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Revolutionizing Diabetic Wound Care: Insight Into Hyperbaric Oxygen Therapy

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1. *INTRODUCTION*

India is home to a significant population of individuals with diabetes, with approximately 25% of these patients at risk of developing diabetic foot ulcers. Furthermore, the country reports around 1 million deaths annually attributed to diabetes-related complications. This alarming trend may be exacerbated by insufficient public awareness, inadequate medical infrastructure, and economic constraints [1].

Diabetic wounds represent a major complication for those living with diabetes. The impaired glucose metabolism characteristic of diabetes leads to hyperglycaemic conditions, which further hinder the wound-healing process, often resulting in chronic wounds that do not heal. Typically, wound healing in non-diabetic individuals takes about 21 to 28 days [2]. However, in diabetic patients, this process is significantly delayed due to disruptions in the inflammatory and proliferative phases of healing. Such delays can have long-lasting adverse effects on quality of life and increased morbidity and mortality rates. Factors that negatively influence the inflammation and proliferation phases include an impaired inflammatory response, reduced angiogenesis, neuropathy, delayed collagen synthesis, infection, ischemia, and hypoxia. India is home to a significant population of individuals with diabetes, with approximately 25% of these patients at risk of developing diabetic foot ulcers. Furthermore, the country reports around 1 million deaths annually attributed to diabetes-related complications. This alarming trend may be exacerbated by insufficient public awareness, inadequate medical infrastructure, and economic constraints.

1.1Factors affecting wound healing –

Local factors	Systemic factors
Oxygenation	Age and gender
Infection	Stress
Foreign body	Ischemia
Venous sufficiency	Disease – Diabetes, keloids, fibrosis
	Obesity
	Medications – Glucocorticoid therapy, NSAIDS[1], chemotherapy
	Alcoholism and smoking

Table (1) Multiple factors can lead to impaired wound healing. Local factors affect only the properties of the wounds while systemic factors influence health or disease states of the individuals [3] .

2. ***ROLE OF OXYGEN IN WOUND HEALING*** –

Oxygen is necessary for effective wound healing, facilitating numerous processes such as collagen deposition, epithelialization, fibroplasia, angiogenesis, and infection resistance. It protects wounds from infection, promotes angiogenesis, and stimulates keratinocyte differentiation and re-epithelialization. Furthermore, enhanced fibroblast proliferation and collagen synthesis contribute to wound contraction, highlighting the mechanistic importance of oxygen. Following tissue injury, oxygen providence to the affected area is temporarily restricted; however, failure to restore adequate oxygen levels during the healing process can impair wound healing. If this condition persists, it may lead to the development of chronic wounds. Sufficient oxygenation at the wound site is crucial for healing, as hypoxia, oxidative stress, or vascular injury can trigger angiogenesis [4]. Conditions of reduced oxygen supply stimulate the migration of growth factors and the activation of pro-angiogenic pathways.

Topical oxygen therapy

Upregulate growth factor expression	Decreased expression of tissue degrading factors	Increased collagen synthesis and facilitating granulation tissue growth

Table (2) Mechanistic role of oxygen in wound healing.

3. ANGIOGENESIS IN WOUND HEALING –

The healing process can be significantly hindered due to its adverse effects on the inflammation and proliferation phases of wound healing. This impairment can result in long-term detrimental consequences for quality of life, as well as increased morbidity and mortality rates. The inflammation and proliferation phases are influenced by various pathophysiological factors, including an inadequate inflammatory response, diminished angiogenesis, neuropathy, delayed collagen synthesis, infection, ischemia, and hypoxia [5].

