Hyperbaric Oxygen Therapy Promotes Bone Healing in Patients with Maxillary Sinus Lateral Augmentation and Diabetic Mice Potentially through the Nrf2 Pathway

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Objective: *To assess the impact of hyperbaric oxygen (HBO) therapy on bone healing in diabetic patients and explore potential mechanisms in an animal experiment.*
Methods: *Four non-diabetic patients undergoing maxillary sinus lateral augmentation were assigned to either standard care (control group) or HBO treatment for 5, 6 or 9 weeks. Bone core samples were collected for immunochemistry during the preparation for implant insertion. Additionally, 12 db/db diabetic mice and 12 control mice with tibia defects were subjected to HBO treatment. After 7 days, the bone repair process was assessed using microcomputed tomography (microCT), histology, immunohistochemistry and Western blot analyses.*
Results: *HBO improved bone formation in the implant areas of patients treated for 5, 6 and 9 weeks, increasing local vascular endothelial growth factor, bone morphogenetic protein-2 and osteocalcin expression. Diabetic mice exhibited impaired bone healing, but HBO-treated groups (diabetic or non-diabetic) showed enhanced new bone formation. Increased osteocalcin and runt-related transcription factor 2 and decreased tartrate-resistant acid phosphatase expression were detected. The nuclear factor erythroid-derived 2-related factor 2 (Nrf2) pathway and its downstream proteins catalase and heme oxygenase-1 were upregulated after HBO.*
Conclusion: *HBO enhances bone healing in both patients and diabetic mice, and is potentially mediated through the Nrf2 pathway.*
Keywords: *bone healing, hyperbaric oxygen therapy, diabetes, Nrf2 signalling pathway*
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The destiny of implantation is determined by the osteointegration efficiency between the implant and its surrounding tissue, which is based on the physiological normalcy of bone metabolism.[1,2] Diabetes patients often experience disturbances in bone metabolism, leading to secondary reductions in bone mass, osteoporosis, loss of peri-implant bone, peri-implantitis and a series of complications.[3,4] With the global prevalence of diabetes, improving implant retention in diabetic patients has become one of the most urgent issues to address in oral implant treatment.

Diabetes-induced bone resorption is a complex process that involves numerous molecules and signalling pathways.[5] Currently, oxidative stress is considered a significant factor contributing to bone resorption in the context of diabetes.[6] Oxidative stress refers to an imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses.[6] Hyperbaric oxygen (HBO) therapy involves administering 100% oxygen at pressures higher than atmospheric pressure, exhibiting potent antioxidant effects that efficiently eliminate intracellular ROS and regulate oxidative stress. Under HBO conditions, the local oxygen content in the regions of bone metabolism increases significantly, fostering osteoblast proliferation and thereby expediting the repair of necrotic bone tissue and accelerating neural tissue regeneration.[7] Although HBO therapy is an established adjunct for bone defects, stroke and traumatic

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injuries,[8,9] its role in implantation warrants deeper exploration.

To address this gap, the present authors pioneered a clinical trial in non-diabetic patients evaluating the efficacy of HBO therapy in bone healing following maxillary sinus lateral augmentation.[10] They identified an optimal therapeutic window (5 to 9 weeks post-surgery) during which HBO significantly upregulated osteogenic markers (bone morphogenetic protein 2 [BMP-2], runt-related transcription factor 2 [RUNX2]) and accelerated graft mineralisation compared to conventional 9-month healing. This clinical foundation prompted a critical question: could HBO counteract diabetes-impaired bone healing, and if so, by which mechanism?

Mechanistically, the Nrf2 signalling pathway emerged as a key target. Nrf2 orchestrates antioxidant enzyme expression to combat oxidative stress.[11] Under oxidative stress, Nrf2 dissociates from the cytoplasm to the nucleus and subsequently binds to antioxidant response elements to regulate the expression of detoxifying or antioxidant enzyme-encoding genes, such as heme oxygenase-1 (HO-1), glutamate cysteine ligase (GCL) and catalase (CAT).[12] Additionally, research has indicated that modulation of the Nrf2 pathway aids in the proliferation and differentiation of osteoblasts.[13] Currently, there is an absence of mechanistic research on whether HBO modulates bone metabolism in diabetic patients through the Nrf2 pathway.

Given the recognised impairment of bone metabolism in diabetes, the present authors further hypothesised that HBO might counteract healing deficits associated with diabetes. To bridge clinical observation with molecular mechanisms, they developed a diabetic murine defect model, specifically targeting the Nrf2 pathway, a master regulator of cellular antioxidant responses. This exploration aimed to uncover how HBO modulates oxidative stress and osteogenesis in both physiological and hyperglycaemic conditions. This translational approach links clinical observations with molecular insights, providing scientific evidence to optimise HBO protocols for diabetic patients requiring bone regeneration therapies.

