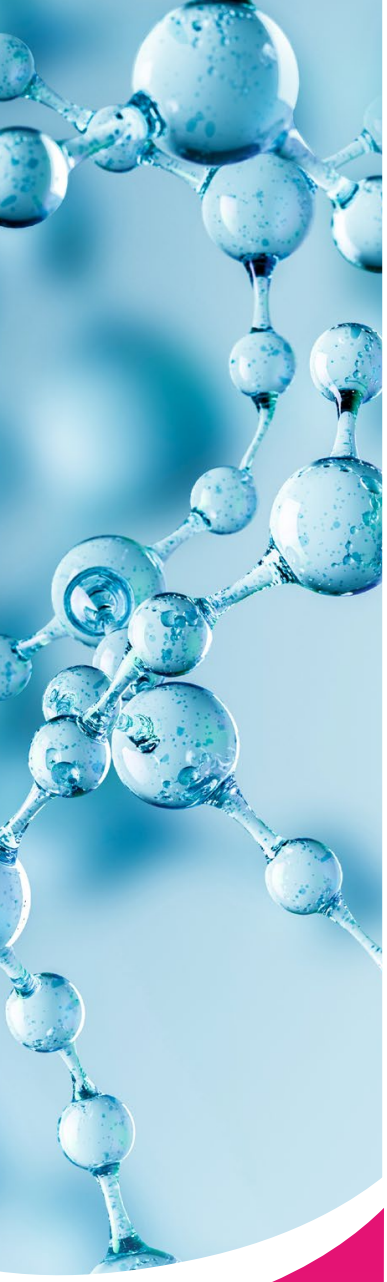

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The Critical Role of Nitric Oxide in Microvasculature Health

—Chris D. Meletis, ND

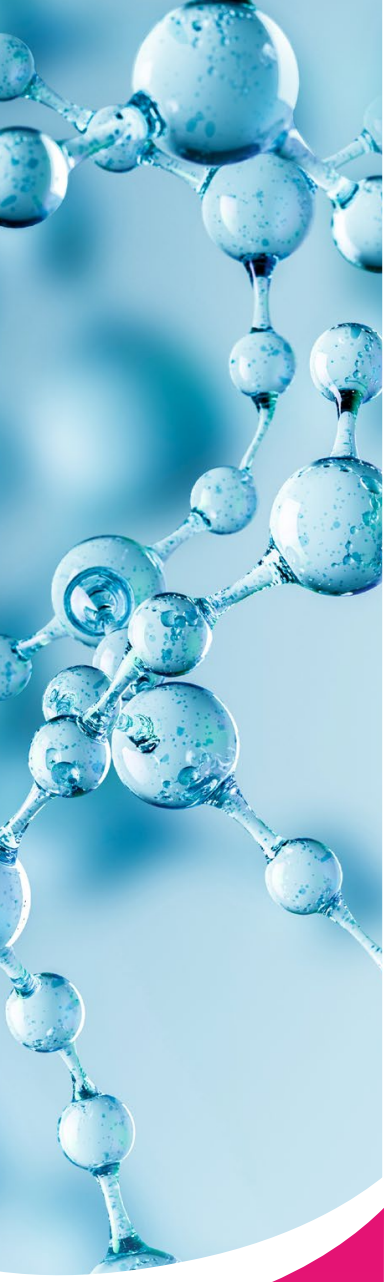
Key Points

- Nitric Oxide (NO) bioavailability is critical for optimal microvascular function.
- NO plays an important role in both diabetic and non-diabetic wound healing as well as the healing of burn injuries.
- Coronary microvascular endothelial inflammation results in reduced NO bioavailability, which leads to heart failure over time.
- Peripheral artery disease (PAD) patients have lowered synthesis or function of NO, which leads to suppression of endothelium-dependent vasodilation.1 Consequently, inorganic nitrate supplementation may have beneficial effects in patients with PAD.
- Replenishing nitrate levels can have beneficial effects on the retinal microvasculature.

The macrovascular system, which includes the body's larger arteries, tends to receive the lion's share of attention when addressing the health of patients. However, it is becoming increasingly clear that the microvascular system, which is composed of small blood vessels including arterioles, capillaries, and venules, is equally instrumental in driving many aspects of health. Impairments in the microvascular system are associated with improper wound healing, coronary microvascular disease, peripheral arterial disease, reduced healing from burn injuries, and declining retinal health.