Oxygen is necessary for effective wound healing, facilitating numerous processes such as collagen deposition, epithelialization, fibroplasia, angiogenesis, and infection resistance. It serves to protect wounds from infection, promotes angiogenesis, and stimulates keratinocyte differentiation and re-epithelialization. Furthermore, enhanced fibroblast proliferation and collagen synthesis contribute to wound contraction,

[1] Non-steroidal Anti-Inflammatory Drugs

highlighting the mechanistic importance of oxygen. Following tissue injury, oxygen providence to the affected area is temporarily restricted; however, failure to restore adequate oxygen levels during the healing process can result in impaired wound healing. If this condition persists, it may lead to the development of chronic wounds. Sufficient oxygenation at the wound site is crucial for healing, as hypoxia, oxidative stress, or vascular injury can trigger angiogenesis. Conditions of reduced oxygen supply stimulate the migration of growth factors and the activation of pro-angiogenic pathways.

To overcome these challenges, there are various 'Advanced wound care therapies' like

- Tissue-growing therapies
- Negative pressure wound therapy (NPWT)
- Hyperbaric Oxygen Therapy (HBOT)
- Stem cell therapy
- Total contact casts
- Nanotherapeutics
- Bioengineered skin grafts
- Electromagnetic therapy
- Ultrasound therapy

Numerous products and technologies have been created to enhance the wound environment, ensuring a pathogen-free, safeguarded, and moist area conducive to healing. Among these advanced wound care therapies is hyperbaric oxygen therapy. This review seeks to deepen the understanding of the mechanisms underlying hyperbaric oxygen therapy and its relevance in the treatment of wound infections [7].

4. HYPERBARIC OXYGEN THERAPY-

Hyperbaric oxygen therapy (HBOT) is a sophisticated treatment modality that involves administering 100 percent pure oxygen to patients under elevated atmospheric pressure. This therapeutic approach was first established in 1879 and has since gained recognition as an effective intervention for various medical conditions. Currently, HBOT is extensively utilized in the management of infectious diseases and inflammatory disorders, as well as in promoting wound healing [8]. Additionally, it plays a critical role in addressing acute medical emergencies such as air embolism and carbon monoxide poisoning.

Hyperbaric Oxygen Therapy (HBOT) is utilized extensively for the treatment of various conditions, including infections in wounds, unsuccessful skin grafts, thermal injuries, radiation-induced injuries, diabetic foot ulcers, and osteomyelitis, among others [9]. In certain instances, conventional treatments may prove ineffective for standard injuries, necessitating the consideration of advanced therapeutic options.

HBOT employs two types of chambers: monoplace (designed for a single patient) and multiplace (accommodating two to fourteen patients) [10]. The monoplace chamber is typically filled with pure oxygen, while the multi-place chamber allows multiple individuals to inhale oxygen simultaneously through face masks, hoods, or endotracheal tubes. The multi-place chamber is often favoured in critical situations due to its capacity for enhanced monitoring of vital signs. Treatment sessions generally last between 1.5 to 2 hours and can be administered one to three times per day. Research indicates that HBOT is particularly beneficial for treating the diabetic ulcers, as it promotes oxygen delivery and angiogenesis, mitigates inflammation and oxidative stress, and encourages the release of growth factors.

4.1 HBOT AND ANGIOGENESIS-

Angiogenesis represents a multifaceted mechanism involved in the repair of blood vessels, triggered by conditions such as hypoxia and oxidative stress. These stimuli lead to the secretion of various growth factors, with VEGF[2] being the most prominent. VEGF facilitates the migration of capillary endothelial cells to the site of injury, where they contribute to the formation of tubular structures that connect to pre-existing vascular networks. Neovascularization typically occurs through two distinct pathways: vasculogenesis and angiogenesis. The latter refers specifically to the proliferation of local endothelial cells to generate new blood vessels, while vasculogenesis involves the migration and differentiation of circulating stem progenitor cells (SPCs[3]) into vascular structures. Hyperbaric oxygen therapy (HBOT) has been shown to influence both of these processes [11].

In the context of diabetic wounds, impaired angiogenesis is a significant complication that severely hampers the healing process. The alterations in angiogenic activity among diabetic patients can vary depending on the specific tissue or organ involved. For instance, in diabetic retinopathy (DR[4]), there is an instance of uncontrolled angiogenesis, leading to a pathological state characterized by microaneurysms, haemorrhages, and vascular edema [12].

