How Oxygen Works in Wound Healing

This is a summary overview of the current scientific and clinical literature regarding the mechanisms and efficacy of oxygen in wound healing. Detailed information with references follows the front page. Information regarding what Continuous Diffusion of Oxygen (CDO) is, how it differs from other oxygen technologies and supporting clinical evidence can be found in the EO_2 guidance document "How CDO Works".[1] CDO is essentially moist wound therapy plus oxygen: pure humidified oxygen is continuously added into an oxygen diffusion dressing.

1. Increases Cell Metabolism and Energy

Oxygen boosts vitality to support increased demand during healing - oxygen is required for intracellular processes like biosynthesis, movement, and transport need energy to be functional, as well as for cell survival

2. Faster Wound Closure (up to 4.6x)

Increasing oxygen levels results in faster cell proliferation, reepithelialization and collagen formation – wounds heal up to 4.6x faster than moist wound therapy alone

3. Rapid Pain Relief (as fast as several hours)

Increasing oxygen levels relieves hypoxic pain resulting in significant pain reduction – some patients report complete pain relief within several hours

4. Greater Wound Perfusion & Angiogenesis

Oxygen levels directly affect the rate and quality of new blood vessel growth in the wound bed - the creation of new blood vessels, angiogenesis, is essential to the growth and survival of repair tissue

5. Naturally Antibacterial

Increased oxygen levels aid the natural capacity to fight infection - oxygen is essential for respiratory burst, the production of reactive oxygen species (ROS), used by phagocytes such as neutrophils and macrophages in bactericidal activity and the removal of necrotic cellular debris

6. Better Strength & Appearance

Oxygen levels directly affect the rate and quality of collagen formation – oxygen is required for proper fiber formation and cross-linking to form organized collagen, resulting in better strength and appearance

7. Promotes Growth Factor Signaling Transduction

Oxygen kicks off a signaling cascade - ROS are essential for the signaling processes of growth factors and processes such as leukocyte recruitment, cell motility, angiogenesis and extracellular matrix formation

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1. Increases Cell Metabolism and Energy

Oxygen is required for intracellular processes like biosynthesis, movement, and transport need energy to be functional, as well as for cell survival[2]

- Oxygen dependent enzymes include:
  - Adenosine triphosphate (ATP) for chemical energy, which fuels most active cellular processes such as during wound healing.[3] Increased energy demand of the healing tissue leads to a hypermetabolic state wherein additional energy is generated from oxidative metabolism increasing the oxygen demand of the healing tissue.[4,5,6,7] ATP thus generated powers tissue repair
  - NADPH (nicotinamide adenine dinucleotide phosphate) oxygenase for respiratory burst (reactive oxygen species release), the activity of which is critically required to produce the redox signals required for wound healing[8,9,10]
- Aerobic glycolysis, β-oxidation of fatty acids, and the citric acid cycle are tightly attached to the energy acquisition by oxidative phosphorylation and are therefore oxygen dependent[11]
- If oxygen levels are too low (<20 mmHg pO_2), cells convert to anaerobic metabolism and go into survival mode in which wound healing activities such as mitosis (cell division, and therefore reepithelialization) and collagen production are impaired[12,13,14]
- Prolonged exposure to extremely low oxygen levels, if not alleviated by oxygen, can result in cell death and tissue necrosis due to the inability of the cells to repair the spontaneous decay of cell components (DNA, RNA, proteins) and inability to maintain calcium pumps which require ATP to function[15,16]

2. Faster Wound Closure (up to 4.6x faster than moist wound therapy)

Increasing oxygen levels results in faster cell proliferation, reepithelialization and collagen formation

- The continuous, topical addition of pure oxygen (CDO therapy) over diabetic wounds has been shown to increase the rate of wound closure, by as much as 460% relative to moist wound therapy[17,18,19,20,61]
- Adding oxygen improves closure in wounds that are larger, more chronic and weight-bearing,[17,18] as well as those that are deeper[21]
- CDO therapy has been shown to achieve full wound healing in a variety of wounds that were resistant to other advanced therapy treatments[17,18,19,21,22,23,30,31]
- CDO has been shown to increase growth factors (TGF-β, VEGF, PDGF & IGF-1) and cytokines (TNF-α, IL-6 & CXCL8) involved in cell proliferation, reepithelialization and collagen formation in excess of 800% in one week[24]
- Fibroblast proliferation and protein production have been reported to be optimal at 160 mmHg, i.e. at pO_2 levels 2-fold to 3-fold higher than those found in healthy tissues[25], indicating that supplemental oxygen increases the rate of wound repair
- Endothelial progenitor cells (EPCs) are essential in wound healing, but their circulating and wound level numbers are decreased in diabetes. Elevated oxygen levels (hyperoxia) reverse the diabetic defect in EPC mobilization[26]
- EPC mobilization into circulation is triggered by hyperoxia through induction of nitric oxide (NO) with resulting enhancement in ischemic limb perfusion and wound healing[27,28,29]

3. Rapid Pain Relief (as fast as complete pain relief within hours)

Increasing oxygen levels relieves hypoxic pain resulting in significant pain reduction –patients have been reported to experience complete pain relief within several hours

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- The addition of a continuous flow of pure oxygen over a variety of wound types has been shown to significantly decrease pain in short time frames – over half of the 20 patients experienced at least a 75% reduction in pain within 4 days[30]
- With a patient serving as her own control, CDO had reduced pain from 8 to 2 and she had ceased pain medication. She removed CDO for a few days and the pain increased to 10. Upon reapplying CDO, pain quickly reduced to 2 again.[31]
- In a study of 10 patients with venous ulcers, CDO therapy was reported to significantly ($P < .009$) reduce pain in a six-week period. The corresponding mean reduction in wound size was 58.9%.[32]
- Several case series reviews report significant pain reduction in very painful wounds.[33,34]

