

# Hyperbaric oxygen for treatment of diabetic foot ulcers: love you more than I can say

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*Comment on:* Santema KTB, Stoekenbroek RM, Koelemay MJW, *et al.* Hyperbaric Oxygen Therapy in the Treatment of Ischemic Lower- Extremity Ulcers in Patients With Diabetes: Results of the DAMO<sub>2</sub>CLES Multicenter Randomized Clinical Trial. *Diabetes Care* 2018;41:112-9.

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Diabetic foot has gradually become a hot topic in the field of diabetes research, on the one hand, because of the rising incidence of diabetes, diabetic foot has become most likely the main reason for non-traumatic amputation, on the other hand, in the face of overextended on the national health care system, the bad treatment effect but with huge cost of diabetic foot seems so eclipse.

This world never lacks solutions to problems, even though some methods maybe controversial, such as the treatment of hyperbaric oxygen for diabetic foot. The first pilot research suggested that amputation rate of diabetic foot ulcers (DFU) is significantly decreased in patients which received the hyperbaric oxygen treatment (HBOT) in 1987 (1). Another review indicated that HBOT is ineffective in patients with diabetic macro-vascular complication at the same year (2). The next year, *Diabetes Care* published the first randomized controlled trial (RCT) research on HBOT for DFU. The investigation time was short (a total of 14 days), and cases were a little (28 patients). And difference between the control and treatment group was not obvious (3). But this does not seem to reduce the enthusiasm of supporters to apply HBOT for DFU. In 2010, Hyperbaric Oxygen Therapy in Diabetics with Chronic Foot Ulcers (HODFU), a randomized single center, double-blind research was published. Patients in the treatment group received HBOT and the control group received high pressure air treatment. The ulcers healed completely within 1 year. It is important that after 2 months of initial HBOT, the ulcers began to heal and gradually improved within

1 year, and it will take time to make its effect. And HBOT does not induce any adverse effects. The research also suggested that the percutaneous oxygen pressure (tcPO<sub>2</sub>) was a good indicator of the healing of the ulcer, not a toe or the ankle brachial index (ABI) (4,5). Researchers held that for chronic DFU, HBOT can improve ulcer healing in the long term and maybe a potential measurement when traditional treatment methods (debridement, dressing, antibiotics and so on) are not effective. Based on this, the International Working Group of Diabetic Foot (IWGDF) in 2015 guidelines recommended the use of HBOT in chronic DFU (mild/moderate recommendation), although there are still need double-blind randomized trials to further clarify the cost-effectiveness of HBOT and to identify the most likely benefit patients (6). Fagher *et al.* declared that the 3-year survival rate of patients who received HBOT in the follow-up HODFU research were significantly increased (7,8). There were still many other researches indicated that HBOT can improve the prognosis of DFU (9-11), a meta-analysis which including nine RCT studies indicated that HBOT may improve the healing speed of DFU, but it has no significant effect on amputation rate and ulcer healing rate (12). Here I won't list one by one.

As previously mentioned, it can be retrieved from first published paper of HBOT for DFU that skepticism seems never absence. At the 2008 American Diabetes Association (ADA) meeting, Dr. Berendt, the orthopedics Center of the Oxford University, questioned HBOT in the treatment of foot ulcer. O'Reilly *et al.* was the main investigator

of hyperbaric oxygen therapy for chronic diabetic lower extremity ulcers. They found that after a series of interventions in 12 weeks, 20% HBOT group and 22% control group healed the foot ulcers. In addition, in other clinical trials of hyperbaric oxygen therapy, the cure rate was very low in the control group (13). They held that patients with chronic DFU can heal in 12–16 weeks after proper and comprehensive wound care, which is not attributable to hyperbaric oxygen. And then, the studies of Löndahl *et al.* and Duzgun *et al.* also suggested the lower cure rate, in the latter study, 50 patients in the control group had not healed at 92 weeks (14,15). In an observational study by Margolis *et al.*, compared with the control group, 793 cases of DFU treated with hyperbaric oxygen did not significantly improve ulcer healing and amputation rate. Some scholars believe that hyperbaric oxygen therapy is not only time-consuming (usually 40 times, 90 minutes/day), also and the price is very expensive, and the lower cost effectiveness (16). Of course, Li *et al.* have been insisting that hyperbaric oxygen is ineffective for diabetic foot. They believe that hyperbaric oxygen has no significant improvement in the quality of life of diabetic foot patients (17). It is so controversial that the Health Quality Ontario evaluation team has the evaluation on the health economics of hyperbaric oxygen therapy for diabetic foot: the evidence makes it difficult to draw any definitive conclusions on the clinical and cost effectiveness of standard wound care plus HBOT versus standard wound care alone for the treatment of DFU (18).

There were two prospective, double-blind, randomized controlled clinical trials which published on *Diabetes Care* recently, they investigated whether the effects of HBOT can effectively reduce major amputation and improve wound healing. The research which launched by Fedorko *et al.* evaluated 157 cases of DFU (Wagner 2–4), the results suggested that 54 patients in the control group had 13 patients with major amputation, 49 cases in group HBOT had 11 patients with major amputation; the control group had 22 patients (22%) healed, HBOT group had ten patients (20%), there were no statistically difference between two groups, there was also no significant difference in other indicators on wound healing between the two groups, researchers believed that HBOT cannot reduce the amputation of DFU or promote ulcer healing by comprehensive wound care. And the DAMO2CLES research was conducted in 120 patients, standard therapy was combined with or without HBOT on diabetic lower limb ischemic patients. The results suggested that HBOT did not significantly improve the healing ability of diabetic

lower limb ischemic wounds and the risk of limb salvage. These are the largest RCT study to date to assess the application of HBOT for DFU (19,20).

However, there were some problems in these researches, the results may not provide new evidence for decision makers about the impact of hyperbaric oxygen therapy on DFU. Although the criteria of these researches were included the Wagner grade of 2–4, there were almost half of ulcers were the Wagner grade of 2, which the guidelines do not recommend these patients to treat with hyperbaric oxygen. It wasted the resources; on the other hand, the results also have bias. In addition, unlike previous research, the research which launched by Fedorko *et al.* (19) determined the outcome of amputation through remote consultation of surgeons to decide whether the need for amputation. Some diabetic foot infectious osteomyelitis does not need amputation, but this study identifies it as amputation, and in fact, many patients did not have amputation. And in DAMO2CLES research, the minor amputations were classified as “healed”, which has been identified as “unhealed” usually, and 21 patients who unable to complete the HBOT protocol did had significantly less major amputations and higher amputation-free survival, it suggested HBOT may have some benefit effects on those patients. Some commentators even think that “*Poorly designed research does not help clarify the role of hyperbaric hyperbaric*” (21). If this research can choose for Wagner grade 3 and grade 4 ulcer patients to have hyperbaric oxygen intervention, and use actual amputation to analysis, the research is more likely to bring more benefit for patients and to provide more accurate information to decision makers.

To sum up, HBOT in DFU, while the market prospects are very attractive to investors, and the future is optimistic, the current evidence is low level, the research scale is small, and the evaluation indicators are more subjective, these may restrict the application of HBOT which recommended for DFU. Of course, except we look forward to more large-scale, well design researches and more objective indicators to verified its effect, how to choose a suitable object and appropriate indicators to evaluation the effect on the objective and fair stand maybe perhaps the most important. Anyway, selection is still and always prior to hardworking.

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### Footnote

**Conflict of Interest:** The author has no conflicts of interest to declare.

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