects model analysis was adopted to assess the proportion of healed ulcers, and subgroup analyses were performed to assess results of trials with short-term follow-up (≤6 months). The results revealed that even short-term HBO treatment (≤6 months) improved healing rates (RR, 1.50; P=.02) without heterogeneity (I^2=0).

Long-term Follow-up (≥1 Year). Seven trials (366 participants), representing 58.6% of all patients in this review,[19-21,29-31,33] had follow-up periods of 1 year or more. There was a statistically significant increase in the proportion of healed ulcers after HBO therapy, and the long-term follow-up results demonstrated a larger RR (2.97) compared with the RR (1.50) of the short-term subgroup results (P<.01).

RCT Subanalysis. A total of 300 patients in 4 RCTs were assessed for wound healing as the primary outcome. There were large heterogeneities in the subanalysis (I^2=79.4%) and in the total population (Figure 2, B). To strengthen the power of the meta-analysis and to decrease heterogeneity, the study by Duzgun et al[20] was excluded because it reported healing only with conservative therapy without surgical intervention. Exclusion of the data of Duzgun et al improved the beneficial effects of adjunctive HBO therapy (RR, 2.13; 95% CI, 1.392-3.259; P=.04).

Major and Minor Amputation

Major Amputation. The most serious complication (ie, major amputations, defined as amputations above the ankle joint) was assessed in 11 trials, which found that there were significantly fewer major amputations in patients undergoing HBO therapy compared with conventional therapy without HBO. The pooled RR (Mantel-Haenszel) was 0.29 (95% CI, 0.19-0.44; P<.01). No heterogeneity was detected (P=.26; Figure 3). As seen in Figure 3, the results of subgroup analyses with only RCTs also demonstrated reduced risk of major amputation (RR, 0.24; 95% CI, 0.12-0.48; P<.01).

Minor Amputation. Five trials, including 4 RCTs, provided data on minor amputations distal to the ankle joint with outcome assessment for up to 55 months. Pooled analysis of these data resulted in an RR of 1.24 (95% CI, 0.83-1.85; P=.30), revealing identical minor amputation rates between HBO and conventional therapy and no evidence to suggest statistical heterogeneity (P=.37) (Figure 4, A). Subgroup analysis with RCTs revealed similar rates of minor amputations (RR, 1.55; 95%

