Practitioner Edition: Nitric Oxide and Erectile Dysfunction

Erectile dysfunction (ED) is a common and complex disorder that significantly impacts quality of life and is recognized as an important public health problem. Defined as an inability to achieve and maintain an erection sufficient for satisfactory sexual intercourse, ED is associated with aging and an increasing number of common systemic diseases including hypertension, cardiovascular disease (CVD), diabetes mellitus, hypercholesterolemia, and depression, as well as behaviors such as smoking, alcoholism, and drug abuse. Evidence suggests that ED may serve as a general marker for occult CVD and as an indicator of general physical and emotional health.

Prevalence of moderate ED in the United States appears to be about 20% in the total adult male population, 30%–50% in those aged 40–70 years, and >60% in men older than 70. Evidence suggests that ED may serve as a general marker for cardiovascular disease (CVD).

The importance of Nitric Oxide (NO)

NO acts as a neurotransmitter of Non-adrenergic, non-cholinergic (NANC) inhibitory nerves which innervates smooth muscles including the penile corpus cavernosum playing a crucial role in the initiation and maintenance of intracavernous pressure and penile erection.

NO activates soluble guanylcyclase to increase Cyclic guanosine monophosphate (cGMP). cGMP regulates activity of calcium channels as well as intracellular contractile proteins that relax smooth muscles of the corpus cavernosum thus allowing engorgement of the tissue.

Current ED medications, such as the phosphodiesterase (PDE5) inhibitors like Viagra and Cialis, prolong the action of cGMP, thus prolonging erections and increasing sexual satisfaction. **However, they do not cause erections.** For this to occur requires sufficient NO to be present and it is precisely the reason that PDE5 inhibitor medications are ineffective in about 50% of Patients.

Androgens enhance NOS expression in penile corpus cavernosum. Testosterone appears to have a dual action in the modulation of the NO/cGMP signaling mechanism by upregulating NOS expression and modulating PDE5 activity in penile tissue.

NO and the factors effecting male sexual function

Oxidative stress and the generation of free radicals play a central role in impairing cavernosal function thus leading to ED. Many of the reasons that oxidative stress increases can be tied

back to increases in NOS uncoupling. NOS plays a vital role in the production of NO through one of the two Nitric Oxide pathways in the body. This NOS dysfunction can occur due to any of the following reasons:

Age: As we age the NOS enzyme becomes uncoupled due a lack of tetrahydrobiopterin (BH4). This causes an increase in oxidative stress and a reduction in NO production. By the time we are 40, our NOS enzymes function around 50%. By the time we are 60, NOS functions around 15%.

Diabetes: Up to 70% of male diabetics will get ED. Men with diabetes will often develop ED 10–15 years earlier than men without diabetes. Expression of arginase II was higher in cavernosal tissues of diabetics with ED. Arginase II is responsible for the down regulation of NO production by competing with NOS (Nitric Oxide synthase) for L-Arginine. Adequate L-Arginine is required for making NO through L-arginine Nitric Oxide pathway.

Oxidative stress is prevalent in diabetics. This further decreases the functionality of NOS therefore increasing oxidative stress even more. Any NO which is being created in the body is being diverted to scavenge free radicals oxidative stress rather than maintaining healthy circulation necessary for normal erections.

In insulin resistant vasculatures there is suboptimal levels of BH4, which increases NOS uncoupling and decreases NO production resulting in oxidative stress and superoxide.

Alcohol: Acetaldehyde, a principal metabolite of ethanol, may contribute to ED mainly by inhibition of the NOS pathway through increasing oxidative stress.

As outlined previously, this decreases the production of NO and increasing superoxide production.

Smoking: Leads to age-independent decrease in penile NOS activity leading to a deficiency of NO and erectile dysfunction.

Summary

The above issues are primarily related to the L-arginine Nitric Oxide Pathway. However, the nitrate pathway is not age dependent. Supporting the nitrate to nitrite to NO pathway with nitrate supplementation has the following benefits:

- increases Nitric Oxide production
- supports recoupling of the NOS enzyme helping the enzyme to function better
- scavenges free radicals thereby decreasing oxidative stress.

References:

1. Toda N, Ayajiki K, Okamura T. Nitric oxide and penile erectile function. Pharmacology & Therapeutics. 2005 May;106(2):233–266. DOI: 10.1016/j.pharmthera.2004.11.011.
2. Burnett, A. L. (2006). The role of Nitric Oxide in erectile dysfunction: implications for medical therapy. Journal of clinical hypertension (Greenwich, Conn.), 8(12 Suppl 4), 53-62. https://doi.org/10.1111/j.1524-6175.2006.06026.x
3. Castela A, Vendeira P, Costa C. Testosterone, endothelial health, and erectile function. ISRN Endocrinol. 2011;2011:839149. doi:10.5402/2011/839149
4. Cartledge J, Minhas S, Eardley I. The role of Nitric Oxide in penile erection. Expert Opin Pharmacother. 2001;2(1):95-107. doi:10.1517/14656566.2.1.95
5. Norman G Hord, Yaoping Tang, Nathan S Bryan, Food sources of nitrates and nitrites: the physiologic context for potential health benefits, The American Journal of Clinical Nutrition, Volume 90, Issue 1, July 2009, Pages 1–10, https://doi.org/10.3945/ajcn.2008.27131
6. Tiso M, Schechter AN. Nitrate reduction to nitrite, Nitric Oxide and ammonia by gut bacteria under physiological conditions [published correction appears in PLoS One. 2015;10(5):e0127490]. PLoS One. 2015;10(3):e0119712. Published 2015 Mar 24. doi:10.1371/journal.pone.0119712
7. Toda, Noboru & Ayajiki, Kazuhede & Okamura, Tomio. (2005). Nitric oxide and penile erectile function. Pharmacology & therapeutics. 106. 233–66. 10.1016/j.pharmthera.2004.11.011.