4. Greater Wound Perfusion & Angiogenesis

The creation of new blood vessels, angiogenesis, is essential to the growth and survival of repair tissue. Oxygen levels directly affect the rate and quality of new blood vessel growth

- Sufficient oxygen levels are required for correct collagen synthesis (posttranslational hydroxylation)[35], without which the new capillary tubes assemble poorly and remain fragile[36,37,38]
- CDO has been shown to increase growth factors (TGF-β, VEGF, PDGF & IGF-1) and cytokines (TNF-α, IL-6 & CXCL8) involved in angiogenesis in excess of 800% in one week[24]
- Supplemental oxygen accelerates blood vessel growth[39]
- Moderate hyperoxia increases the appearance of new blood vessels in wounds[40]
- The rate of angiogenesis is directly proportional to oxygen levels in injured tissues and rates of collagen deposition increase proportionally with oxygen levels to more than 250 mmHg[37]
- Conversely, hypoxic wounds deposit collagen poorly and become infected easily[41,42]

5. Naturally Antibacterial

Oxygen is essential for respiratory burst, the production of reactive oxygen species (ROS), used by phagocytes such as neutrophils and macrophages in bactericidal activity and the removal of necrotic cellular debris

- NADPH oxidase, also known as leukocyte oxidase, supports macrophage survival (delay of apoptosis)[43] and enables dead cell cleansing by phagocytosis[44]
- NADPH oxidase in wound phagocytes, such as neutrophils and macrophages, produces superoxides (O_2^- and H_2O_2) for bactericidal activities[45] – in fact, ~98% of oxygen consumed by these cells is used to produce ROS during phagocytosis[46]
- Leukocyte activity (production of ROS and hence oxidative killing) is directly proportional to local oxygen concentration[47,48]
- Optimal ROS production is seen at oxygen levels of greater than 300 mmHg[19], levels which can only be achieved with supplemental oxygen[49]
- At the wound site, ROS are generated by almost all wound-related cells[53]
- The efficacy of supplemental oxygen has been shown to be similar to antibiotic administration and has additive effects when used together[50,51]

6. Increases Collagen Synthesis and Tensile Strength

Oxygen is essential to make and properly organize collagen, which is the primary component of skin, accounting for 70-80% (dry weight – without water) and acts as the structural scaffold of skin. Organized collagen is bundled into fibers (like strands in rope), which are interwoven and can be stretched in multiple directions without tearing (the collagen fibers are woven similar to

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fabric)

- Oxygen is required for the hydroxylation of proline and lysine in procollagen[52]
- Several posttranslational steps in collagen synthesis are oxygen dependent. The enzymes prolyl hydroxylase, lysyl hydroxylase and lysyl oxidase all require oxygen[53,54,55]
    - Formation of cross-linked triple-helices via the oxygen-dependent enzyme prolyl hydroxylase and excreted as collagen fibers
    - Collagen fibers are arranged into linear fibrils via cross-linking by lysyl hydroxylase
    - Linear fibrils are cross-linked by lysyl oxidase - a necessary step to achieve the necessary tensile strength for healed wounds
- Higher oxygen concentrations increase the amount of collagen deposition[42] and tensile strength[56,57,58]
- The rate limiting step is the rate of prolyl hydroxylation[54,55]
- The oxygen level required for optimal prolyl hydryoxlase activity is at oxygen levels approaching 250 mmHg, exceeding those present in normal wounds[59,60]
- CDO has been shown to increase growth factors (TGF-β & VEGF) and cytokines (TNF-α & IL-6) involved in collagen synthesis & remodeling in excess of 800% in one week[24]
- It has been shown that increasing oxygen above normal physiologic levels enhances collagen synthesis and tensile strength in both animal and human subjects[56,57,58] and can increase the level of collagen organization[61]
- Correction of vasoconstriction and hypoxia can result in a 10-fold increase in collagen deposition in wound repair[42,57,62,63]

7. Promotes Growth Factor Signaling Transduction

Reactive oxygen species (ROS) are essential for the signaling processes of growth factors and processes such as leukocyte recruitment, cell motility, angiogenesis and extracellular matrix formation

- Signal transduction of growth factors happens through ROS[64]
- ROS such as hydrogen peroxide (H_2O_2) increase vascular endothelial growth factor (VEGF) production in macrophages and keratinocytes[65,66]
- VEGF is a major long-term angiogenic stimulus at the wound site
    - oxygen treatment induces VEGF mRNA levels in endothelial cells and macrophages[67,68,69]
    - oxygen treatment increases VEGF121/165 protein expression in wounds[70] and facilitates the release of VEGF165 from cell-associated stores[71]
- Platelet-derived growth factor (PDGF) requires ROS in its role to regulate cell growth and division[72], and PDGF plays a significant role in blood vessel formation (angiogenesis)[53]
- ROS has effects on other processes such as cytokine action, cell motility and extracellular matrix formation[8]
- CDO has been shown to increase growth factors (TGF-β, VEGF, PDGF & IGF-1) and cytokines (TNF-α, IL-6 & CXCL8) involved in signaling transduction in excess of 800% in one week[24]
- Conversely, tissue hypoxia will limit redox signaling and disable the function of several growth factors (e.g., PDGF, VEGF, keratinocyte growth factor, insulin-like growth factor, transforming growth factor-a) and numerous molecular mechanisms (e.g., leukocyte recruitment, cell motility, integrin function), which rely on redox signaling[10,73,74]

NOTES:

- Text from some citations is directly extracted from the referenced literature without quotations
- Recommended summary articles on oxygen in wound care include articles by Sen[2], Tandara and Mustoe[11],

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Gordillo and Sen[53] and Schreml et al[75]

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