

# The Crucial Role of Oxygen for Health

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Chris D. Meletis, ND\*  
Kimberly Wilkes<sup>†</sup>

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## ABSTRACT

The human body is dependent upon oxygen for its survival. Yet, various factors such as aging, psychological stress, obstructive sleep apnea, exposure to cigarette smoke, living at high altitude, high-intensity exercise, or a sedentary lifestyle can all lead to a hypoxic state. Hypoxia may be involved in the pathogenesis of a number of disorders including impaired immunity, hormonal imbalances, fibromyalgia, cardiovascular diseases, type 2 diabetes, depression, and anxiety. Hyperbaric oxygen therapy and massage are two means by which to improve oxygen perfusion. Certain dietary supplements such as *Ginkgo biloba*, coenzyme Q10, and beetroot juice can increase oxygenation through enhanced blood flow while branched-chain amino acids and omega-3 fatty acids can improve maximum oxygen consumption  $\dot{V}O_2\text{max}$ . Additionally, omega-3 fatty acids and vitamin D may reduce the incidence of sleep apnea while N-acetyl cysteine may protect against hypoxia injury related to sleep apnea.

**Keywords:** Hypoxia; Oxygenation; Perfusion; Hyperbaric oxygen therapy

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\*Corresponding author: Associate Professor of Natural Pharmacology, National University of Natural Medicine, Portland, OR, USA, Tel.: +1-503-466-2722; E-mail: DrMeletis@gmail.com

<sup>†</sup>15455 NW Greenbrier Parkway Way, Portland, OR 97006, USA.

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## INTRODUCTION

Every tissue and organ in the body is dependent upon oxygen to function effectively. The human brain, for example, needs 20% of the oxygen pumped from the heart while at rest.<sup>1,2</sup> The brain's oxygen requirement is the highest of any tissue or organ, even though it accounts for only 2% of the average person's body weight.<sup>2</sup> Every time we take a breath in, oxygen is transported via the alveoli of the lungs to the capillaries and subsequently into the bloodstream. In the blood, hemoglobin, a protein in red blood cells (RBC), binds oxygen and shuttles it to tissues where the oxygen assists with nutrient breakdown and energy production. This process of delivering oxygen to tissues is known as perfusion. If tissues do not receive enough oxygen, a condition known as hypoxia develops, which results in pain and suboptimal cellular function. Tight muscles are reflective of a hypoxic state. Soreness that occurs after exercising harder than normal or exercising after a sedentary period is due to low blood oxygen levels during exercise and the buildup of lactic acid. Ongoing exercise, on the other hand, encourages more blood oxygen to be pumped throughout the body, allowing for greater ability to move without feeling pain, assuming we don't exceed our individual aerobic threshold.

According to the Mayo clinic, 95%–100% oxygen saturation is considered normal blood oxygen levels.<sup>3</sup> However, in clinical practice, many patients with a 95% oxygen saturation often show signs and symptoms of hypoxia, such as marginal night time oxygenation trending towards apnea. This article describes factors that lead to hypoxia, diseases associated with hypoxia, and ways to support better tissue perfusion.

## CAUSES OF HYPOXIA

Oxygen levels decline as part of the aging process. The greatest loss in oxygen levels – up to 10 points – occurs between 30 and 40 years old.<sup>4</sup> Stress is another factor that can deplete oxygen levels. During psychological stress, the fight or flight system is hyperactive, leading to shallower breathing and therefore reduced oxygen supply. Studies

indicate there is decreased oxygen supply and a greater oxygen demand in the wounds of stressed animals. Optimal oxygen levels play an important role in wound healing, while low oxygen levels can reduce the healing rate.<sup>5</sup>

In a rodent model of stress-impaired healing, mice were divided into four groups: controls, controls with hyperbaric oxygen therapy (HBO), stressed animals, and stressed animals administered HBO.<sup>5</sup> Each of the mice in the four groups was administered two cutaneous wounds. The stressed groups of mice were subjected to restraint stress prior to and after wounding. The control groups were deprived of food and water during the same period, to control for the inability of the stressed animals to access food and water while restrained. HBO – which delivers 100% oxygen – was administered twice per day to one group of stressed mice and to one control group during early wound repair. In the stressed mice, the HBO significantly decreased the detrimental effects of stress on healing, and increased healing to nearly the level of that of control animals. HBO did not result in any significant effect on wound healing in control animals.<sup>5</sup>

Another study in rodents showed that stress aggravates periodontitis by decreasing tissue oxygenation.<sup>6</sup> Gum disease severity was linked to the level of psychological stress and decreased oxygenation in the periodontal tissue.