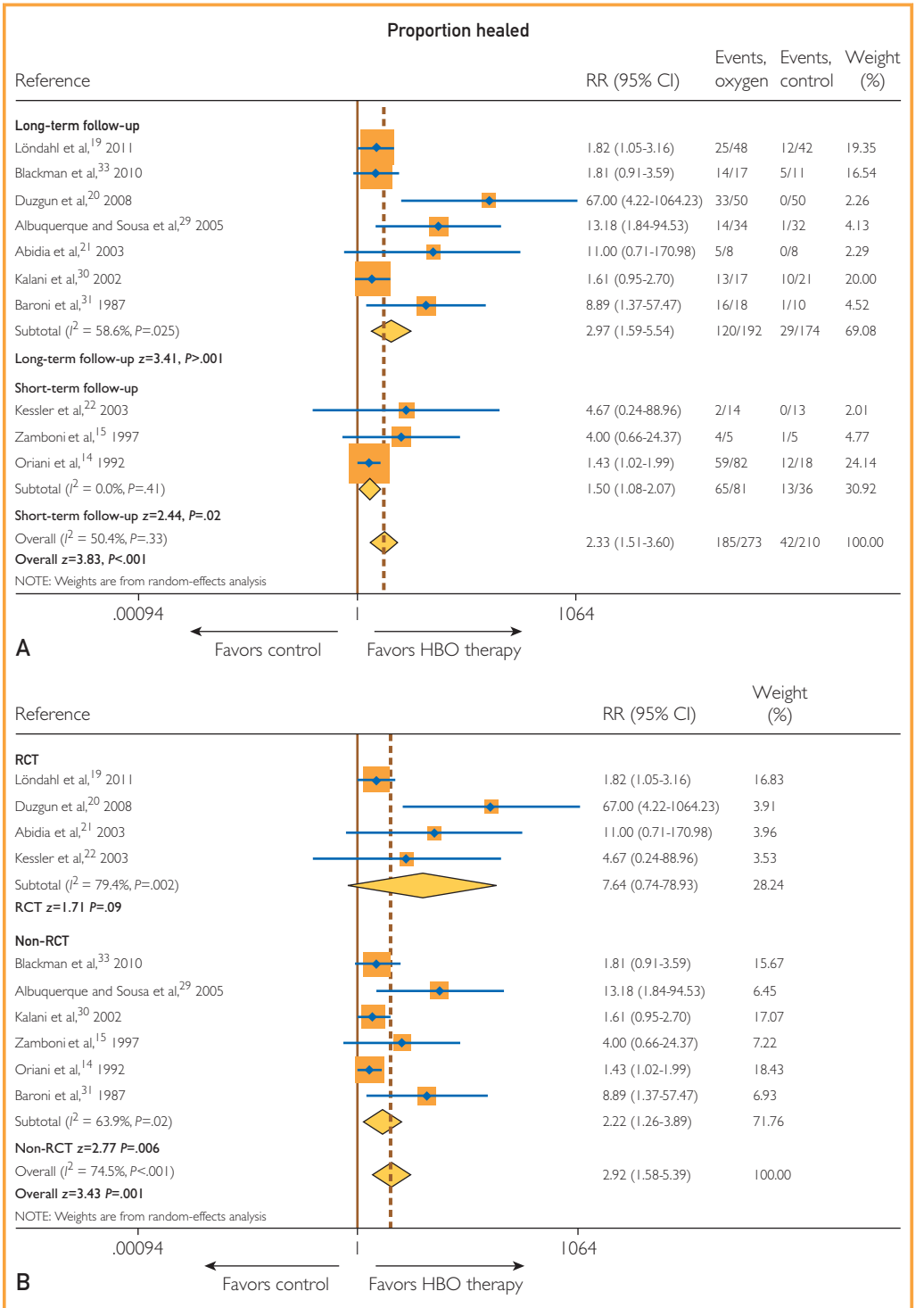

FIGURE 2. Forest plots for meta-analyses comparing the healing rate of foot ulcer treated with or without hyperbaric oxygenation (HBO). A, Subgroup analyses with short-term (6 months) or long-term (≥1 year) follow-ups. B, Subgroup analyses only including randomized controlled trials (RCTs). Ulcer healing was defined as complete epithelial regeneration. RR = relative risk.

