endothelial NO function is associated with several cardiovascular disorders, including atherosclerosis, which is due either to decreased production or to increased degradation of NO.[6] A number of studies provide evidence that endothelial NO dysfunction is not only associated with all major cardiovascular risk factors, such as hyperlipidemia, diabetes, hypertension, smoking, and severity of atherosclerosis, but also has a profound predictive value for future atherosclerotic disease progression.[7–10] There is also an increasing evidence pool linking NO to neurodegenerative diseases, such Alzheimer's disease (AD). Decreased levels of nitrite and nitrate (collectively referred to as NOx) have been detected in patients with different forms of dementia, especially AD.[11] The exact etiology of sporadic AD is unclear, but it is interesting that cardiovascular risk factors including hypertension, hypercholesterolemia, diabetes mellitus, aging, and sedentary lifestyle are associated with higher incidence of AD (all conditions associated with NO insufficiency).[12] The link between cardiovascular risk factors and AD has yet to be identified; however, a common feature is endothelial dysfunction; specifically, decreased bioavailability of NO.[13]

Insulin has vasodilator actions that depend on endothelium-derived NO.[14] Type 2 diabetes mellitus accounts for 80% to 90% of diabetes cases in the US and is associated with an increased risk for a number of life-threatening complications. These include heart disease and stroke, high blood pressure, blindness, kidney disease, nervous system disease, amputation, and complications of pregnancy and surgery. Incidentally, all of the above complications are associated with insufficient NO production.[15] Endothelial dysfunction with reduced NO generation and bioavailability plays a key role in the pathogenesis of diabetic vascular disease and complications and likely serves as the key link between metabolic disorders and cardiovascular disease (CVD).[16]

Medical literature is rich with clear assocaitions and near causal relationships between NO levels and onset and progression of chronic diseases, yet there are no protocols to use NO in the treatment/therapautic domain. Some common prescription medications even reduced NO bioavalibitiy and production. Many lifestyle and dietary habits that lead to chronic disease are linked to insufficient NO production or availability and the standard of care for patients in intensive care units. An overview of select lifestyle choices and medical procedures and pharmacological therapies that are known to be linked to NO will be reviewed.

Diet and Nutrition

There is now an established and accepted role for nitrite and nitrate in the diet contributing to NO homeostasis.[17–19] In fact, the nitrate-nitrite-nitric oxide pathway has been suggested and demonstrated to be the mechanism of action for health benefits from certain diets.[20,21] The Dietary Approaches to Stop Hypertension (DASH) studies found that diets rich in vegetables (i.e., 8–10 servings) and low-fat dairy products could lower blood pressure to an extent similar to single hypotensive medications.[22,23] These and other findings point to a widely acknowledged hypothesis that the content of inorganic nitrate (NO3 –) in certain vegetables provides a physiologic substrate for reduction to nitrite (NO2 –), NO, and other metabolic products that produce vasodilation, decrease blood pressure, and support cardiovascular function.[20,24–26] It has been reported that dietary nitrate reduces blood pressure in healthy volunteers, prevents platelet aggregation, and is vasoprotective.[27–29] One of early studies indicates that homeostatic levels of tissue nitrite and nitrate are affected by dietary NOx intake.[30] Furthermore, enriching dietary intake of nitrite and nitrate in mice translates into significantly less injury from heart attack, and diets with insufficient nitrite and nitrate cause increased injury and increased mortality.[31] Nitrite in the diet can prevent microvascular inflammation and restore normal endothelial function.[32] Dietary nitrate has also been demonstrated to reduce leukocyte recruitment to inflammation in a process involving attenuation of P-selectin and ICAM-1 upregulation.[33] Nitrite supplementation reverses vascular endothelial dysfunction and large elastic artery stiffness with aging.[34] Emerging evidence now suggests antioxidant effects of nitrate/nitrite.[32,35–37] Dietary nitrate has been shown to reverse metabolic syndrome in experimental animals.[38]

Furthermore, in the stomach, nitrite-derived NO seems to play an important role in host defense and in regulation of gastric mucosal integrity.[39,40] Oral nitrite has also been shown to reverse L-NAME induced hypertension and serve as an alternate source of NO in vivo.[41] Nitrite and nitrate therapy or supplementation may restore NO homeostasis from endothelial dysfunction and provide benefit in a number of diseases characterized by NO insufficiency.[18] This will provide a host of new dietary guidelines for maintaining good health and a solid basis for new preventative and therapeutic regimens. However, this requires sufficient ingestion from eating nitrate-enriched foods. Unfortunately for those in the US, the typical Western diet is composed of dairy products, cereals, refined cereals, refined sugars, refined vegetable oils, fatty meats, salt, and combinations of these foods, which are not good sources of nitrite and nitrate.[26,42] Fresh, leafy vegetables are especially rich in nitrite and nitrate, and incorporating these into the daily Western diet would thus lead to better disease prevention. Long-term trials and epidemiological research will be needed to confirm this hypothesis.

Antiseptic Mouthwash/Antibiotics

The bioactivation of nitrate from dietary or endogenous sources requires its initial reduction to nitrite, and because mammals lack specific and effective nitrate reductase enzymes, this conversion is mainly carried out by commensal bacteria in the mouth and gastrointestinal tract and on body surfaces.[39] Dietary nitrate is rapidly absorbed in the upper gastrointestinal tract. In the blood, it mixes with the nitrate formed from the oxidation of endogenous NO produced from the nitric oxide synthase (NOS) enzymes. After a meal rich in nitrate, the levels in plasma increase and remain high for a prolonged period of time (plasma half-life of nitrate is 5–6 hours). The nitrite levels in plasma also increase after nitrate ingestion in some persons.[43] Nitrate (approximately 25%) is actively taken up by the salivary glands and is concentrated up to 20-fold in saliva.[43,44] Once in the mouth, commensal facultative anaerobic bacteria reduce nitrate to nitrite during respiration by the action of nitrate reductases.[39,45] The salivary nitrate levels can approach 10 mM and nitrite levels 1 to 2 mM after a dietary nitrate load.[43] When saliva enters the acidic stomach (1–1.5 L per day), much of the nitrite is rapidly protonated to form nitrous acid (HNO2; pKa ~ 3.3), which decomposes further to form NO and other nitrogen oxides.[46,47] The enterosalivary circulation of nitrate and subsequent reduction to nitrite in saliva can equate to as much as 40 to 100 mg of nitrite per day from eating a high-nitrate

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