Heiden and colleagues studied 24 healthy subjects (12 males and 12 females) who performed a 45-minute standardized mouse-operated computer task on two occasions. On one occasion, the subjects were given a deadline to meet and a more demanding task. On the other occasion, the subjects were told to perform a less demanding task. Throughout the study, tissue oxygen saturation in the trapezius and the extensor carpi radialis muscle of the forearm operating the mouse was measured. During the more demanding task, oxygen saturation in the extensor carpi radialis muscle of the forearm decreased ( $P < 0.05$ ) compared to when the subjects performed the less demanding task. Females had lower oxygen saturation than males, during both rest and the computer tasks ( $P < 0.01$ ). Ratings of tenseness and fatigue also were higher in the

subjects who performed the more demanding task.<sup>7</sup> The effects of stress on oxygen supply has implications that extend beyond acute stressors to chronic stress, as many individuals in modern society are in a near perpetual fight-or-flight state due to various perceived threats such as traffic jams, job and relationship stress, and feeling overburdened with too many daily tasks.

In addition to being a result of chronic and acute stress, hypoxia can also cause psychological stress through a mechanism that may involve alterations in the hypothalamic-pituitary-adrenal (HPA) axis and elevation of cortisol levels.<sup>8</sup> Subjects with obstructive sleep apnea (OSA) were shown to have substantially higher 24-hour cortisol levels compared with controls, whereas treatment with a continuous positive airway pressure (CPAP) device dramatically reduced cortisol levels similar to those of controls.<sup>8</sup>

Chronic obstructive sleep apnea is a common cause of hypoxia. According to The American Sleep Apnea Association<sup>9</sup> and the National Sleep Foundation, an estimated 18 million Americans have sleep apnea. Many individuals who have the disorder go undiagnosed, suggesting this number may actually be much higher.<sup>9</sup> Hypoxia caused by obstructive sleep apnea (OSA) has been shown to exacerbate the effects of air pollution by preventing the clearance of particulate matter from the lungs.<sup>10</sup> It may be a vicious cycle as air pollution itself can deprive the body of oxygen. This may lead to the development of sleep apnea, which has a greater prevalence in poor urban environments, where pollution is more common. Furthermore, in patients with post-traumatic stress disorder (PTSD), the presence of severe OSA was related to suicidal ideation, indicating that hypoxia can exacerbate the negative consequences of chronic stress.<sup>11</sup>

Even in the absence of OSA, pollution is a common cause of hypoxia. Although the harmful effects of pollution are mostly attributed to the presence of toxic substances such as polycyclic aromatic hydrocarbons (PAHs) and other organic components such as endotoxins, its potential to deplete oxygen levels is an important concern. A study of 32 elderly subjects found that greater exposure to air pollution (both traffic and non-traffic industrial sources) reduced oxygen saturation. The study authors suggested this was the result of an inflammation

response in the lungs or vascular dysfunction due to exposure to airborne particles.<sup>12</sup> Cigarette smoke and secondhand smoke,<sup>13</sup> weight gain,<sup>14,15</sup> drinking alcohol,<sup>16,17</sup> living at high altitude, or too much or too little exercise<sup>18,19</sup> are other factors that deprive the body of optimal oxygen levels.

## CELLULAR REACTION TO OXYGEN DEPLETION

Two of the primary cellular consequences of low oxygen levels involve the mitochondria and the switch from aerobic to anaerobic respiration.