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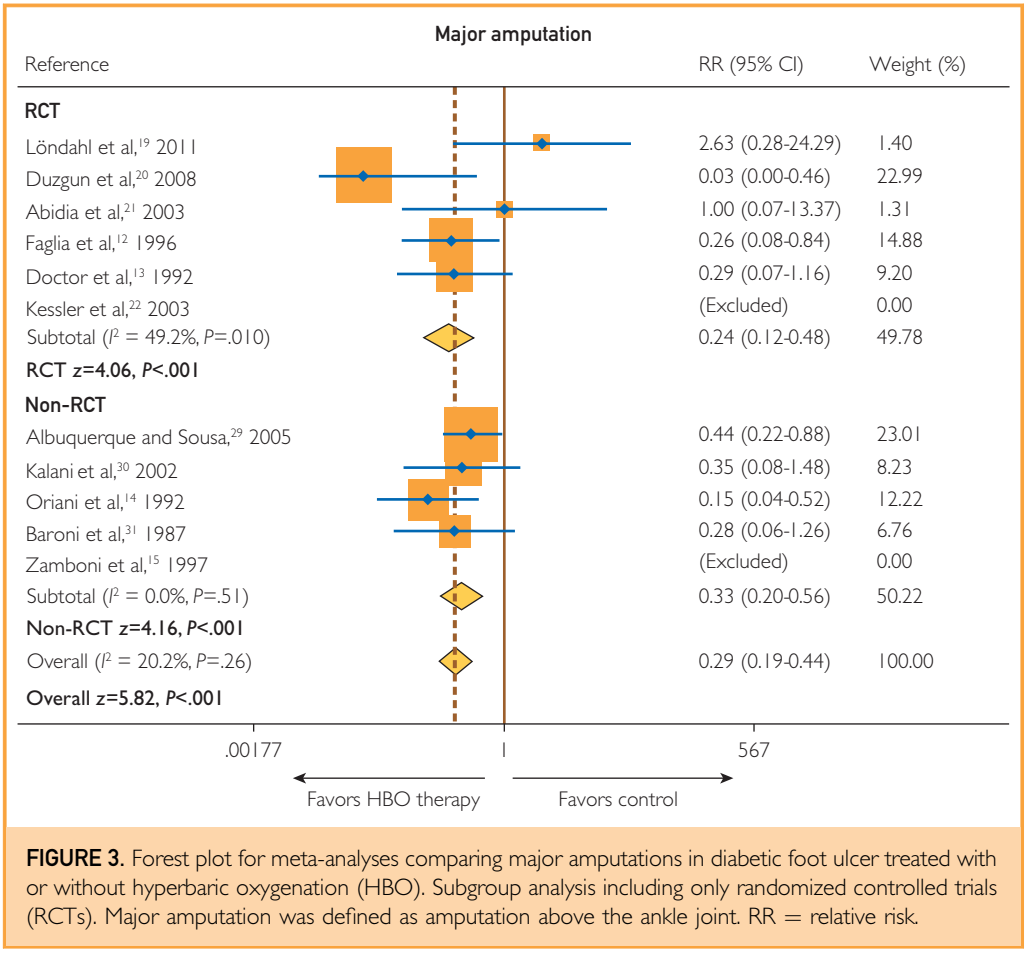

FIGURE 3. Forest plot for meta-analyses comparing major amputations in diabetic foot ulcer treated with or without hyperbaric oxygenation (HBO). Subgroup analysis including only randomized controlled trials (RCTs). Major amputation was defined as amputation above the ankle joint. RR = relative risk.

CI, 0.97-2.47; *P*=.78; Figure 4, B). Finally, we found that HBO therapy demonstrated a lower risk in total amputation rate compared with conventional therapy (13.63% vs 30.07%).

Adverse Events

Four studies, including 3 RCTs and 1 prospective study, reported adverse events related to HBO therapy, including barotraumatic lesions, oxygen toxicity, confinement anxiety, and ocular effects. Overall, no statistically significant difference was found in adverse event rates between the HBO-treated and the control groups (RR, 1.41; 95% CI, 0.66-2.98; *P*=.37) (Figure 5). Moreover, the pooling analysis of 4 RCTs also found no significant difference in adverse events between the 2 groups (RR, 1.41; 95% CI, 0.66-2.98; *P*=.37).

Quality of Life

Only 106 patients in 2 trials provided information on quality of life on the basis of self-reported questionnaires. The most recent RCT[19] provided some evidence to suggest that HBO treatment might improve long-term quality of life, although another trial[21] implied that it did not produce significant improvements in quality of life.

Infection-Related Issues

One RTC[13] investigated treatment of infection as the outcome end point. When compared with individuals treated without HBO, individuals treated with HBO had fewer infections, indicated by lower bacterial colony counts. Although foot infection was not investigated as an end point in most trials, these trials indirectly demonstrated better infectious outcomes, such as ulcers healed, reduced ulcer size, and amputations.

