A Personalized Lifestyle Medicine Approach to Erectile Dysfunction

Joseph Debé, DC, DACBN

The factors commonly contributing to erectile dysfunction may be psychogenic, neurologic, hormonal, or vascular. Erectile dysfunction is usually the result of endothelial dysfunction and is often a prelude to more advanced cardiovascular disease.[1] A personalized lifestyle medicine approach has the potential to correct the underlying cause of erectile dysfunction while improving cardiovascular and overall health.

Phosphodiesterase-5 inhibitors (PDE5i) are the conventional medicine treatment of choice for erectile dysfunction. These drugs slow the breakdown of cGMP- the chemical responsible for the smooth muscle relaxation in the corpus cavernosum that results in increased blood flow and resultant erection. These medications fail to help 50% of patients - probably because they fail to address the underlying cause: inadequate nitric oxide (NO) production. Nitric oxide is the signaling molecule that binds to the enzyme guanylyl cyclase, which converts GTP to cGMP. If there is inadequate nitric oxide, cGMP will also be lacking, and erectile function impaired. Nitric oxide also plays a role as a neurotransmitter in neurologic control of erection. Although there are other causes of erectile dysfunction, endothelial dysfunction, mediated through nitric oxide insufficiency, is the most common cause. Nitric oxide not only leads to blood vessel dilation but inhibits plaque formation in the arteries by reducing platelet and white cell adhesion.

Erectile dysfunction increases in incidence in men after age 40 and is commonly associated with hypertension, diabetes, dyslipidemia, heart disease, and depression. The decline in nitric oxide levels with age may relate to these conditions. At 40 years of age there is a 50% reduction in nitric oxide compared to peak levels at age 20.

A natural lifestyle approach to endothelial dysfunction, and, therefore erectile dysfunction, includes diet, exercise, smoking cessation, moderation of alcohol consumption, and correction of obesity.[2] This is a solid foundation to start from but *personalized* lifestyle medicine may yield better results by tailoring treatment to the individual based on unique genetic and environmental factors. Thorough history, including lifestyle and medication review, physical examination, and laboratory evaluation may be employed to systematically identify and correct the underlying causes of the patient's endothelial dysfunction. One may begin with a reductionistic view to determine the pathophysiological mechanisms and then "zoom out" to identify the likely environmental (internal and external) and lifestyle modifiers of the process.

There are two main pathways for nitric oxide production in the human body. Endothelial cells lining blood vessels have an enzyme, endothelial nitric oxide synthase (eNOS), which generates nitric oxide from the amino acid L-arginine. This reaction not only declines with age but can be impaired by multiple factors that are potentially modifiable. In a general sense, eNOS, like any enzyme, is sensitive to hydration status, pH, oxidative stress, inhibition by organotoxins, and damage by glycation. Assuring the patient is adequately hydrated and consuming an alkaline-ash diet is worthy of attention. Evaluating for toxicity, glycation, and oxidative stress should also be done. Nitric oxide synthase production of nitric oxide requires oxygen, NADPH, FAD^+, tetrahydrobiopterin, heme iron, glutathione, and calcium/calmodulin. These cofactors can be evaluated to some degree and can be optimized. For example, glutathione status may be inadequate as a result of oxidative stress or toxicity. Therefore, testing for heavy metals may be of value.

The production of nitric oxide is inhibited by asymmetric dimethylarginine (ADMA), levels of which do indeed correlate with erectile dysfunction.[3]

One study found decreases in ADMA with testosterone replacement therapy. A comprehensive endocrinological evaluation should be undertaken. ADMA is a target for personalized lifestyle medicine. About 10% of ADMA is excreted by the kidneys. For optimal erectile function, kidney dysfunction and disease should be evaluated and treated. Incorporation of dietary soy protein and flaxseeds, for example, may improve renal conditions.[4] ADMA production by methionine-dependent protein arginine N-methyltransferase (PRMT) is increased by stress, LDL cholesterol and oxidized LDL. Patients should be evaluated for need for stress reduction techniques. A comprehensive

lipid profile including oxidized LDL cholesterol should be ordered. Correction of any abnormalities identified can potentially help improve erectile function. Treatment can be immediate or lead to further investigation into more foundational causative factors. For example, an immediate treatment of elevated LDL cholesterol might be supplementation of berberine, which has also been shown to increase nitric oxide levels.[5] Alternatively, factors causing LDL cholesterol elevation, such as hypothyroidism, for example, may be investigated and treated.

The fate of the majority of ADMA is degradation by dimethylarginine dimethylaminohydrolase (DDAH) to citrulline. ADMA clearance is inhibited by hypercholesterolemia, oxidized LDL, elevated homocysteine, insulin resistance, and hyperglycemia. Of course, a comprehensive personal lifestyle program to address insulin resistance and hyperglycemia (or diabetes) should be instituted. A recent study found proton pump inhibitors (PPIs) also impair degradation of ADMA.