Materials and methods

Clinical experiment

The clinical experiment process was described in the present authors' previous study.[10] Briefly, four non-diabetic patients were enrolled. All subjects signed informed consent forms, which were approved by the Ethics Committee for Human Clinical Research at China-Japan Friendship Hospital (zryyec/2015/27-1). All patients underwent preoperative CBCT for bone density assessment and to identify possible intrasinus pathologies as well as anatomical sinus morphology. After surgery for maxillary sinus lateral augmentation, each patient was assigned to one of the following healing protocols: control (without HBO), or HBO for 5, 6 or 9 weeks. HBO therapy was performed under the action of 100% oxygen at twice the atmospheric pressure (2.5 atm); it took 30 minutes to raise the pressure of the oxygen cure tank. The pressure was maintained for 60 minutes and then lowered for the following 30 minutes to complete the treatment. HBO therapy was administered daily for 10 days, followed by a 5-day rest period. This 15-day cycle was repeated until the patient reached the total treatment duration specific to their assigned group (5, 6 or 9 weeks). Contraindications to HBO therapy were observed strictly. All surgical sites were located unilaterally in the maxillary molar regions. Bone core samples were collected after 6 months of surgery when implants were inserted.

Animal experiments

Twelve male diabetic mice with db/db were randomly divided into two groups, while 12 male control mice with db/m at 10 weeks old were also randomly divided into two groups. Before the experiment, the blood glucose levels of the mice were measured. The tibial defect model was conducted unicortically using a 1.0-mm drill burr on the proximal tibia. Six mice in each group were under HBO therapy (2.5 atm, 60 minutes) once a day or control treatment. All mice were sacrificed on day 7. The animal experiments in this study were approved by the Ethics Committee of China-Japan Friendship Hospital (zryhyy 61-23-03-06).

Microcomputed tomography (microCT) scans

The surrounding tissues were removed with scissors and immersed in 4% paraformaldehyde for 24 hours at 4°C. The movement of the tooth and the alveolar bone was observed by microCT (Skyscan1276 X-ray Microtomograph, Bruker, America) at a resolution of 6.5 μm. 3D image reconstruction was performed with N-Recon software, and 3D analysis was performed with CT-AN software.

Enzyme-linked immunosorbent assay (ELISA)

Peripheral blood samples were collected and allowed to clot for 15 minutes at room temperature to obtain

serum. The samples were then centrifuged for 10 minutes at 3,000 rpm, and the supernatant was transferred to a new tube. Further tests were performed using an osteoprotegerin (OPG) ELISA kit (Thermo Fisher Scientific, Waltham, MA, USA).

Histological staining

After fixation in 4% paraformaldehyde at 4°C for 24 hours (alveolar bone and teeth must be decalcified with 10% ethylenediaminetetraacetic acid (pH 7.4) for 4 weeks), the samples were dehydrated in a series of alcohol baths beginning with 50% and progressing to 100%. Samples were embedded in paraffin, and 8 μm horizontal sections were stained with haematoxylin and eosin, osteocalcin (OCN) (Proteintech, Hubei, China), BMP-2 (Proteintech), vascular endothelial growth factor (VEGF) (Abcam, Cambridge, UK), RUNX2 (Abcam), tartrate-resistant acid phosphatase, Nrf2 (Proteintech), HO-1 (Proteintech), CAT (Proteintech) and tartrate resistant acid phosphatase (TRAP) (Proteintech).

Western blot analysis

Western blot analysis was performed as previously described.[14] Briefly, tissues were cut and ground and then lysed in radioimmunoprecipitation buffer. Proteins were separated by 12% sodium dodecyl sulphate–polyacrylamide gel electrophoresis and transferred to polyvinylidene fluoride membranes. After blocking the membranes with 5% bovine serum albumin (BSA) (Solarbio, Beijing, China), proteins were detected by overnight incubation with primary antibodies against TRAP (Proteintech), OCN, Runx2 (Cell Signaling Technology), Nrf2 (Proteintech), HO-1 (Proteintech), CAT (Proteintech) and β-actin (Zhongshan Goldenbridge, Beijing, China) at a 1:1,000 dilution. After the membranes had been washed, they were incubated with secondary antibodies (1:10,000; Zhongshan Goldenbridge) at room temperature for 2 hours. Proteins were visualised using an enhanced chemiluminescence (ECL) kit (Applygen, Beijing, China). Quantitative analysis of the images was performed using ImageJ software (National Institutes of Healh, Bethesda, MD, USA).