Cost-effectiveness Analysis

Only one study evaluated cost-effectiveness. This double-blind RCT demonstrated a potential saving in total cost of treatment for each patient

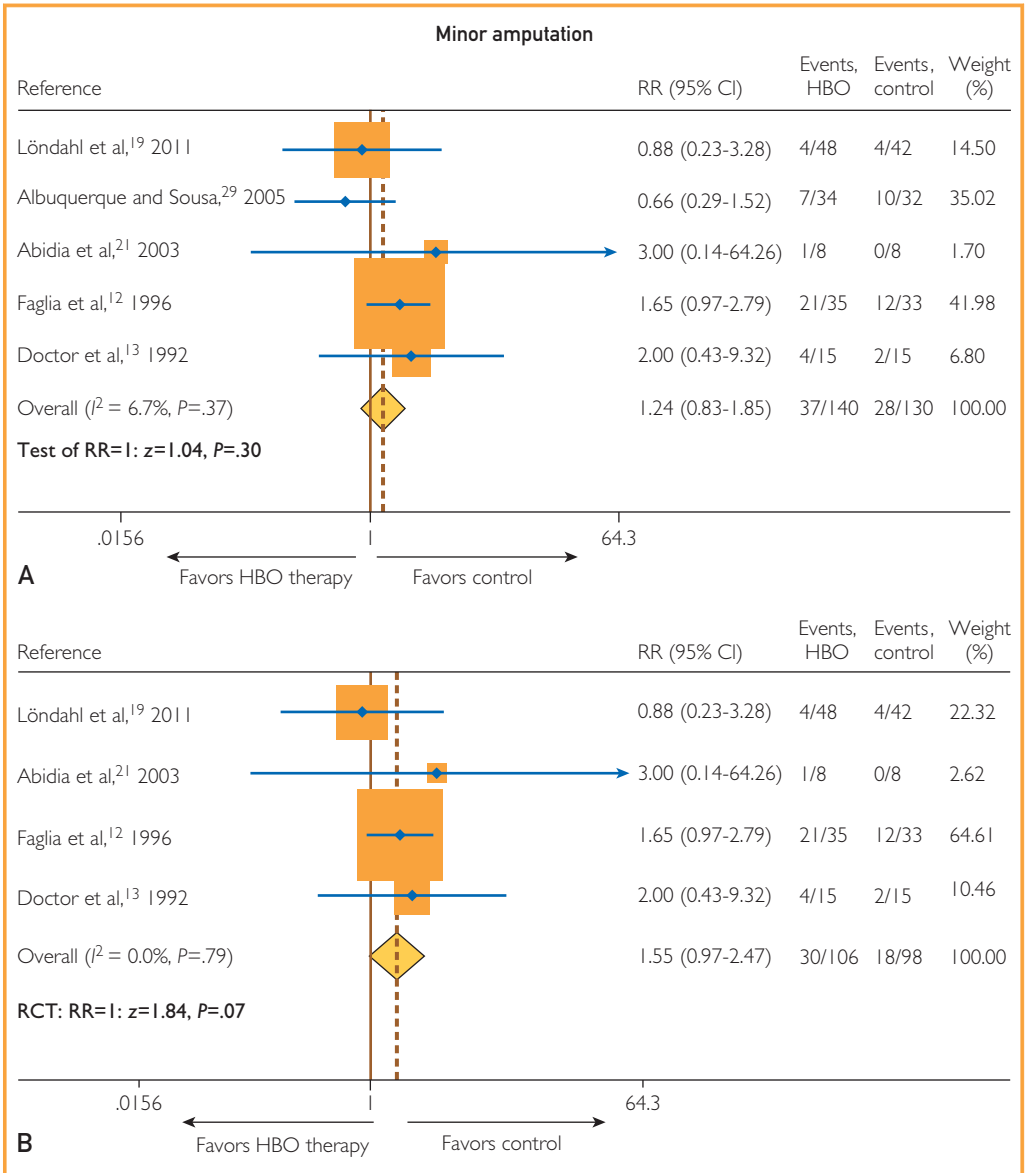

FIGURE 4. Forest plot for meta-analyses comparing minor amputation in diabetic foot ulcer treated with or without hyperbaric oxygenation (HBO). A, Overall analyses. B, Subgroup analyses including only randomized controlled trials (RCTs). Minor amputation was defined as amputation below ankle joint. RR = relative risk.

treated with HBO.[21] Because the healing of ulcers takes place during a long period, it possibly results in a higher cost for HBO-treated patients compared with those undergoing a conventional therapy or amputation.

