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Tissue-specific role of Nrf2 in the treatment of diabetic foot ulcers during hyperbaric oxygen therapy.

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Abstract

Hyperbaric oxygen (HBO) therapy is proven to be very successful for diabetic foot ulcer (DFU) treatment due to its antimicrobial effect, increased angiogenesis and enhanced collagen synthesis. The molecular mechanism underlying HBO therapy particularly the involvement of Nrf2 in the wound healing process was investigated in the present study. In addition, we have studied the levels of angiogenic markers in ulcer tissues and their correlation with Nrf2 during HBO therapy compared with standard therapy (Non-HBO) for DFU. A total of 32 Patients were recruited and randomized to standard wound care procedure alone (n = 17) or HBO therapy in combination with standard wound care procedure (n = 15) for 20 days. Our results showed that the tissue levels of Nrf2 along with its downstream targets were significantly increased in patients who underwent HBO therapy when compared to Non-HBO therapy. Further, HBO therapy induced angiogenesis as assessed by increased levels of angiogenesis markers such as EGF, VEGF, PDGF, FGF-2 and CXCL10 in the tissue samples. The expressions of eNOS and nitrite concentrations were also significantly increased in HBO therapy when compared to Non-HBO therapy subjects. Moreover, HBO therapy sensitises the macrophages to release FGF-2 and EGF thereby promotes angiogenesis. Further, it increased the levels of neutrophil attractant CXCL-8 thereby promotes the release of chemokine CCL2, a well-known mediator of neovascularization. The Pearson correlation showed that Nrf2 has a positive correlation with EGF, VEGF and PDGF. In conclusion, the findings of the present study suggest that HBO therapy promotes wound healing by increasing oxygen supply and distribution to damaged tissues, stimulating angiogenesis, decreasing inflammation, and increasing the nitrite levels. Increased levels of Nrf2 transiently regulate the expression of angiogenic genes in wound biopsies, which may result in accelerated healing of chronic wounds.

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