Furthermore, HBOT has been associated with enhanced angiogenesis, making it a viable option for skin graft procedures. Numerous studies, including those utilizing wound models in rats and trials involving human participants, have demonstrated that HBOT promotes the production of active VEGF. Various mechanisms have been proposed to explain the effects of HBOT on angiogenesis.

4.2 HBOT AND INFECTION-

Hyperbaric oxygen therapy (HBOT) has demonstrated significant utility in managing various infections, particularly deep-seated infections, such as necrotizing fasciitis and osteomyelitis. Its effectiveness extends to chronic soft tissue infections and infective endocarditis. The clinical relevance of HBOT in treating soft tissue infections and osteomyelitis is well established, particularly in cases associated with hypoxic conditions resulting from anaerobic and antibiotic-resistant pathogens, including Pseudomonas aeruginosa and Staphylococcus aureus [13].

The primary advantage of HBOT lies in its antimicrobial properties, particularly in the context of necrotizing soft tissue infections (NSTIs[5]), Fournier's gangrene, and gas gangrene, where it exhibits efficacy against a broad spectrum of gram-positive, gram-negative, aerobic, and anaerobic bacteria. Evidence from clinical practice indicates that HBOT effectively targets anaerobic bacterial infections, as these pathogens are susceptible to elevated levels of oxygen pressure. In instances of Fournier's gangrene, HBOT has been beneficial in addressing severe complications such as bacteraemia and sepsis, with clinical trials indicating favourable outcomes. Furthermore, it represents a superior therapeutic approach for intracranial abscesses (ICA[6]), which are predominantly caused by bacterial infections.

Osteomyelitis, characterized as a chronic infection of the bone marrow caused by bacteria and mycobacteria, poses significant treatment challenges. HBOT emerges as a promising intervention, enhancing antibiotic activity through mechanisms such as promoting angiogenesis, facilitating leukocyte oxidative killing, and supporting the osteogenesis process [9].

[2] Vascular Endothelial Growth Factor
[3] Stem Progenitor Cells
[4] Diabetic Retinopathy
[5] Necrotizing Soft Tissue Infections
[6] Intracranial Abscesses

4.3 HBOT AND DIABETIC WOUND –

Hyperbaric oxygen therapy (HBOT) stands out as the most efficacious among advanced wound care treatments for diabetic foot ulcers. Evidence suggests that the implementation of HBOT significantly enhances the healing rates of foot ulcers in patients with diabetes and reduces the necessity for amputation procedures. Furthermore, HBOT offers a cost-effective alternative to more complex and expensive surgical interventions, making it a more accessible option in clinical settings [14].