### LOW OXYGEN AND MITOCHONDRIA

The mitochondria require oxygen to manufacture ATP. Oxygen serves as a fuel for cytochrome oxidase, the final enzyme in the electron transport chain that generates ATP.<sup>18</sup> Because diffusion would be an inefficient means of supplying cells with oxygen, hemoglobin and myoglobin act as oxygen-carrying molecules to perfuse the tissues.<sup>20</sup> As blood circulates through capillaries, oxygen bound to hemoglobin diffuses via a steep pressure gradient into tissues and subsequently into the mitochondria.<sup>20</sup> This oxygen delivery to cells is tightly regulated with only enough myoglobin present to deliver the optimal amount of oxygen.<sup>20</sup>

One group of researchers described the mitochondria's role as "rheostats within a cell to orchestrate cellular responses to various stimuli, including hypoxia."<sup>21</sup> Oxygen concentrations are an important contributor to such responses. However, carbon monoxide and nitric oxide also compete for oxygen-binding sites on enzymes such as cytochrome C oxidase and thus may also play a role in oxygen signaling.<sup>22</sup> Improvement in mitochondrial function can parallel increases in oxygen saturation. After hyperbaric oxygen administration, improved mitochondrial complex IV activity has been recognized as a marker of recovery from acute carbon monoxide poisoning.<sup>23</sup>

### AEROBIC VS. ANAEROBIC RESPIRATION

Cells exposed to oxygen undergo aerobic metabolism whereas oxygen-deficient cells switch to

anaerobic metabolism. The goal of both aerobic and anaerobic metabolism is to transform nutrients into ATP. Aerobic metabolism is as much as 15 times more efficient than anaerobic metabolism at producing ATP. Aerobic metabolism generates approximately 29–30 ATP molecules per one molecule of glucose. Conversely, anaerobic metabolism, yields only two ATP molecules per one molecule of glucose.<sup>24</sup> Another negative consequence of anaerobic metabolism is that it produces lactic acid in muscles, which is responsible for post-exercise pain. The lactic acid is produced as a result of fermentation that occurs under anaerobic conditions. When the body switches to anaerobic metabolism for a short duration, such as during intense exercise, no long-term adverse consequences result. However, when anaerobic metabolism is utilized most of the time, this can lead to adverse effects.

## DISORDERS ASSOCIATED WITH HYPOXIA

### HORMONAL IMBALANCES

Hypoxia can interfere with hormone metabolism. In individuals with chronic low oxygen due to chronic obstructive airway disease or pulmonary fibrosis, testosterone concentrations are often low.<sup>25</sup> Low testosterone levels also are frequently observed in patients with obstructive sleep apnea. In men with excessive abdominal fat and who also suffered from sleep apnea, hypoxia severity during sleeping hours was associated with lower testosterone levels, independent of body mass index and abdominal fat.<sup>26</sup> Furthermore, in men with chronic obstructive airways disease, the severity of arterial hypoxia was inversely correlated with testosterone concentrations.<sup>27</sup>

Additionally, administering testosterone can have profound effects on oxygen levels. In rabbits fed a high-fat diet, hypoxic fat accumulated in the visceral tissue.<sup>28</sup> When researchers administered testosterone to the rabbits, it restored the proper oxygenation level in the visceral fat tissue. However, in the conventional medical model, testosterone administration to men with severe OSA is contraindicated due to concerns that it may exacerbate the OSA.

Passavanti and associates investigated the effect of hyperbaric oxygen therapy on 14 male patients (23–72 years old) who were suffering from a variety of injuries and conditions including leg fractures, diabetic foot wounds, firearm injuries, or underwater diving embolism.<sup>29</sup> The effect of hyperbaric oxygen on six healthy male volunteers (37–51 years old) was also studied. The study authors measured plasma testosterone immediately before the first hyperbaric oxygen session and the day after the last session. At the end of hyperbaric oxygen treatment, 12 patients fully recovered and two diabetic patients with foot wounds experienced a marked improvement. Both patients and controls had a pronounced rise in their testosterone levels after hyperbaric oxygenation therapy.