Statistical analysis

Statistical analyses were performed with SPSS version 25.0 (IBM, Armonk, NY, USA). All data were expressed as mean ± standard deviation, and differences were calculated using a Student *t* test between two groups and a one-way analysis of variance (ANOVA) followed by a Student-Newman-Keuls post hoc test among multiple groups. Two-way ANOVA was used in multiple groups with multiple factors. Two-tailed P values < 0.05 were considered statistically significant.

Results

HBO promoted bone healing in maxillary sinus lateral augmentation

In tissue samples from patients who underwent maxillary sinus lateral augmentation surgery, elevated expression of BMP-2, VEGF and OCN was observed in HBO-treated groups compared to the control group. Specifically, the bone formation–related markers BMP-2 and OCN showed a progressive increase with longer duration of HBO therapy, with the highest expression in the patient who received HBO therapy for 9 weeks. VEGF expression peaked in the 5-week HBO group, with slightly lower levels in the 6-week and 9-week groups. (Fig 1a and b).

Bone healing in db/db mice was promoted by HBO

Figure 2a schematically illustrates the experimental group design, comprising both non-diabetic and diabetic mice. Prior to experimentation, the diabetic mouse model was confirmed by measuring blood glucose levels (Fig 2b). Following the experiment, the volume of new bone in the defect area was calculated using microCT scans. The bone volume to tissue volume (BV/TV ratio) indicated that the bone formation capacity of db/db mice was weaker than that of normal mice; however, regardless of whether db/m or db/db mice were used, bone formation in the defect area increased after HBO treatment (Fig 2c and e). Other measurement parameters of microCT presented in Table 1 showed that after HBO therapy, bone surface to bone volume (BS/BV) ratio, trabecular number (Tb.N) and bone mineral density (BMD) increased in both db/db and db/m mice. The serum samples from the mice were further collected for ELISA testing, which showed that OPG levels were lower in dm/dm mice than in normal mice. After HBO treatment, serum OPG levels increased approximately fourfold in both groups of mice (Fig 2d).

Masson staining revealed bone fibres in the defect area (shown in blue), indicating that new bone formation was lower in db/db mice than in db/m mice, and after HBO treatment, new bone formation increased in db/db mice, without a statistically significant difference compared to db/m mice (Fig 2f). Western blotting dem-