Publication Bias Assessment and Sensitivity Analysis

We assessed publication bias using the Begg rank correlation analysis. The Begg linear regression test was performed for the quantitative evaluation of the symmetry of the meta-analysis funnel plot. *P* values of the Begg test were greater than .99, and their 95% CIs of intercept included zero in the Begg publication bias plots. This result indicates that the meta-analysis funnel plots were symmetrical without publication bias. Simultaneous sensitivity analysis was performed by using different sample sizes or effect models. We did not identify

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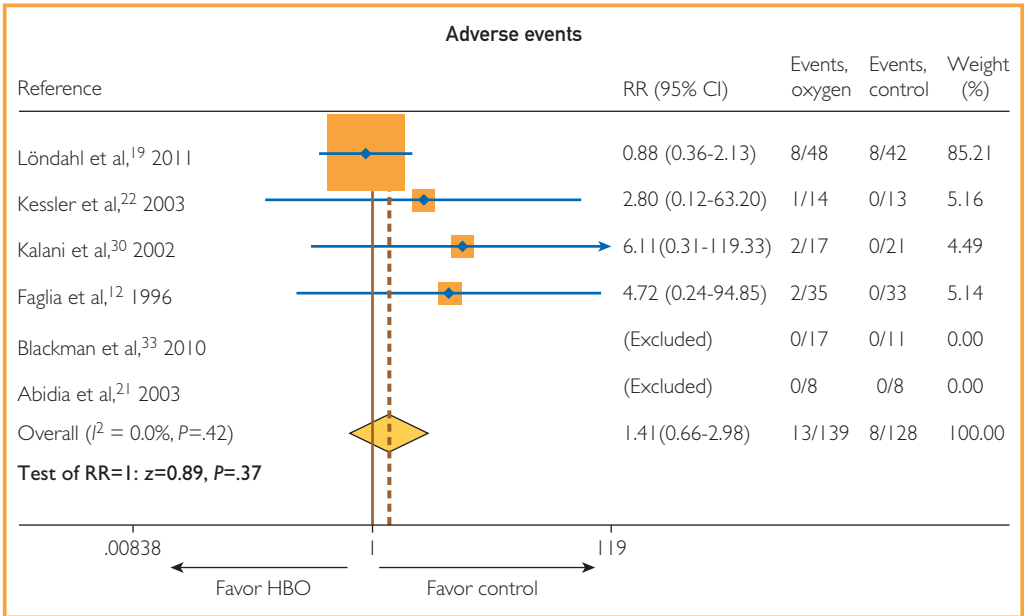

FIGURE 5. Forest plot for meta-analyses comparing adverse events, including barotraumatic lesions, oxygen toxicity, confinement anxiety, and ocular effects, in diabetic foot ulcer treated with or without hyperbaric oxygenation (HBO). RR = relative risk.

any marked difference in the RR and heterogeneity for the outcome of interest using both random-effects and fixed-effects models (Figure 6).

DISCUSSION

Diabetic foot ulcers are notoriously prone to complications and resistant to therapy. Even with the best conventional treatment, which includes improved glycemic control, pressure off-loading, and local and appropriate systemic antibiotics if clinically infected, many ulcers remain unhealed. There are many reasons why ulcers in patients with diabetes do not heal, including edema, anemia, and poor perfusion, all of which impede normal wound healing. Hyperbaric oxygenation therapy has been reported to decrease tissue hypoxia and has been proposed as treatment for chronic foot ulcers for at least 45 years. However, despite promising in vitro and in vivo findings in animal models, the effectiveness of HBO therapy in healing of chronic ulcers has remained controversial.[21,34]

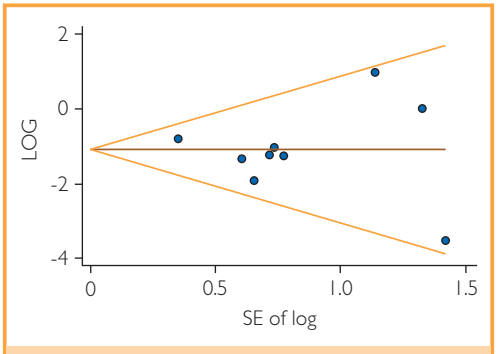

FIGURE 6. The Begg funnel plot with pseudo 95% CIs of publication bias of all clinical studies that reported healing proportion. If publication bias is not present, the funnel plot is expected to be roughly symmetrical.