### EFFECTS ON IMMUNE FUNCTION

Inflamed, infected, or injured tissue is characterized by hypoxia. Immune cells are able to infiltrate and perform their functions in tissues with reduced levels of nutrients and oxygen.<sup>30</sup> Most bacteria and viruses thrive in low-oxygen environments. The ability of hyperbaric oxygen therapy to improve immune cell function is due to a resolution of that low-oxygen state. The increased oxygen provided by hyperbaric oxygen therapy enhances the bacteria-killing ability of white blood cells, reduces edema, and allows new blood vessels to grow more rapidly into affected areas.<sup>31</sup>

In one study, 331 patients who had typhoid, diphtheria, meningococcal infection, or viral hepatitis were treated with hyperbaric oxygen therapy while 363 controls did not receive hyperbaric oxygen.<sup>32</sup> The patients who underwent hyperbaric oxygenation experienced improved oxygen saturation of blood compared to controls. Other improvements were observed, including a more favorable course and outcome of their disease process. In an animal experiment, ozone treatment caused a pronounced reduction of bacterial counts in rats with MRSA.<sup>33</sup> When combined with the antibiotic vancomycin, the ozone was associated with an even greater decline in bacterial counts.<sup>33</sup>

Hyperbaric oxygen therapy increases the production of reactive oxygen intermediates (ROIs) throughout the body. ROIs are known to eliminate enveloped viruses, such as the human immunodeficiency

virus (HIV). This is likely the mechanism by which hyperbaric oxygen has been used effectively in acquired immune deficiency syndrome (AIDS) patients.<sup>34</sup> Hyperbaric oxygen in cell culture studies also has been shown to have viricidal actions. In one study, researchers found that in HIV-infected cells exposed to hyperbaric oxygen, HIV viral load was decreased.<sup>35</sup> In uninfected cells exposed to hyperbaric oxygen and then to HIV, only a small amount of the HIV virus entered the cells.

The hepatitis virus is also vulnerable to oxygen therapy. Researchers administered hyperbaric oxygen therapy to 30 male subjects who had hepatitis B, whereas another 30 male subjects were treated with conventional therapy alone.<sup>36</sup> The participants treated with hyperbaric oxygen recovered faster, gained appetite, and improved their sense of well-being more quickly than the control subjects. Additionally, the hyperbaric oxygen resulted in a faster improvement in symptoms such as itching and normalization of liver function. Moreover, hepatitis B virus surface antigen became negative more quickly in patients in the hyperbaric oxygen group. These patients also had an overall shorter duration of hospital stay and convalescence compared to controls.

## FIBROMYALGIA

Fibromyalgia (FM) is a common chronic pain condition affecting approximately 10 million people in the United States and an estimated 3%–6% of the global population.<sup>37</sup>

Evidence indicates that the muscle pain and fatigue that occurs in fibromyalgia may be associated with impaired muscle tissue microcirculation and oxygen metabolism.<sup>38</sup> A number of studies have observed lower skin/muscle blood flow or oxygen consumption in fibromyalgia patients.<sup>39–42</sup> Moreover, recovery times for oxygen levels after muscle ischemia or aerobic exercise are longer in individuals with fibromyalgia.<sup>43,44</sup> Another study found evidence of low tissue oxygenation in fibromyalgia patients as evidenced by abnormal or low muscle oxygenation in the trigger point area of painful muscles.<sup>45</sup>

Furthermore, studies have demonstrated that fibromyalgia symptoms are exacerbated in lower

atmospheric pressure climates where there is decreased oxygen pressure.<sup>46</sup> Fibromyalgia patients respond successfully to the increased oxygen pressure in hyperbaric chamber treatment as well as to coenzyme Q10 supplementation, which enhances the body's use of oxygen.<sup>46</sup>

## CARDIOVASCULAR DISEASE

Heart disease and high blood pressure are linked to sleep apnea, which has a higher prevalence in patients with cardiac disorders compared to healthy controls.<sup>47</sup> Even mild sleep apnea is associated with an increased risk for cardiovascular disease due to apnea-induced arterial stiffness.<sup>48</sup> In one study, 91% (51 of 56) of subjects who had suffered a stroke had sleep apnea.<sup>49</sup> The combination of strokes and sleep apnea was associated with an increased risk of silent strokes and white matter lesions, increasing the risk of disability at hospital discharge. There is also a higher risk of cardiac arrhythmia in people who have sleep apnea.<sup>50,51</sup>