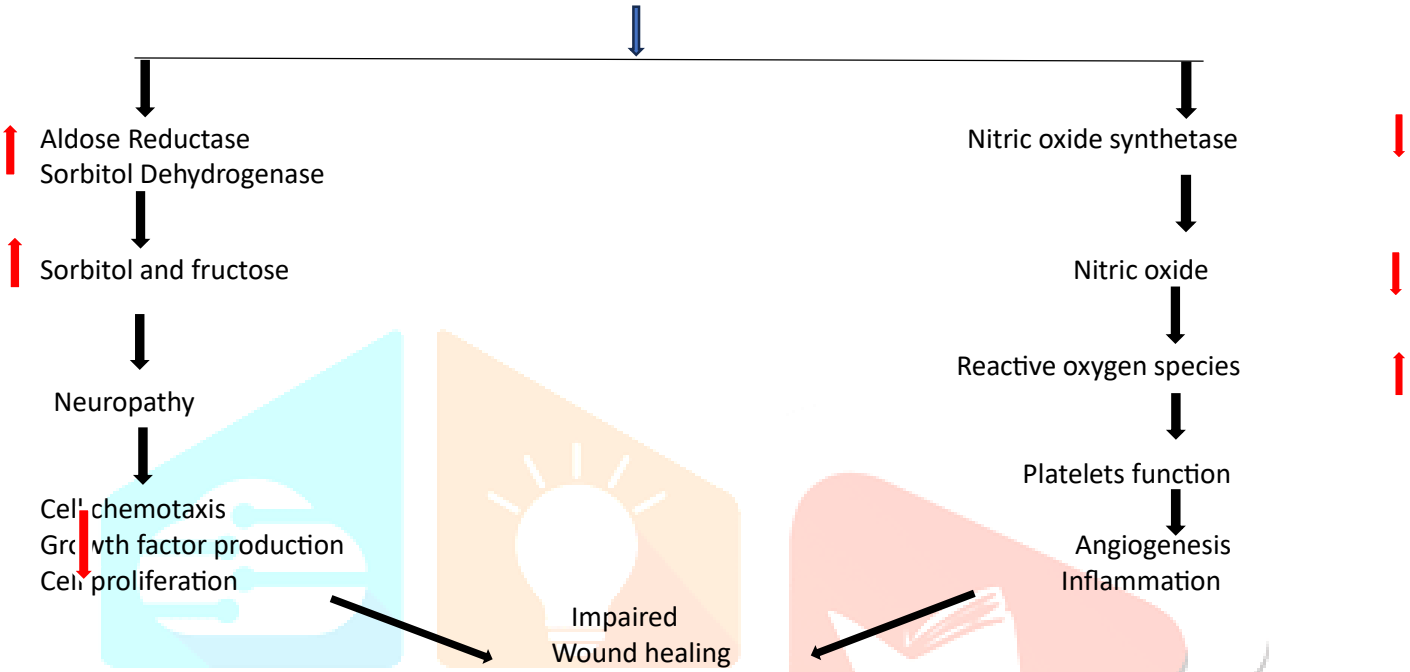

Chart (1) Mechanistic pathways responsible for delayed and impaired wound healing in diabetes [2].

Two decades prior, the inaugural controlled trial assessing hyperbaric oxygen therapy (HBOT) was published, demonstrating its efficacy in treating diabetic wounds [15]. HBOT serves as an adjunctive therapy for diabetic foot ulcers, primarily functioning through mechanisms that promote angiogenesis, alleviate wound tissue hypoxia, decrease edema, and stimulate both collagen synthesis and fibroblast proliferation.

1. Oxygen delivery to the wound site: As HBOT involves breathing 100% oxygen at pressures greater than atmospheric pressure, this significantly increases the oxygen in plasma and also enhances oxygen delivery to diffuse further into hypoxic tissues and support cellular metabolism [4].

2. Promotes angiogenesis: HBOT stimulates the release of vascular endothelial growth factor (VEGF) and other pro-angiogenic growth factors, initiating and promoting the growth of new capillaries.

3. Collagen synthesis: Oxygen is the primary requirement of fibroblasts to produce collagen. Collagen provides structural support to wounds. HBOT increases the activity of fibroblasts, improving collagen deposition and wound strength [16].

4. Reduces inflammation: HBOT reduces pro-inflammatory cytokines and increases anti-inflammatory cytokines, modulating the immune response. This helps control chronic inflammation often seen in diabetic wounds [17].

5. Immune function: HBOT enhances immune function by boosting the white blood cells for their phagocytic action bacteria through enhanced production of reactive oxygen species (ROS[7]). It also supports the action of antibiotics and inhibits the growth of anaerobic bacteria by creating a high-oxygen environment [18].

[7] Reactive Oxygen Species

6. Reduces edema: The increased pressure during HBOT helps reduce swelling and edema by facilitating the removal of excess fluid from the tissues.

Numerous studies have shown that HBOT improves wound healing outcomes in diabetic patients, especially in cases of chronic or non-healing ulcers. It is particularly effective when combined with other standard wound care practices.