In the current study, we conducted a meta-analysis of 7 prospective randomized and 4 prospective nonrandomized trials and 2 case-control studies. To our knowledge, this is the first comprehensive analysis of adjunctive HBO therapy for diabetic foot ulcers. It offers an up-to-date overview of human clinical trials on this subject and avoids problems related to insufficient statistical power and other methodologic weaknesses that are common in studies with a small sample size.

Another recent meta-analysis[35] has found that HBO treatment in 3 trials led to an increased rate of ulcer healing at short-term follow-up (6 weeks) but not at longer-term follow-up (1 year). In addition, the major amputation rate in that analysis was unchanged.

Therefore, it seemed that our results differed from those of the Cochrane analysis by Kranke et al.[35] The reason for the differences may be the different characteristics of the 2 studies and sample sizes. Only 7 RCTs were used in the meta-analysis by Kranke et al,[35] whereas 7 RCTs, 4 prospective trials, and 2 case-control studies were represented in our meta-analysis. Our larger sample size likely decreased publication bias and strengthened the power of analysis. Furthermore, in the study by Kranke et al,[35] only 2 trials assessed ulcer healing within 1 year. This causes problems with forest plots and assessing publication bias. More importantly, comparing healing rates of ulcers between HBO and conventional therapy, there was significant heterogeneity in the study by Kranke et al[35] (I^2=50%).

Our review provides evidence that HBO therapy in patients with diabetic ulcers decreases the overall risk of amputations, especially major amputation, when compared with therapy without HBO (13.63% vs 30.07%; RR, 0.29; 95% CI, 0.13-0.71).

The RR ratio revealed a significant effect in favor of adjunctive HBO therapy in patients with short-term follow-up (≤6 months). Although there was more heterogeneity in the subanalysis for patients with follow-up of more than 12 months, we found a tendency toward even larger positive effects of HBO treatment compared with those seen within 6 months. These results are consistent with a report by Kalani et al[30] in which 76% of the patients treated with HBO had healed ulcers after 3 years, compared with only 48% of patients treated without HBO. Furthermore, Albuquerque and Sousa[29] reported that long HBO treatment (mean, 45 months) increased significantly (approximately 13-fold) the healing rate of chronic lower limb ulcers in diabetic patients.

Both efficacy and safety of HBO therapy were assessed in this meta-analysis. Six studies that contained safety data found no significant differences between therapy with or without HBO. The incidence of adverse events was low and involved middle ear and nasal sinus problems. All these adverse events could be treated easily and rarely resulted in termination of the HBO therapy. Therefore, HBO therapy can be considered as a useful adjunct in the treatment of diabetic foot ulcers with an acceptable complication rate as long as safety guidelines concerning preexaminations, contraindications, therapeutic schemes, and monitoring of the patients are followed.

Cost-effectiveness needs to be considered by physicians and patients. The cost of HBO therapy varies, depending on region, setup costs, ongoing costs, and the number of treated patients. The only economic analysis included in this meta-analysis revealed that despite the extra cost of the equipment, the total cost for each patient treated with HBO was probably reduced in the long run. For example, in 2006 in the United States,[36] the mean cost of therapy for an infected foot ulcer was $17,000 and was increased 2- to 3-fold by a major amputation. Considering the increased ulcer healing, the reduction of major amputations, and the reduced frequency of office visits, HBO treatment appears to have the potential of providing cost savings for the treatment of diabetic foot ulcers.