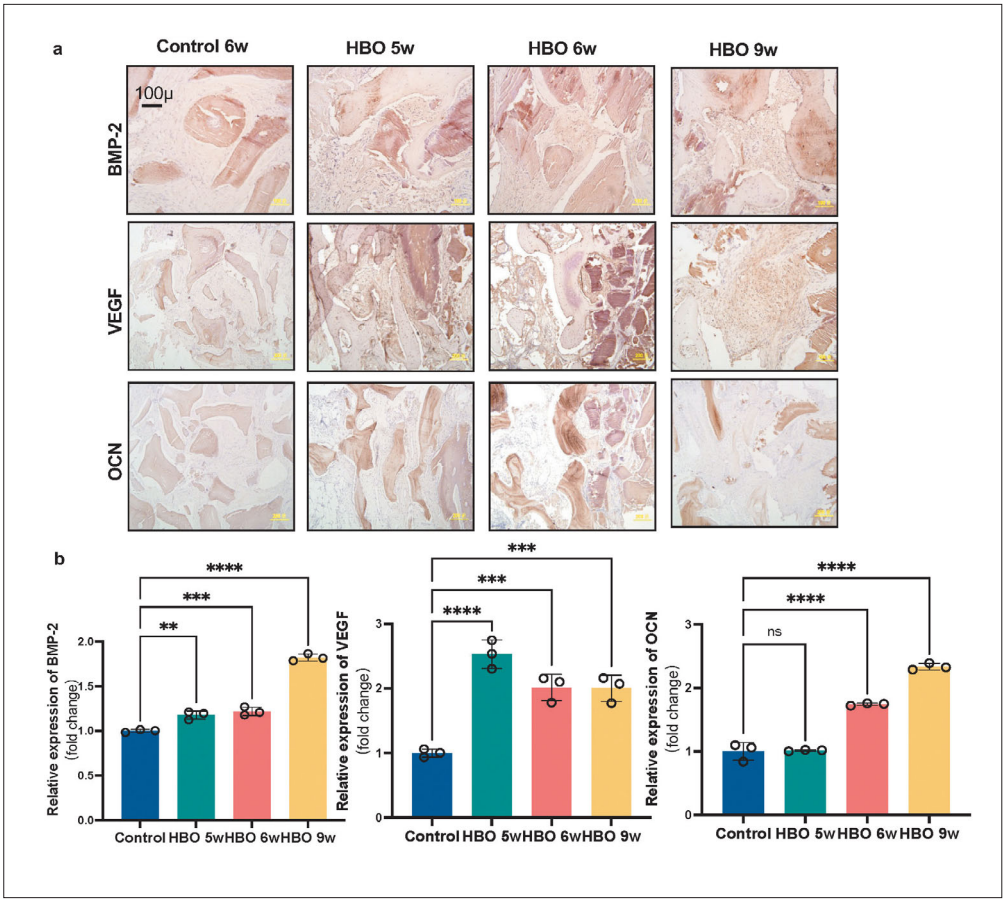

Fig 1a and b Bone healing in db/db mice was promoted by HBO. Immunohistochemical results of BMP-2, VEGF and OCN in the defect area (a). Quantitative results of immunochemistry (b). $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$; ns, non-significant differences.

onstrated increased expression of OCN and RUNX2, whereas the bone resorption marker TRAP showed decreased expression in the tissues of the defect area after HBO treatment (Fig 3a). Immunohistochemistry yielded similar results; after HBO treatment, there was an increase in the expression of the bone-related proteins OCN and RUNX2, whereas the osteoclast marker TRAP was inhibited (Fig 3b).

Bone healing induced by HBO is related to the Nrf2 pathway

Following protein extraction from the defect tissues, the expression levels of Nrf2 and its downstream target proteins were examined. The results revealed that after HBO treatment, both db/db and db/m mice exhibited increased expression of the Nrf2 protein at the defect site. Similarly, downstream proteins of the Nrf2 pathway, CAT and HO-1, showed similar expression patterns (Fig 4a). Immunohistochemical staining of tissues corroborated these findings. In particular, Nrf2 expression in db/db mice was lower than that in db/m mice but increased after HBO treatment, showing no statistically significant differences from the db/m group. Furthermore, normal mice showed increased Nrf2 expression after HBO treatment, and a similar trend was observed for the downstream proteins HO-1 and CAT (Fig 4b, 5a and 5b).

Discussion

Therapeutic potential of HBO therapy in diabetic bone healing

HBO enhances bone healing primarily by promoting angiogenesis and osteogenesis.[15,16] The increased expression of bone formation markers, including BMP-2 and OCN, after HBO treatment underscores its positive impact on osteogenesis. The present authors also observed a significant increase in the expression of VEGF, a factor associated with angiogenesis, after HBO treatment, with the highest expression after 5 weeks. This suggests that the early pro-angiogenic effects of