A number of different factors can lead to a microvascular system that is not working optimally. Many of these risk factors are the same that can result in macrovascular problems. Smoking, high cholesterol, obesity, high blood pressure, not exercising, diabetes, insulin resistance, estrogen deficiency, polycystic ovary syndrome, age, and chronic inflammation can all adversely impact the microcirculation.[2]

An unhealthy diet, which predisposes to most of the aforementioned factors, can also contribute to microvascular problems. This was illustrated in a randomized, single-blind, crossover trial of healthy men, where drinking sugar sweetened beverages reduced both microvascular and macrovascular endothelial function and Nitric Oxide (NO) bioavailability.[3] Conversely, eating a diet rich in dietary nitrates or supplementing with NO donors can improve microvascular health. However, the drop in NO that occurs with aging and disease is extensive enough that eating a nitrate-rich diet of vegetables



is not always sufficient enough to compensate. Furthermore, few adults are eating the recommended 2 ½ to 3 cups servings of vegetables daily. This white paper will address the role of NO in microvascular health and the clinical usefulness of nitrate-rich supplements in a number of health concerns that involve the microcirculation.

Nitric Oxide and Wound Healing

Between 2.4 and 4.5 million people in the United States suffer from chronic wounds such as pressure ulcers, vascular ulcers, and diabetic ulcers.[4] These type of wounds are notoriously challenging to treat. The systemic complications of diabetes such as tissue hypoxia, impaired inflammatory response, and decreased collagen production interfere with typical treatment strategies such as debridement of necrotic tissue, use of topical antibiotics, and application of a wound dressing as well as negative pressure therapy, hyperbaric oxygen therapy, or application of growth factors. In fact, chronic wounds are the primary cause of amputations due to diabetes.5 Consequently, interest in NO as a potential therapeutic agent has increased.

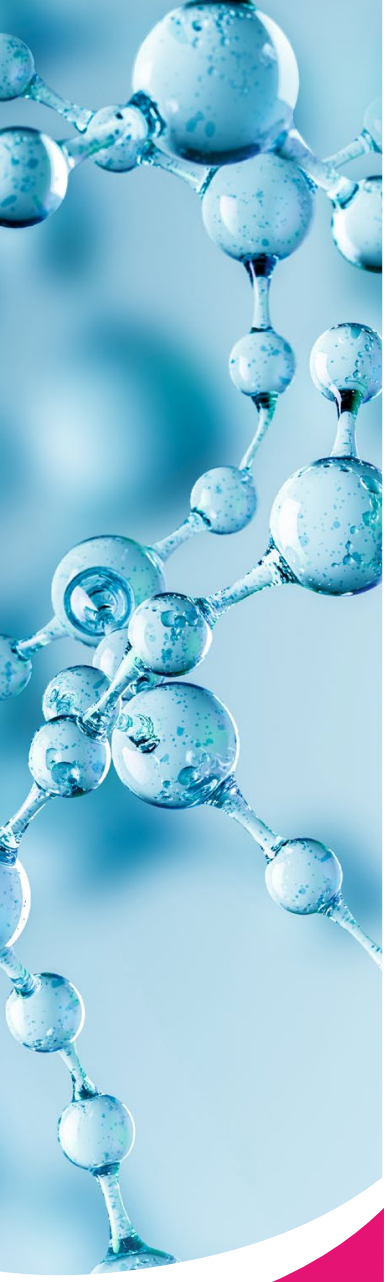
NO plays an important role in both diabetic and non-diabetic wound healing. The mechanism by which hyperbaric oxygen therapy increases the healing rate of wounds is due to an increase in local wound levels of NO.[6] NO is an important regulator of normal tissue repair.[7] NO production and bioavailability govern several processes involved in normal wound repair including microvascular homeostasis, as well as angiogenesis (the growth of capillary-sized microvessels), epidermal migration, collagen deposition, and granulation tissue formation.[6] Many of these processes depend upon the microvasculature and its related cellular and metabolic components.8 For example, angiogenesis relies upon microvascular remodeling.[8]

Further supporting the role of NO in wound healing is the relationship between impaired bioactivity of NO and slower diabetic wound healing due to reduced accumulation of collagen.[9] Additionally, NO regulates inflammation and has antibacterial properties, making it an ideal agent for wound healing.5 Unfortunately, endogenous levels of NO are often low in diabetic patients.[5]

Furthermore, replenishing NO levels may have beneficial effects in repairing burn injuries. A rodent study found that giving an NO precursor to rats with burn injuries improved microcirculation in the animals and increased their survival time.[10]

Coronary Microvascular Disease

Coronary microvascular disease, also referred to as small vessel disease or small artery disease, affects the endothelial lining of small coronary artery blood vessels. It has also been called cardiac syndrome X and nonobstructive coronary heart disease. It occurs more commonly in women, often at a younger age than macrovascular coronary heart disease, especially in women whose estrogen levels are lower than normal even before menopause or whose high systolic blood pressure precedes menopause. Risk factors include hypertension, high cholesterol, obesity, smoking, a sedentary lifestyle, aging,



diabetes, and a family history of heart disease.[2] Symptoms of coronary microvascular disease include microvascular angina, shortness of breath, insomnia, and fatigue.[2]