5. CLINICAL EVIDENCES

Currently, hyperbaric oxygen therapy (HBOT) is utilized across a diverse spectrum of medical treatments, with 14 recognized indications, encompassing various complications such as air embolism, severe anemia, and specific infectious diseases [9]. The latest European Consensus Conference on Hyperbaric Medicine highlighted HBOT's role as a primary treatment for certain conditions supported by moderate to high levels of evidence, such as post-carbon monoxide poisoning, and as a potential adjunctive therapy for other conditions with moderate scientific backing, like diabetic foot ulcers [19].

Recent evaluations indicate that incorporating HBOT into the management of refractory diabetic wounds significantly reduces the likelihood of major amputations, with an odds ratio of 0.236 (95% confidence interval [CI[8]] 0.133–0.418). Furthermore, the adjunctive application of HBOT in diabetic wound care enhances healing, reflected by an odds ratio of 11.64 (95% CI 3.457–39.196) [15].

A notable study conducted by Duzgun et al. in 2008 involved a comparative analysis of 100 patients suffering from diabetic foot ulcers, with treatment administered over one month. The findings revealed that HBOT resulted in significantly higher wound healing rates (66% compared to 0%), reduced the need for surgical interventions (debridement, amputation, or skin flap/graft; 16% versus 100%), and led to fewer lower extremity amputations (8% versus 82%) [15].

Additionally, a Cochrane review published in 2015 assessed the efficacy of HBOT for chronic wounds, analyzing eight randomized controlled trials involving patients with diabetic foot ulcers. The review concluded that HBOT appears to facilitate short-term wound healing (up to six weeks) and may lower the incidence of major amputations [20].

Approved indications for HBOT-

1. Carbon monoxide poisoning
2. Carbon monoxide poisoning with cyanide poisoning
3. Skin grafts and flaps
4. Crush injury and other acute traumatic ischemia
5. Radiation injury
6. Soft tissue infection
7. Thermal injury
8. Air embolism [21]

6. TREATMENT RISKS

- Can induce seizures and pulmonary damage due to oxygen toxicity.
- Therapy requires specialized equipment, which is expensive and inaccessible to some patients.
- While considerable potential exists in many emerging applications, they often fall short of rigorous clinical validation. Central nervous system (CNS) oxygen toxicity is identified as a significant adverse effect that may arise during this treatment. The occurrence of CNS oxygen toxicity is estimated to be between 1 and 4 cases per 10,000 patient treatments [22].

[8] Confidence Interval

7. FUTURE ASPECTS

HBOT demonstrates significant therapeutic potential when used with other advanced treatments, such as stem cell therapy. Innovations in chamber design and monitoring technologies are being developed to enhance the future efficacy of this therapy. Furthermore, HBOT has yielded encouraging outcomes in regenerative medicine and exhibits anti-aging properties through various biological mechanisms [23]. Its potential is underscored by its capacity to modulate numerous physiological functions while maintaining a low incidence of adverse effects, positioning it as a valuable intervention for mitigating the detrimental impacts of aging and promoting overall health.

In addition to HBOT, future strategies for managing diabetic wounds may encompass therapies involving recombinant growth factors, platelet-rich plasma, sphingosine 1-phosphate, substance P, stem cell therapy, matrix metalloproteinase inhibitors, shock-wave therapy, laser therapy, and treatments derived from natural products.

8. CONCLUSION

In this article, we summarized Impaired glucose metabolism has long-term negative effects on wound healing. Oxygen helps with various processes in the healing of wounds, including collagen deposition, epithelization, fibroplasia, angiogenesis, and resistance to infection. Hyperbaric oxygen therapy is one of the advanced wound care therapies. Hypoxic tissue, reperfusion injury, chronic wounds, infectious wounds, burns, and necrotizing infections have all been shown to respond favorably to HBOT. As we learn more about how HBOT benefits wounds by promoting neovascularization as it stimulates growth factor release and angiogenesis, the potential benefits to wound healing become clearer. It decreases the incidence of amputation in diabetic wounds. Overall, HBOT is the most accessible therapy for all patients, as it nullifies the use of expensive equipment and critical procedures. It is a highly versatile and effective therapy, which shows promise in emerging areas; further research is needed to validate its efficacy and expand its applications.