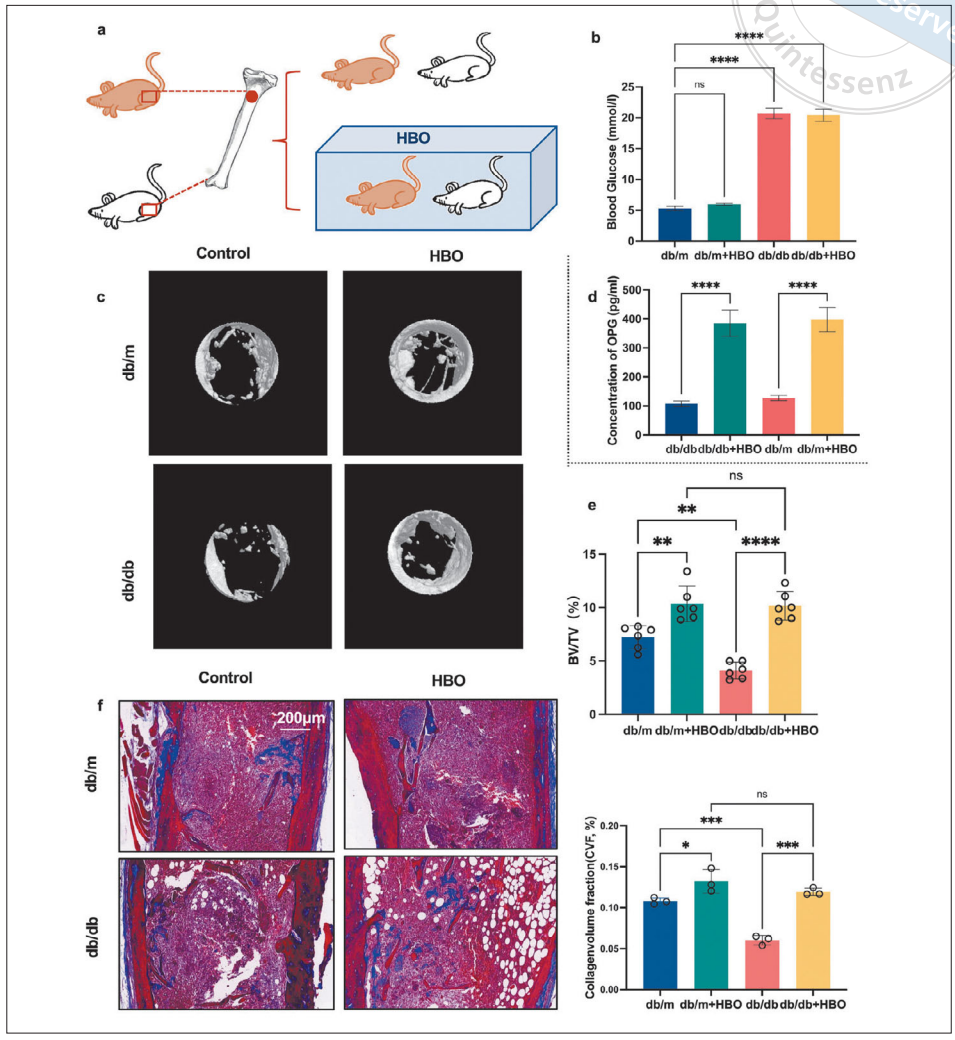

Fig 2a to f Bone healing in db/db mice was promoted by HBO. Tibial defect model of mice; different colours refer to db/db mice and db/m mice (a). Blood glucose results of the db/db and db/m mice before the experiment (b). The result of the microCT scan showed that new bone had formed in the defect area (c). ELISA results of the blood concentration of OPG in db/db and db/m mice before the experiment **(d)**. Result of BV/TV analysis (e). Results of Masson staining (left, the blue area represents the newly formed collagen) and quantitative results (right) **(f)**. $^{**}P < 0.01$; $^{****}P < 0.0001$; ns, non-significant differences.

Table 1 microCT evaluation

Group	BS/BV (1/mm)	Trabecular number (1/mm)	Structure Model Index	Connectivity density ($1/mm^3$)	BMD/TV
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
db/m	57.783 ± 6.689	0.874 ± 0.095	2.530 ± 0.178	21.714 ± 1.285	0.166 ± 0.021
db/m + HBO	50.831 ± 5.753	1.377 ± 0.049	2.411 ± 0.148	32.617 ± 2.935	0.262 ± 0.040
P value*		0.0004			0.0047
db/db	67.893 ± 1.389	0.602 ± 0.099	3.753 ± 0.299	11.972 ± 2.705	0.144 ± 0.011
db/db + HBO	47.156 ± 0.721	1.411 ± 0.087	2.233 ± 0.309	22.451 ± 4.085	0.263 ± 0.009
P value†	0.0021	< 0.0001	0.0003		0.0012

*db/m compared with db/m + HBO.

†db/db compared with db/db + HBO.

BMD/TV, bone mineral density to tissue volume ratio; BS/BV, bone surface to bone volume ratio.

HBO precede osteoblast activation, aligning with its known capacity to elevate local oxygen tension and stimulate collateral circulation.[7]

To evaluate the potential of HBO in diabetic bone repair, the present authors extended this paradigm to a murine model. The 7-day HBO protocol was selected based on prior evidence that short-term intervention effectively captures early repair phases (e.g., inflammation resolution and osteoblast activation).[17] Previous studies demonstrate that short-term HBO significantly