It is estimated that 30% of people with angina also have coronary microvascular disease, which correlates with increased morbidity and mortality in this group of patients.[11] Additionally, a large study of 1,439 people found that two-thirds of patients who had chest pain without obstructive coronary artery disease had coronary microvascular disease.[12] Other data indicate that coronary microvascular disease was present in 42% of mostly obese patients who visited an emergency department with chest pain and who did not have a myocardial infarction (MI).[13] Coronary microvascular disease often occurs before the development of large artery atherosclerosis and can predict cardiovascular events in individuals with atherosclerotic cardiovascular disease or without.[14]

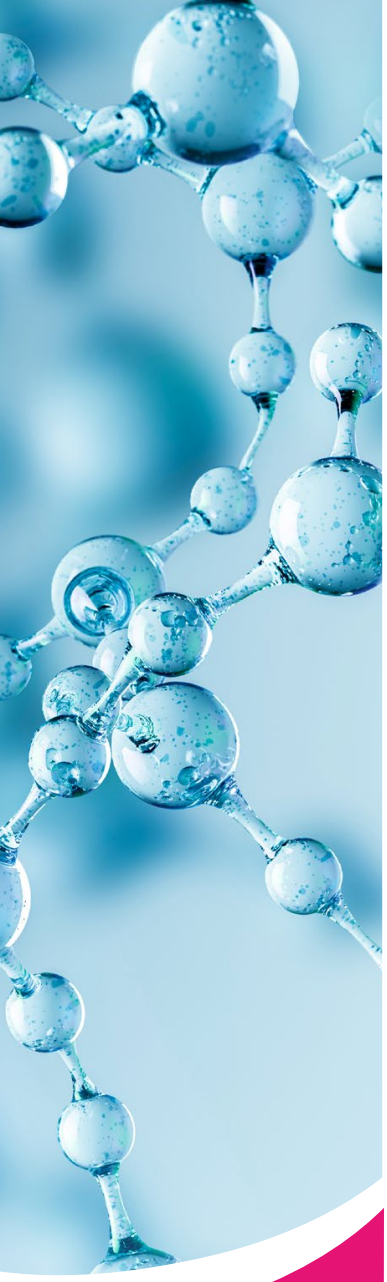
Low-grade vascular inflammation is involved in the pathogenesis of coronary microvascular disease, especially in people with diabetes, chronic inflammatory rheumatoid diseases, obesity, and heart failure with preserved ejection fraction.[15-17] It is thought that coronary microvascular endothelial inflammation leads to reduced Nitric Oxide bioavailability, which causes heart failure over time.[17] Furthermore, elevated homocysteine levels in people with coronary microvascular disease reduce NO activity and synthesis, which leads to endothelial dysfunction.[18]

Peripheral Artery Disease

In peripheral artery disease (PAD), the arteries supplying the extremities undergo atherosclerotic stenosis, which correlates with an elevated risk of fatal cardiovascular events.[19] More than eight million Americans suffer from PAD.[20] Patients with PAD may have intermittent claudication and critical limb ischemia, which are linked to poor functional capacity that interferes with the ability to perform daily duties and exercise. This functional impairment may be related to atherosclerosis, but functional capacity is not restored even after revascularization.[21] Consequently, it is thought that the impaired functional capacity that occurs in PAD patients is related to microvascular dysfunction rather than the extent of atherosclerotic stenosis.[20]

Microvascular blood flow is governed by a complex relationship between vasodilatory and vasoconstrictor messaging.[20] In PAD patients, endothelium-dependent vasodilation is suppressed partly due to lowered synthesis or function of NO.[1] Consequently, inorganic nitrate supplementation may have beneficial effects in patients with PAD. This was shown in a study of inorganic nitrate given as a single dose, which enhanced exercise tolerance in a group of PAD patients.[22]

A study by Bock and colleagues of patients with PAD determined whether inorganic nitrate supplementation increases limb blood flow in the lower-limbs, and whether it could improve vasodilatory and functional capacities.[20] The researchers measured microvascular function in the forearm and calves of the patients with PAD. Supplementation with inorganic nitrate increased the total distance walked during a six-



minute walk test. The improvement was likely due to the improvement in microvascular blood flow in the calves of the subjects and enhanced vasodilation that occurred after nitrate supplementation. The researchers concluded, "Given the prevalence of ischemia in patients with PAD and the low NO bioavailability in this patient population, supplementation of inorganic nitrate has significant potential to improve functional outcomes in patients with PAD." The researchers recommend using inorganic nitrate supplements together with exercise.

Confirming these results was another study by Woessner and associates where beetroot juice as a source of inorganic nitrate was more effective at enhancing exercise tolerance and blood flow in patients with PAD compared to exercise alone.[23] The study authors concluded, "Specifically, our data suggests that increasing plasma nitrite before exercise may allow PAD subjects to train with less pain, at higher workloads for longer durations at each training session, thereby maximizing the beneficial peripheral vascular and skeletal muscle adaptations."