Some of the factors contributing to elevated homocysteine include smoking, excessive alcohol and caffeine consumption, nutrient deficiencies, insulin resistance, hypothyroidism, renal failure, and certain medications (acid-suppressing medicines, antibiotics, testosterone, estrogen, Metformin, NSAIDs, aspirin, oral and inhaled steroids). Single nucleotide polymorphisms are important with regard to homocysteine and erectile dysfunction. A study of 75 patients with erectile dysfunction examined the connection between methylenetetrahydrofolate reductase (MTHFR) genotype, homocysteine and folic acid levels, as well as response to the PDE5i, sildenafil. Eighteen patients with C677TT or C677TC polymorphisms failed to respond to sildenafil and had elevated homocysteine and low folic acid levels. These eighteen patients continued on sildenafil and were supplemented with folic acid and vitamin B6 for another six weeks. This led to improvements in homocysteine and folic acid levels and improved erectile function in 16 of the 18 men.[6]

Oxidative stress may uncouple eNOS, resulting in excessive superoxide radical, which combines with nitric oxide to form peroxynitrite. Oxidative stress can be evaluated with a number of laboratory tests, including F_2-isoprostane, lipid peroxides, 8-Hydroxy-2-deoxyguanosine, or oxidized LDL cholesterol. The finding of oxidative stress should prompt utilization of antioxidant-rich foods and supplements, particularly those that have been demonstrated to improve erectile and/or endothelial function. The Mediterranean-style diet, rich in unrefined plant foods, has been demonstrated to improve erectile dysfunction. Particular foods to include are blueberries, pomegranate juice, cocoa, red wine, green and black teas. Supplemental antioxidants are also helpful. The powerful antioxidant, pycnogenol, was found in combination with l-arginine aspartate to improve erectile dysfunction, increase eNOS and testosterone, while lowering blood pressure and cholesterol.[7] A review of the patient's diet for antioxidant content should be undertaken. The diet should also be evaluated for glycemic load, fat quality and quantity, protein adequacy and type, sodium, potassium, other minerals and vitamins, and glycotoxins. Investigation into the cause of the oxidative stress can be further accomplished with laboratory evaluation of inflammation, glucose metabolism, glycation, insulin resistance, nutrient deficiency, and toxicity. Inflammation can be evaluated by measuring, among others, high sensitivity C reactive protein and Lp-PLA2. The finding of inflammation should lead to utilization of supplemental fish oil and plant extracts such as curcumin or tetrahydro *iso*-alpha acids from hops. The latter was found in an animal study to reduce intestinal permeability and absorption of bacterial LPS secondary to a high-fat diet. Metabolic endotoxemia is likely a common cause of endothelial dysfunction. LPS has been demonstrated to activate the renin-angiotensin system in producing superoxide and endothelial dysfunction.[8] Therefore, in cases of dysbiosis or leaky gut syndrome accompanying erectile dysfunction, one might consider supplementing bonito peptides - a natural angiotensin converting enzyme (ACE) inhibitor.

Like peeling an onion, if inflammation is identified, a search for the contributing factors can be undertaken. Certainly, if the patient exhibits gastrointestinal symptoms, laboratory evaluation to assess intestinal microbiota by way of PCR (poymerase chain reaction) with hybridization of DNA should be considered. At minimum, a probiotic supplement could be administered. *Lactobacillus plantarum 299v* is a probiotic that has exceptional cardiovascular benefits. It was found in a study of smokers to decrease systolic blood pressure, leptin, fibrinogen, F_2-isoprostanes, and interleukin 6, as well as monocyte adhesion to native and stimulated human umbilical vein endothelial cells.[9]

Another source of inflammation to consider is food sensitivity reactions. A study contrasting obese and normal weight children found the obese children had increased common carotid artery intima media thickness, which correlated with C-reactive protein and anti-food IgG antibody concentrations.[10]

Among the many other sources of inflammation to consider is obesity. Measurements of body fat percentage by bioimpedance analysis or other methods, along with measures of waist circumference should be done to determine if a body composition improvement program is indicated.

The inflammation produced by periodontal disease can contribute to endothelial and erectile dysfunction. In a fascinating study of 120 men with moderate or severe erectile dysfunction and chronic periodontitis, the effect of periodontal treatment on erectile dysfunction was examined. Periodontal health improved in the 60 men who were treated when compared to the 60 who were not. Three months after treatment there was an improvement in erectile function in the treated compared with the untreated group.[11]

Although arginine is the substrate for eNOS conversion to nitric oxide, arginine supplementation does not consistently produce favorable results. In some cases, arginine supplementation may actually be harmful.[12] When eNOS is uncoupled, giving arginine will result in oxidative stress.