Sleep apnea is associated with hypertension and 45% of individuals who have sleep apnea also have high blood pressure.<sup>52</sup> The severity of the sleep apnea often correlates with severity of daytime hypertension.<sup>53</sup> Sleep apnea is also associated with treatment-resistant hypertension.<sup>54</sup>

Hyperbaric oxygen has been shown to have other cardiovascular applications. In one randomized, controlled study, researchers investigated the effects of hyperbaric oxygen therapy on patients undergoing first-time elective coronary artery bypass graft surgery (CABG).<sup>55</sup> Prior to surgery, 41 subjects received hyperbaric oxygen therapy twice for 30-minutes, with a five minute interval between treatments, whereas 40 subjects received no hyperbaric oxygen before surgery. Although not statistically significant, the researchers found that the group treated with hyperbaric oxygen prior to CABG surgery experienced less postoperative heart injury, an 18% reduction ( $P=0.05$ ) in length of stay in the intensive care unit (ICU), a 57% reduction in intraoperative blood loss ( $P=0.02$ ) as well as 11.6% reduced blood loss post-surgery ( $P=0.09$ ). Fewer patients in the hyperbaric oxygen group required a blood transfusion compared to untreated controls ( $P=0.4$ ) and there was an 11% reduction in atrial fibrillation ( $P=0.6$ ), a 12.7% reduction in pulmonary complications ( $P=0.8$ ), and a 7.6%

reduction in wound infections ( $P=0.4$ ) in the hyperbaric oxygen group.

## EFFECTS ON BLOOD SUGAR

There is an increased risk of developing insulin resistance and type 2 diabetes in individuals with sleep apnea.<sup>56,57</sup> Additionally, enhancement of oxygen levels is associated with an improvement in blood sugar. For example, a study showed that treatment with a positive airway pressure device (CPAP) in people who had sleep apnea and type 2 diabetes caused an increase in insulin sensitivity and a decline in HbA1c levels.<sup>58</sup>

## MOOD DISORDERS

Oxygen levels play an important role in maintaining mood and mental health. Veterans with sleep apnea have a pronounced increase in depression, anxiety, psychosis, and post-traumatic stress disorder.<sup>59</sup> Moreover, in one study of 32 newly diagnosed sleep apnea patients who also suffered from depression, researchers found a connection between the severity of depression and the degree of hypoxia; the severity of depression correlated to the degree of sleepiness and to low oxygen saturation.<sup>60</sup> After treatment for sleep apnea, the patients' depression improved.

## OTHER CONDITIONS

Low oxygen levels have been associated with a number of other health concerns. The hypoxia that occurs at high altitude may be a trigger for inflammatory bowel disease (IBD) flare ups.<sup>61</sup> Learning and memory is also affected by oxygen levels. In animal models of Alzheimer disease, hyperbaric oxygen combined with *Ginkgo biloba* protected rats against damage to brain cells.<sup>62</sup> Compared to untreated animals, *Ginkgo* combined with hyperbaric oxygen also improved the rats' ability to find their way through a water maze, increased levels of antioxidant enzymes in the brain, and lowered markers of oxidant damage. Hyperbaric oxygen and *Ginkgo* administered separately protected against cell death; however, the combination of both enhanced the beneficial effects. In another study, rats with vascular dementia experienced increased neurogenesis as well as improved blood supply to the brain after hyperbaric oxygen treatment.<sup>63</sup>

One of the few human studies on the topic investigated 64 patients with vascular dementia. The study authors compared hyperbaric oxygen used together with the drug donepezil to the use of donepezil alone. Patients receiving hyperbaric oxygen plus donepezil had significantly better cognitive function than the donepezil-only group after 12 weeks.<sup>64</sup>