CONCLUSION

This meta-analysis demonstrates that adjunctive treatment with HBO increases the likelihood of healing in diabetic foot ulcers and reduces the need for major amputations. In addition, adverse events are rare and acceptable. Therefore, we believe that the long-term quality of life of patients treated with HBO therapy could be improved by its judicious application.

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Drs Liu and Li contributed equally to this work.

Abbreviations and Acronyms: **HBO** = hyperbaric oxygenation; **RCT** = randomized controlled trial; **RR** = relative risk

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REFERENCES

1. Boulton AJ, Vileikyte L, Ragnarson-Tennvall G, Apelqvist J. The global burden of diabetic foot disease. *Lancet*. 2005;366(12):1719-1724.

2. Pecoraro RE, Reiber GE, Burgess EM. Pathways to diabetic limb amputation: basis for prevention. *Diabetes Care*. 1990;13(5):513-521.
3. Apelqvist J, Bakker K, van Houtum WH, Nabuurs-Franssen MH, Schaper NC. International consensus and practical guidelines on the management and the prevention of the diabetic foot. *Diabetes Metab Res Rev*. 2000;16(suppl 1):84-92.
4. Humphrey AR, Dowse GK, Thoma K, Zimmet PZ. Diabetes and nontraumatic lower extremity amputations: incidence, risk factors, and prevention—a 12-year follow-up study in Nauru. *Diabetes Care*. 1996;19(7):710-714.
5. Lehto S, Ronnemaa T, Pyorala K, Laakso M. Risk factors predicting lower extremity amputations in patients with NIDDM. *Diabetes Care*. 1996;19(8):607-612.
6. Lipsky BA. A report from the international consensus on diagnosing and treating the infected diabetic foot. *Diabetes Metab Res Rev*. 2004;20(suppl 1):68-77.
7. Cavanagh PR, Lipsky BA, Bradbury AW, Botek G. Treatment for diabetic foot ulcers. *Lancet*. 2005;366(9498):1725-1735.
8. Schaper NC, Bakker K. The international consensus on the diabetic foot. In: *The Foot in Diabetes*. Vol 4 4th ed. London, England: John Wiley & Sons; 2006:352-355.
9. Singer AJ, Clarck RA. Cutaneous wound healing. *N Engl J Med*. 1999;341(10):738-746.
10. Meltzer T, Myers B. The effect of hyperbaric oxygen on the bursting strength and the rate of vascularization of skin wounds in the rat. *Am Surg*. 1986;52(12):659-662.
11. Roberts GP, Harding KG. Stimulation of glycoaminoglycan synthesis in cultured fibroblasts by hyperbaric oxygen. *Br J Dermatol*. 1994;131(5):630-633.
12. Faglia E, Favales F, Aldeghi A, et al. Adjunctive systemic hyperbaric oxygen therapy in treatment of severe prevalently ischemic diabetic foot ulcer: a randomized study. *Diabetes Care*. 1996;19(12):1338-1343.
13. Doctor N, Pandya S, Supe A. Hyperbaric oxygen therapy in diabetic foot. *J Postgrad Med*. 1992;38(3):112-114.
14. Oriani G, Michael M, Meazza D, et al. Diabetic foot and hyperbaric oxygen therapy: a ten-year experience. *J Hyperb Med*. 1992;7:213-221.
15. Zamboni WA, Wong HP, Stephenson LL, Pfeifer MA. Evaluation of hyperbaric oxygen for 2diabetic wounds: a prospective study. *Undersea Hyper Med*. 1997;24(3):175-179.
16. Wunderlich RP, Peters EJ, Lavery LA. Systemic hyperbaric oxygen therapy: lower-extremity wound healing and the diabetic foot. *Diabetes Care*. 2000;23(10):1551-1555.
17. Bakker DJ. Hyperbaric oxygen therapy and the diabetic foot. *Diabetes Metab Res Rev*. 2000;16(suppl 1):S55-S58.
18. Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Control Clin Trials*. 1996;17(1):1-12.
19. Löndahl M, Landin-Olsson M, Katzman P. Hyperbaric oxygen therapy improves health-related quality of life in patients with diabetes and chronic foot ulcer. *Diabet Med*. 2011;28(2):186-190.
20. Duzgun AP, Satir HZ, Ozozan O, Saylam B, Kulah B, Coskun F. Effect of hyperbaric oxygen therapy on healing of diabetic foot ulcers. *J Foot Ankle Surg*. 2008;47(6):515-519.
21. Abidia A, Laden G, Kuhan G, et al. The role of hyperbaric oxygen therapy in ischaemic diabetic lower extremity ulcers: a double-blind randomised-controlled trial. *Eur J Vasc Endovasc Surg*. 2003;25(6):513-518.
22. Kessler L, Bilbault P, Ortéga F, et al. Hyperbaric oxygenation accelerates the healing rate of nonischemic chronic diabetic foot ulcers: a prospective randomized study. *Diabetes Care*. 2003;26(8):2378-2382.
23. Leslie CA, Sapico FL, Ginunas VJ, Adkins RH. Randomized controlled trial of topical hyperbaric oxygen for treatment of diabetic foot ulcers. *Diabetes Care*. 1988;11(2):111-115.
24. Moher D, Cook DJ, Eastwood S, Olkin I, Rennie D, Stroup DF. Improving the quality of reports of meta-analyses of randomized controlled trials: the QUOROM statement. *Lancet*. 1999;354(9193):1896-1900.
25. Clarke MO. Cochrane Reviewer's Handbook 413. In: *The Cochrane Library, Issue 3*. Oxford, England: John Wiley & Sons; 2001:164-167.
26. Londahl M, Katzman P, Nilsson A, Hammarlund C. Hyperbaric oxygen therapy facilitates healing of chronic foot ulcers in patients with diabetes. *Diabetes Care*. 2010;33(5):998-1003.
27. O'Reilly D, Linden R, Fedorko L, et al. A prospective, double-blind, randomized, controlled clinical trial comparing standard wound care with adjunctive hyperbaric oxygen therapy (HBOT) to standard wound care only for the treatment of chronic, non-healing ulcers of the lower limb in patients with diabetes mellitus: a study protocol. *Trials*. 2011;12:69.
28. Löndahl M, Katzman P, Nilsson A, et al. A prospective study: hyperbaric oxygen therapy in diabetics with chronic foot ulcers. *J Wound Care*. 2006;15(10):457-459.
29. Albuquerque E, Sousa J. Long-term evaluation of chronic diabetic foot ulcers, non-healed after hyperbaric oxygen therapy. *Rev Port Cir Cardiotorac Vasc*. 2005;12(4):227-237.
30. Kalani M, Jorneskog G, Naderi N, Lind F, Brismar K. Hyperbaric oxygen (HBO) therapy in treatment of diabetic foot ulcers: long-term follow-up. *J Diabetes Complications*. 2002;16(2):153-158.
31. Baroni G, Porro T, Faglia E, et al. Hyperbaric oxygen in diabetic gangrene treatment. *Diabetes Care*. 1987;10(1):81-86.
32. Jain KK. Physical, physiological and biochemical aspects of hyperbaric oxygenation. In: *Textbook of Hyperbaric Medicine*. Toronto, Vol 2 Ontario, Canada: Springer; 1990:480-495.
33. Blackman E, Moore C, Hyatt J, Railton R, Frye C. Topical wound oxygen therapy in the treatment of severe diabetic foot ulcers: a prospective controlled study. *Ostomy Wound Manage*. 2010;56(6):24-31.
34. Berendt AR. Counterpoint: hyperbaric oxygen for diabetic foot wounds is not effective. *Clin Infect Dis*. 2006;43(2):193-198.
35. Kranke P, Bennett MH, Martyn-St James M, Schnabel A, Debus SE. Hyperbaric oxygen therapy for chronic wounds. *Cochrane Database Syst Rev*. 2012;4:CD004123.
36. Kruse I, Edelman S. Evaluation and treatment of diabetic foot ulcers. *Clinical Diabetes*. 2006;2(24):91-93.