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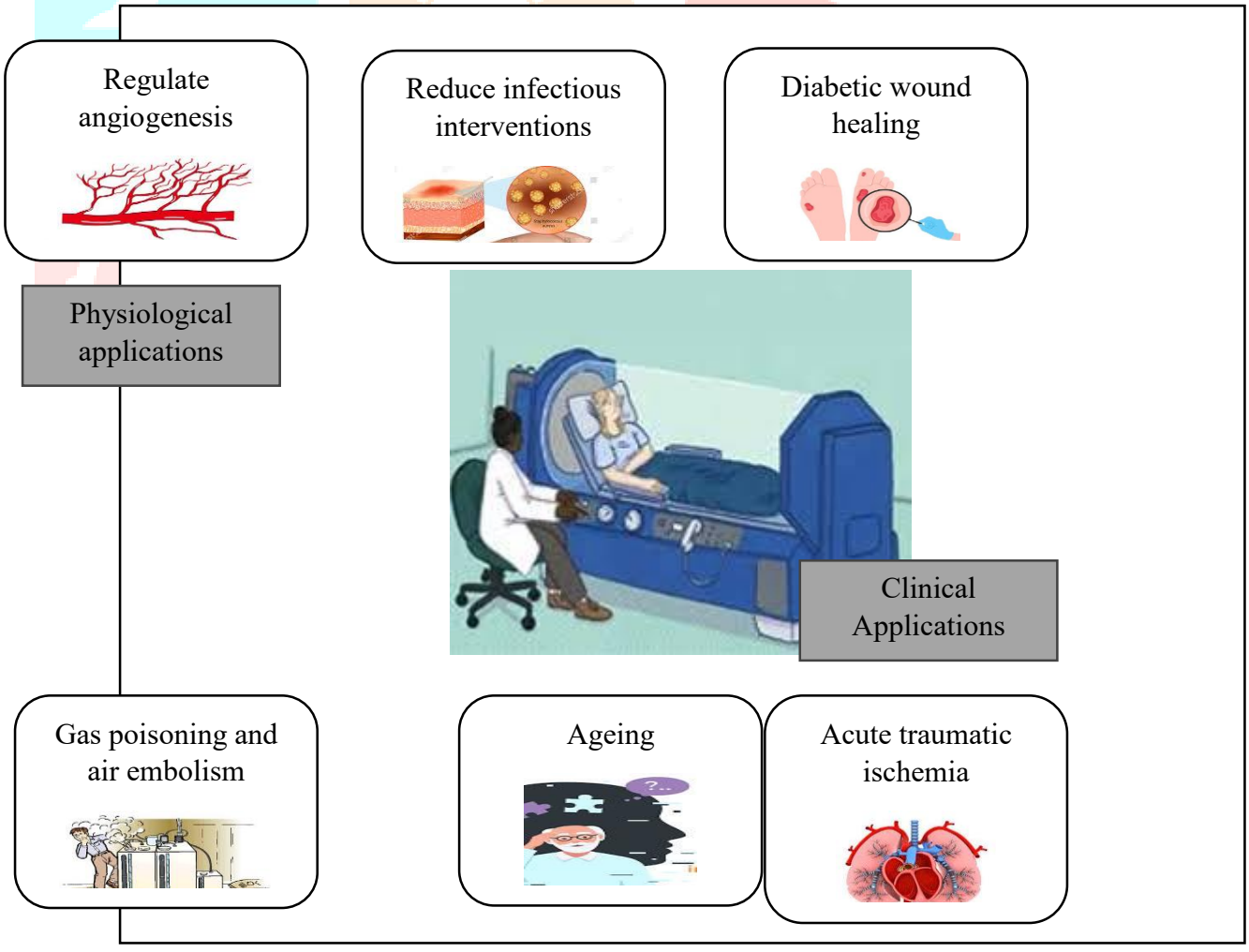

Figure_1 The representative schematic diagram of various physiological and clinical applications of HBOT [23].