A review of nine trials including 201 patients indicates headaches are another health disorder linked to hypoxia.<sup>65</sup> Five of the trials compared hyperbaric oxygen therapy to placebo therapy in acute migraine,<sup>65</sup> two studies compared the effects of hyperbaric oxygen to a placebo on cluster headaches, and two studies measured the effects of one atmosphere oxygen breathing (NDOT) on cluster headaches.<sup>65</sup> Pooling of data from three of the trials indicated that although hyperbaric oxygen did not prevent migraine attacks or reduce the incidence of nausea, it relieved migraine headaches compared with the placebo ( $P=0.01$ ). These data indicated that more than 70% of individuals with migraines who are treated with HBO may achieve relief of pain within about 40 minutes. One trial included in the review found a significantly greater number of subjects with cluster headaches achieved relief after 15 minutes of NBOT compared to a placebo therapy with air. Of the patients treated with NBOT, 9 of 16 subjects (56%) reported complete relief or significant reduction in headache intensity ( $P=0.04$ ) compared to only 1 of 14 (7%) in the control group reporting improvement.<sup>65</sup>

## MEASURING OXYGEN LEVELS

An oximeter is the device normally used to determine oxygen levels ( $SpO_2$ ). However, this standard device can vary in accuracy depending on a number of factors. It has a number of limitations that can result in inaccurate readings in some cases.<sup>66</sup> In a survey of 551 critical care nurses, 37% were unaware that patient motion compromises the accuracy of oximeters, 15% did not know that poor signal quality can affect reading accuracy, and 30% thought that  $SpO_2$  readings could be a replacement for arterial blood gas samples when managing ICU patients.<sup>67,68</sup> Values are

also inaccurate when the patient's finger is cold. Although arterial blood gas analysis is a more accurate means of determining oxygen concentration, for most clinical purposes, pulse oximetry is considered sufficiently accurate, as long as the clinician recognizes its limitations.<sup>69</sup>

## IMPROVING OXYGEN PERFUSION

A number of strategies can be employed to increase blood flow to tissues and thus improve oxygenation. The many benefits of massage therapy including reducing pain and improving functionality in patients with osteoarthritis and fibromyalgia,<sup>70,71</sup> relieving low back pain,<sup>72</sup> reducing blood pressure<sup>73</sup> and the incidence of chronic tension headaches,<sup>74</sup> and improving mitochondrial function<sup>75</sup> may all be associated with increased oxygen perfusion to tissues. Studies have shown that massage can increase muscle blood flow and oxygenation in people with low back pain who drive frequently,<sup>76</sup> individuals with restless legs syndrome,<sup>77</sup> and after exercise-induced muscle injury,<sup>78</sup> among other applications. However, benefits of massage can be short term and disappear after treatment stops.<sup>70</sup> Bad posture, stress, and other factors can eliminate the beneficial effects. Therefore, it has been proposed by some clinicians that administering oxygen during a massage could extend the benefits.

Evidence indicates that increased oxygen perfusion can also be achieved with certain nutrients and botanicals that have been shown to increase blood flow and oxygenate the tissues. Coenzyme Q10 (CoQ10) is one such nutrient. Patients with fibromyalgia, who suffer from musculoskeletal oxygenation alterations, were successfully treated with CoQ10, which improved their oxygen usage.<sup>46</sup> In a rodent study, CoQ10 reduced the hypoxic damage that occurred when the animals were exposed to the organophosphate pesticide mevinphos.<sup>79</sup> Furthermore, CoQ10 reduced hypoxia-reperfusion damage in neural stem cells in part by inhibiting free radical formation and by increasing the expression of survival-related proteins.<sup>80</sup>

*Ginkgo biloba* is another dietary supplement known for its ability to increase blood flow, thus increasing oxygen perfusion to tissues. As noted earlier in this

article, *Ginkgo* has been found to work synergistically with hyperbaric oxygen in reducing amyloid-beta protein burden in rodents.<sup>62</sup> The mechanism of action of these two synergistic treatments involved reducing cell toxicity and oxidative stress by inhibiting mitochondria-controlled apoptosis signaling.<sup>62</sup> In a human study, *Ginkgo biloba* combined with hyperbaric oxygen either resolved or improved tinnitus in approximately 80% of the patients ( $P=0.046$ ).<sup>81</sup>