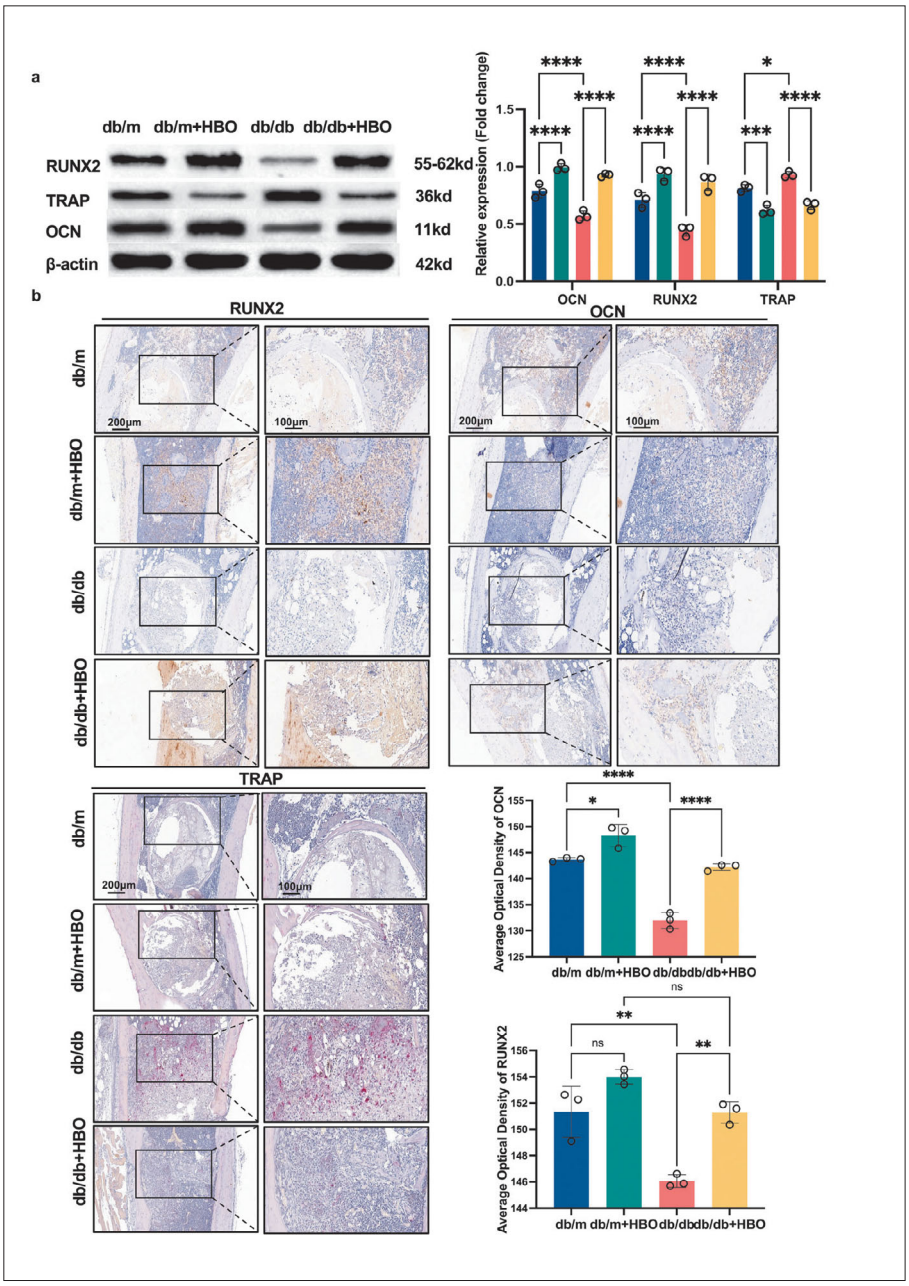

Fig 3a and b Bone healing in db/db mice was promoted by HBO. The western blot results of the expression of bone-related proteins and quantitative results are shown below (a). Immunohistochemical results of RUNX2, OCN and TRAP. The left column displays the area of tibial injury, and the right column shows enlarged images of the region within the black frame on the left (b). *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001; ns: non-significant differences.

enhances new bone formation in murine defect models.[18] To optimise the detection of the effects of HBO, the present authors aligned the observation period with prior studies using the same bone defect model.

Consistent with clinical observations, HBO restored bone formation in diabetic mice to levels comparable with non-diabetic controls, eliminating baseline deficits. Similar conclusions have been drawn in previous experiments. Eldisoky et al[15] found that HBO has a beneficial effect on bone regenerative capacity, both qualitatively and quantitatively. Dial et al[19] reached the same conclusion in diabetic mice; however, these studies did not delve deeply into the underlying mechanisms.