Retinal Health

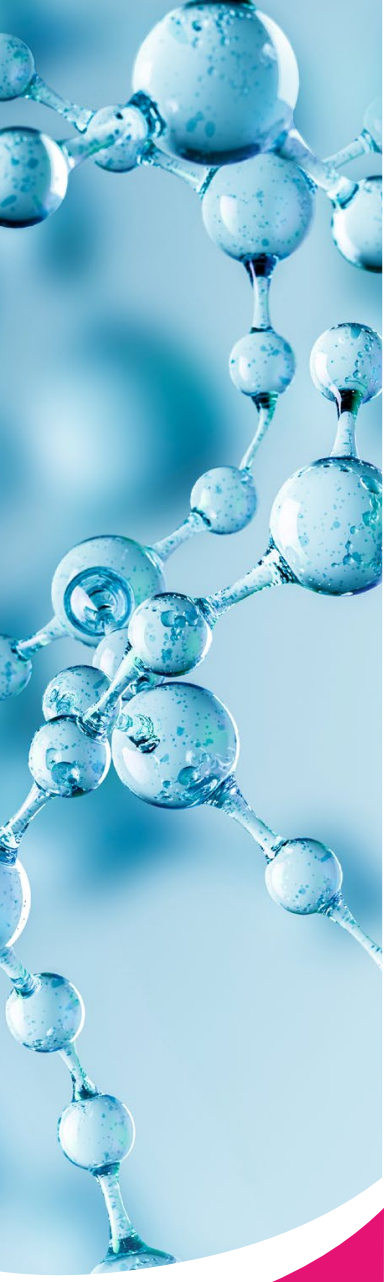
Narrowing of retinal arterioles and widening of venular caliber are adverse alterations that occur in the retinal microvasculature.[24] These changes can be indicative of pre-clinical alterations that are occurring in the cerebral and coronary microcirculation and therefore correlate with an elevated risk of poor vascular outcomes.[24]

Replenishing nitrate levels can have beneficial effects on the retinal microvasculature. One study assessed the relationship between intake of dietary nitrate from both vegetable and non-vegetable sources and the microvascular status of older adults (aged 49 or older).[24] Retinal arterioles were significantly narrower in participants who ate the lowest amount of vegetable nitrate. Higher intake of total nitrate and vegetable nitrate correlated with wider retinal arterioles. Eating more nitrate-rich vegetables was also associated with narrower retinal venules compared to people who ate less nitrate-rich vegetables.

Utilizing a Nitrate-Rich Supplement to Enhance Microvascular Health

NO is clearly involved in the function of the microvasculature. Therefore, enhancing NO bioavailability with the use of a nitrate-rich supplement can be advantageous to patients who can benefit from improving their microcirculation. In addition to the human studies previously mentioned in this white paper, other studies have shown that enhancing nitrate through supplementation with beetroot can improve skeletal muscle microvascular oxygenation[25] and support healthy blood pressure and microvascular function.[26,27] Therefore, replenishing NO levels can be a viable strategy for optimizing the microvascular health of patients.

**These statements have not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure or prevent any disease.*



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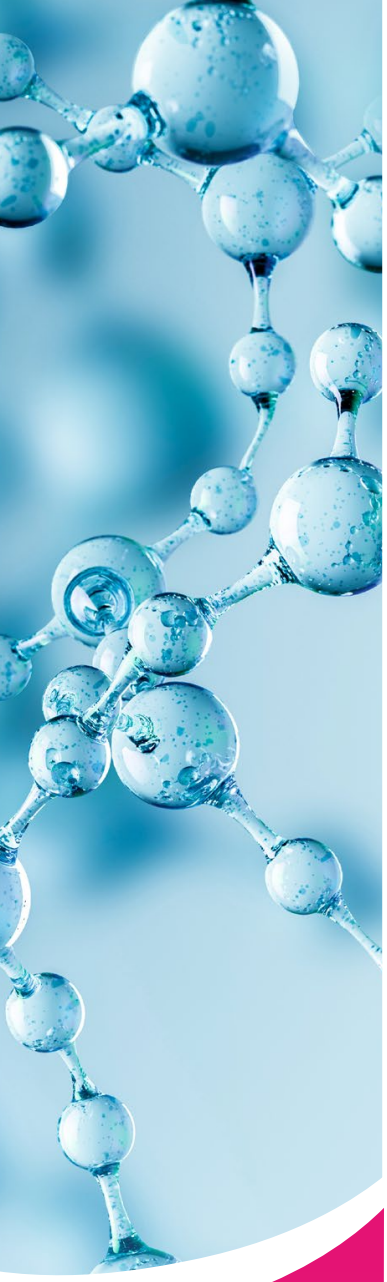

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