In addition to evaluation and treatments to optimize nitric oxide production through eNOS there is another strategy for boosting nitric oxide levels and, therefore, improving erectile function. It does not utilize arginine or depend upon adequate oxygen or cofactors for eNOS. It is not limited by an unhealthy endothelium. It involves the human nitrogen cycle.

Nitric oxide can also be manufactured from nitrite (NO_2). Where does the nitrite come from? It is made from dietary nitrate (NO_3). This system may supply 50% of the body's nitric oxide.

Nitrate is found in highest concentration in certain vegetables. Kale, Swiss chard, arugula, spinach, and beet root are among the richest sources of nitrate. As an example of the potential benefit for endothelial function, ingestion of beet juice lowered blood pressure and O_2 consumption during walking and running.[13] Patients with erectile dysfunction would do well to eat an abundance of these foods. The nitrate content of vegetables differs dramatically and the potential impact on erectile function of eating the "recommended" number of servings daily will likely vary widely, based on nitrate content.

The conversion of nitrate to nitrite is accomplished by nitrate reductase enzyme supplied by oral bacteria on the tongue. Nitrite is swallowed in saliva and is converted to nitric oxide in the acidic environment of the stomach. The nitric oxide has local effects within the stomach, including improving blood flow, motility, mucus secretion, and antimicrobial effects. It thus protects against ulcers. The nitric oxide produced within the stomach is also absorbed and circulates on thiols and hemoglobin. This source of nitric oxide can bypass a dysfunctional eNOS and restore erectile function. Nitrite is also absorbed intact. There is an enterosalivary nitrite circuit with dietary and systemic nitrite being concentrated by the body in saliva. A portion of ingested nitrate is swallowed unaltered and about 25% of this is absorbed in the small intestine and returned to the saliva. Nitrate reductase enzymes in mitochondria can convert nitrate to nitric oxide. The body recycles nitric oxide to nitrite and nitrate. Nitrite can also be oxidized to nitrate. Immune activation and oxidative stress, however, can act to deplete the body's nitrogen pool.

Thirty to forty percent of people lack the oral bacteria that convert nitrate to nitrite. Perhaps these are individuals more prone to erectile dysfunction and heart disease. Researchers are working to develop a probiotic to supply these organisms. There is also an iatrogenic source of oral dysbiosis that will impair nitrite and subsequent nitric oxide production: Antibiotics and antiseptic mouthwash can impair this nitrogen cycle. A study of 19 healthy volunteers examined the influence of 7 days of daily antiseptic (chlorhexidine-based) mouthwash on oral nitrite production, plasma nitrite levels, and blood pressure. The mouthwash reduced oral nitrite production by 90% and plasma nitrite levels by 25%. Blood pressure rose within a day of starting the mouthwash intervention and persisted for the duration. Patients with erectile dysfunction (and everyone for that matter) should consider a natural alternative to antiseptic mouthwash.

Another possible roadblock in nitric oxide formation is inadequate saliva. Saliva delivers nitrite to the stomach where there is a burst of nitric oxide production. Health conditions and medications causing impaired salivation should be evaluated in patients with erectile dysfunction.

Finally, nitric oxide production from nitrite requires an acid environment in the stomach. Hypochlorhydria is increasingly common with age and can occur in younger people for multiple reasons, including autoimmunity, H. pylori infection, nutrient deficiencies, stress, excessive alcohol consumption, and food sensitivities. Individuals with erectile dysfunction should be evaluated for hypochlorhydria and given betaine HCL replacement if indicated. Could the second biggest selling drug be contributing to erectile dysfunction? The proton pump inhibitor, omeprazole, was found to reduce stomach nitric oxide production by 95%.[15] It would seem prudent to question the wisdom of using PPIs in patients with erectile dysfunction.

It is important to note that a leading nitric oxide researcher has developed a uniquely effective nitric oxide-generating nutritional supplement. It contains a patented, proprietary mix of ingredients, including sodium nitrite, beet root, L-citrulline, hawthorn berry extract, vitamins C and B12. This product is not dependent on eNOS for production of nitric oxide. Importantly, its ability to generate nitric oxide is also not dependent upon oral bacteria or hydrochloric acid. It supplies a safe "rescue" source of nitric oxide and has the potential to help many individuals who otherwise would not be able to generate optimal nitric oxide levels.

Don't smoke, eat your vegetables, and exercise is good advice. With some thorough evaluation and personalization, however, we can give patients superior guidance in improving erectile dysfunction and, in the process, cardiovascular and overall health.

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