Key mechanisms and clinical implications

The diabetes-induced reduction in bone formation is a complex process involving numerous molecules and signalling pathways.[5] Currently, oxidative stress is considered a significant factor in bone resorption under diabetic conditions.[6] The Nrf2 signalling pathway, which is closely associated with oxidative stress and is involved in the regulation of apoptosis, proliferation, differentiation

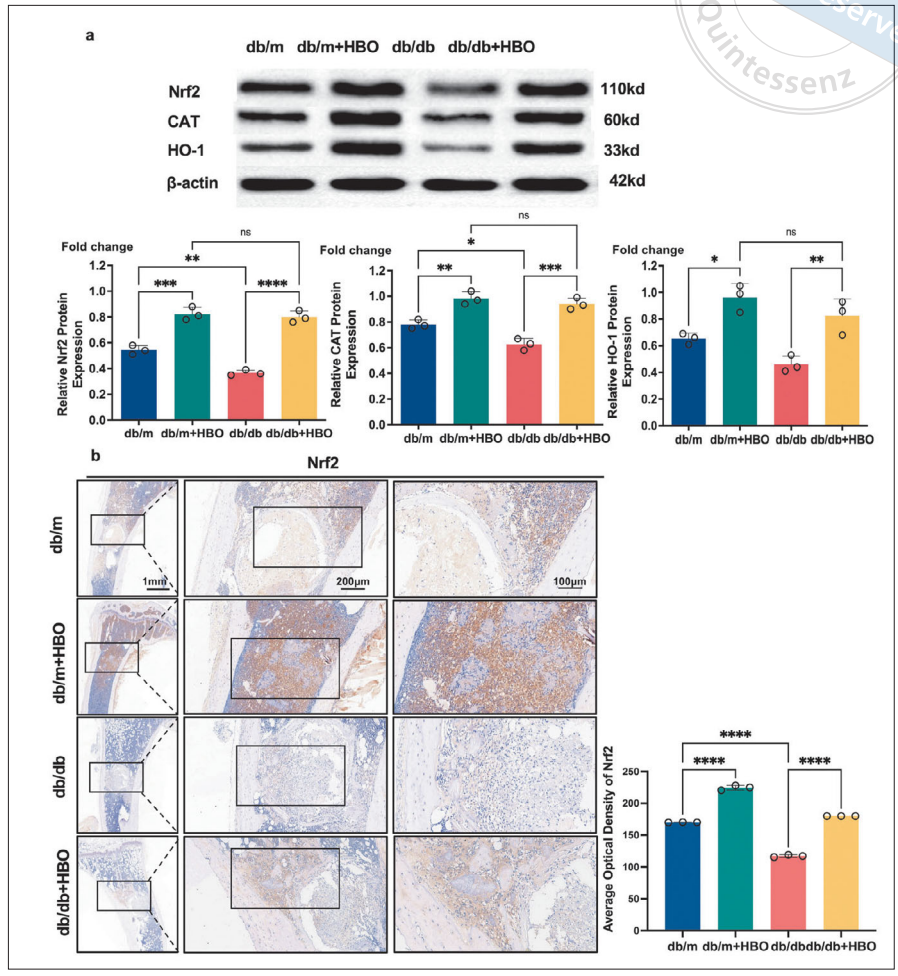

Fig 4a and b Bone healing induced by HBO is related to the Nrf2 pathway. The western blot results of the expression of proteins related to the Nrf2 pathway and the quantitative results are given below (a). Immunohistochemical results of Nrf2 in the defect area. The left column displays the area of tibial injury, and the right column shows enlarged images of the region within the black frame in the left (b). *P < 0.05; **P < 0.01; ***P < 0.001; ****P < 0.0001; ns: non-significant differences.

and metabolism, has garnered increasing attention.[20]

Clinical studies have demonstrated that HBO therapy facilitates the healing of diabetic foot ulcers by activating the Nrf2 signalling pathway and its downstream target genes.[21] Similarly, this study also observed a relationship between HBO and the Nrf2 pathway. The expression of Nrf2 and the downstream genes HO-1 and CAT in healthy and diabetic mice increased after 1 week of HBO treatment. Furthermore, Nrf2 plays a vital regulatory role in the metabolic balance of bone cells. Mice with Nrf2 gene knockout exhibit significantly lower bone mass in the distal femur compared to the control group.[22] In age- and sex-matched mice, the inactivation of Nrf2 further exacerbates radiation-induced bone loss,[23] which is also evident in the bone fracture healing process. These findings suggest that Nrf2 plays a significant role in bone regeneration. This mechanism aligns with clinical observations where HBO increased BMP-2 and RUNX2 expression within 5 to 9 weeks, suggesting that it may regulate the osteogenic process through activation of the Nrf2 pathway.

Osteoclasts are essential for bone homeostasis, but diabetes disrupts this balance, causing excessive resorption and compromised bone integrity. Critically, HBO suppressed TRAP expression in both diabetic and non-diabetic mice. This aligns with evidence that Nrf2 activation inhibits osteoclast differentiation[24,25] and that HBO downregulates osteoclastogenic factors RANKL, NFATc1 and Dc-STAMP,[26] leading to the alleviation of bone resorption symptoms in clinical patients after HBO treatment.[27] Further supporting this mechanism, Zhu et al[28] demonstrated that Nrf2/CAT signalling suppresses osteoclastogenesis. The present results showed that TRAP expression decreased, accompanied by an increase in Nrf2 and the downstream protein CAT, suggesting that HBO inhibits osteoclast activity through the activation of the Nrf2/CAT pathway.