*In vitro*, *Ginkgo biloba* has been shown to protect human vascular endothelial cells and retinal pigment epithelial cells against injury from hypoxia.<sup>82,83</sup> *Ginkgo biloba* also has been shown to increase ocular and cerebral blood flow.<sup>84–86</sup> Cerebral injury related to low oxygen perfusion after surgery is one of the main causes of post-surgery disability and death.<sup>87</sup> *Ginkgo biloba* extract has been shown to enhance cerebral oxygen supply, lower cerebral oxygen extraction rate and consumption, and help regulate the balance between cerebral oxygen supply and consumption after surgery.<sup>87</sup>

Beetroot (*Beta vulgaris*) juice is another substance that has beneficial effects due to its ability to increase levels of nitric oxide, which is involved in improving blood flow.<sup>88</sup> Hypoxia can impair exercise performance in athletes while the use of beetroot juice may reduce this hypoxia-induced effect on cardiorespiratory endurance.<sup>88</sup>

## SUPPLEMENTS TO IMPROVE MAXIMUM OXYGEN CONSUMPTION ( $\dot{V}O_2\text{max}$ )

$\dot{V}O_2\text{max}$  is the maximum amount of oxygen used by the lungs during one minute of strenuous exercise. Increasing oxygen levels can increase  $\dot{V}O_2\text{max}$  by 11% or more.<sup>89</sup> It is thought that improved  $\dot{V}O_2\text{max}$  is responsible for the enhanced exercise tolerance that occurs after oxygen administration during exercise. Certain dietary supplements are known to improve  $\dot{V}O_2\text{max}$ . For example, supplementation of overweight women with omega-3 fatty acids combined with lifestyle alteration that included healthy diet education and aerobic exercise significantly improved  $\dot{V}O_2\text{max}$  outcome ( $P=0.03$ ).<sup>90</sup> Branched-chain amino acid supplementation has also been known to improve endurance exercise capacity in part by increasing  $\dot{V}O_2\text{max}$  in trained male subjects ( $P<0.05$ ).<sup>91</sup>

## SUPPLEMENTS FOR SLEEP APNEA

Use of a CPAP machine is the standard treatment for obstructive sleep apnea patients. Certain dietary supplements can be administered concurrently with use of a CPAP machine or used proactively to possibly inhibit the development of obstructive sleep apnea (OSA). Vitamin D insufficiency is associated with an increased risk for OSA.<sup>92</sup> The relationship of reduced vitamin D levels with the development of OSA is thought to be due to the relationship between vitamin D insufficiency and immune system modulation, myopathy, and inflammation.<sup>92</sup> Insufficient intake of omega-3 fatty acids may also be linked to sleep apnea. Ladesich and colleagues observed the association between RBC levels of docosahexaenoic acid (DHA) and OSA severity in 350 patients involved in sleep studies.<sup>93</sup> The authors noted an inverse relationship between RBC, DHA, and OSA severity. For each 1-standard deviation (SD) of increase in DHA concentrations, the study subjects were 53% less likely to be diagnosed with severe OSA. Antioxidant therapy may be beneficial in individuals diagnosed with obstructive sleep apnea. For example, compared with a placebo control, N-acetyl cysteine (NAC) supplementation led to a decline in muscle sympathetic nerve activity in 16 human subjects in response to intermittent hypoxia ( $P<0.02$ ), suggesting it may have therapeutic potential in OSA.<sup>94</sup>

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## CONCLUSION

Proper perfusion of oxygen to tissues and organs throughout the body is crucial for optimal health. Hypoxia has been associated with a number of health concerns, whereas administering oxygen in a hyperbaric chamber or improving sleep apnea has been beneficial in cardiovascular health, immunity, cognitive function, and other disorders. Improvement in oxygen perfusion can be achieved through the utilization of dietary supplements such as CoQ10, *Ginkgo biloba*, beetroot juice, omega-3 fatty acids, and branched-chain amino acids. Furthermore, individuals diagnosed with sleep apnea or at risk of sleep apnea should be tested for vitamin D insufficiency and supplementation be implemented accordingly. Omega-3 fatty acids and NAC may also be beneficial in this population.

## COMPETING INTERESTS

The authors declare they have no competing interests.

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