Study limitations

Although the clinical results of the present study are promising, the small sample size limits generalisability.

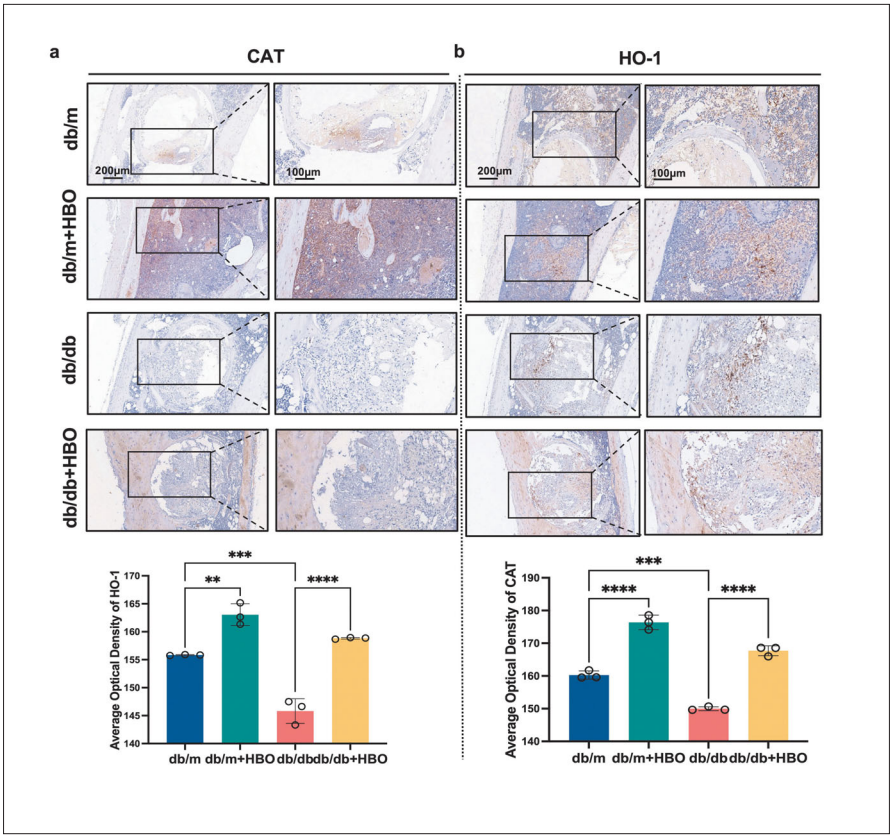

Fig 5a and b Bone healing induced by HBO is related to the Nrf2 pathway. Immunohistochemical results of CAT and quantitative results (a). Immunohistochemical results of HO-1 and quantitative results (b). The left column displays the area of tibial injury, and the right column shows enlarged images of the region within the black frame in the left. $^{**}P < 0.01$; $^{***}P < 0.001$; $^{****}P < 0.0001$.

Future multicentre randomised trials with standardised protocols are essential to validate the efficacy of HBO therapy and optimise treatment parameters such as different pressures and duration. Additionally, the animal experiments focused on short-term outcomes (7 days). Although the duration captured early-phase molecular responses, it did not fully reflect long-term bone remodelling, and despite the fact that the Nrf2 pathway was identified as a potential key mediator, the precise regulatory mechanisms remain unexplored, and further in vitro experiments are necessary.

Conclusion

In conclusion, this study establishes HBO as a promising adjuvant therapy, optimising the timing of bone healing in non-diabetic patients while rescuing the impaired bone repair through Nrf2 activation in a mouse model. By bridging clinical innovation with mechanistic rigour, the present study provides a translatable framework to improve implant outcomes in an era of rising diabetes prevalence. Subsequent research should prioritise large-scale clinical validation and further mechanistic exploration.

Conflicts of interest

The authors declare no conflicts of interest related to this study.

Author contribution

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Drs Yue WANG and Qiang SUN and HBO therapy was performed by Dr Jing YANG. The first draft of the manuscript was written by Dr Yue WANG and was reviewed and edited by Drs Bao Hua XU and Qiang SUN. All authors commented on previous versions of the manuscript and approved the final manuscript.

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