Healthy Living and Longevity Medical Center

Function Higher—Physically, Mentally, Sexually®

ABOUT NITRIC OXIDE

Nitric oxide is a gas. It plays a dominant role in the body and becomes depleted with age. It is important to replenish depleted levels for optimal health.

Functions of Nitric oxide:

1. Cognitive Enhancement
2. Making new mitochondria. We now know that NO acts as a key messenger to activate the mitochondrial biogenesis program in various cell types. The authors state that true relevance of NO-induced mitochondrial biogenesis for prevention of aging-related diseases. Enzo Nisoli* and Michele O. Carruba. Nitric oxide and mitochondrial biogenesis. Journal of Cell Science 119, 2855-2862
3. The Effects of Aging on Hormones and Nitric Oxide Production.
4. Several hormones positively stimulate endothelial Nitric Oxide Synthase (eNOS) in the production of NO.
5. These hormones include: Estrogen ●Testosterone ● Progesterone ●DHEA ●Insulin ●Growth Hormone ●Triiodothryonine (T3) Hormone production naturally declines as part of the aging process. As a result, this combined with other factors of aging cause eNOS function to decrease to around 50% by the time a person is 40 years old. By the time a person ages to 60 years old, eNOS only functions at 15% of capacity.

Why do Nitric Oxide levels diminish?

Age

Diet- SAD devoid of essential nutrients and cofactors and nitrate rich veggies.

Lack of exercise.

Medications- antibiotics, antidepressants, birth control pills, NSAID, PPI's (proton pump inhibitors) actually inhibit both pathways of producing NO.

EMF- increases oxidative stress.

NOS- increases superoxide production and decreases NO.

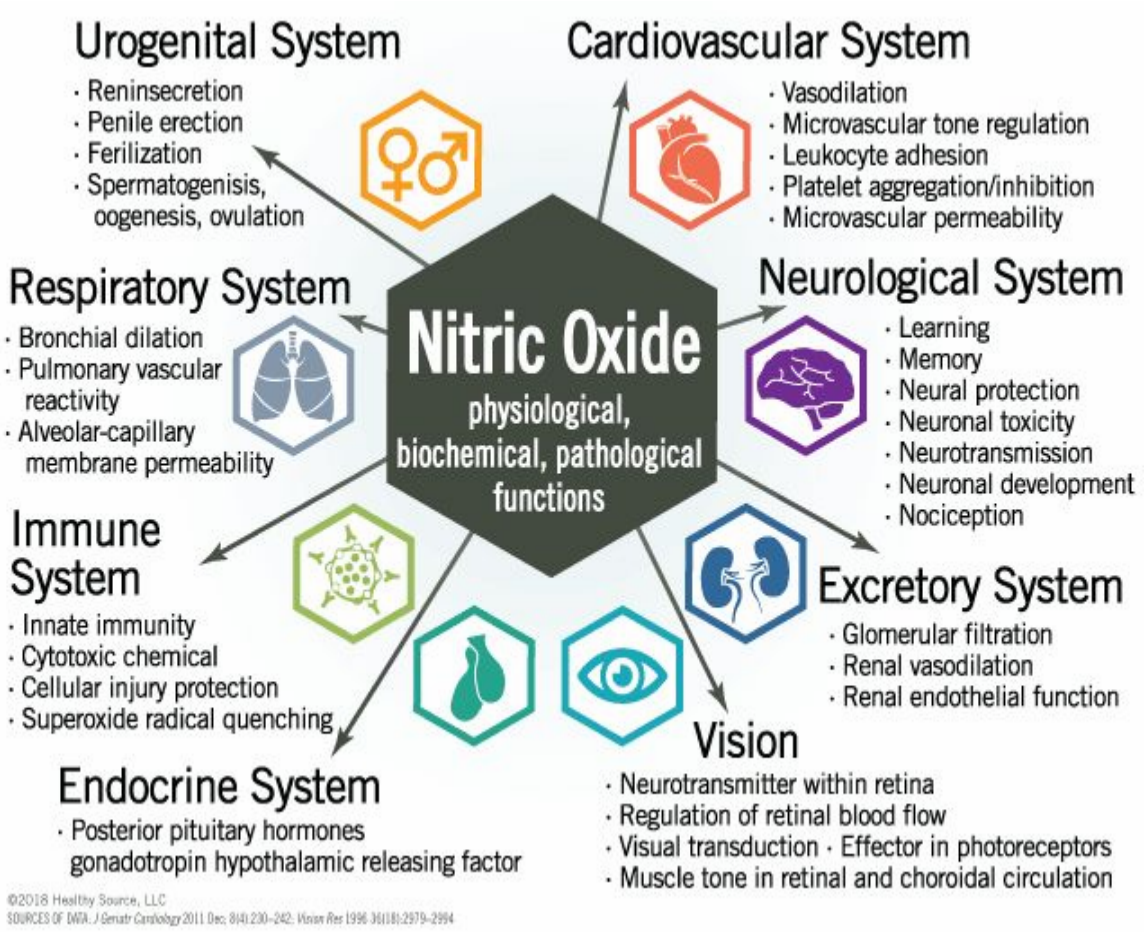
Pollution- increases oxidative stress.

Glyphosate- uncouples NOS.

Genetic SNP's- NOS, anything that increases oxidative stress like SOD, catylase, HFE, anything that influences BH4 like QDPR, DHFR, MTHFR (A1298C).

Stress.

By the time we are 40 years old, NOS functions around 50%, and by the time we are 60, our NO production through NOS is only 15%.



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Fertility:

NO linked to almost all physiological functions of male & female aspects of reproduction, from erection & sperm health in male to ovulation, implantation, carrying baby to full term & labor in female.

Latest WHO data (2023) - 1 in 6 women struggle with getting pregnant or staying pregnant.

No in men - physiological mediator of erection
Significant role in testis
Sperm motility
Testicular perfusion
Activation of gonadotropins
Regulation of blood flow
Cell permeability
Steroid synthesis

NO in females
Regulation of meiosis
Oocyte quality maintenance & maturation
Fertilization
Embryo development
Fetal implantation
Folicular growth-Inhibition of apoptosis
Regulation of ovulation
Regulation of steroid synthesis
Regulation of contractile activity & prevention of tubal ectopic pregnancy
Impact movement of epidermal cells, cilia & embryo
Stimulation of sperm motility
Protection of egg/sperm against free oxygen radicals
Regulation of some growth factor receptors
Contraction & relaxation of uterus
Removal of remaining placenta

Hormones influenced by NO:

Estrogen stimulates eNOS to produce nitric oxide. However, estrogen declines with age. This results in a noticeable decrease in eNOS function around the time of menopause. As a result. 85% of women in the US are hypertensive by the age of 85. When available, estrogen also suppresses oxidative stress. As less NO is needed to scavenge superoxide, this occurrence increases NO's bioavailability.

Progesterone acts directly on epithelial cells of the endometrium to stimulate expression of eNOS.

Testosterone deficiency induces endothelial dysfunction. Deficiency can lead to erectile dysfunction and/or vascular dysfunction. Testosterone has been shown to regulate the NO/cGMP pathway, which directly influences endothelial function and endothelial progenitor cells (EPCs). These cells are key for the endothelial repair system.

The **adrenal glands** require adequate nitric oxide to work effectively. Glucocorticoid production in the adrenal glands is increased in the absence of NO. Cortisol is the only hormone that naturally increases with age.

All of this has the effect of:

- Inhibiting iNOS, thus impairing immune response
- Inhibiting eNOS, thus causing cardiovascular complications such as hypertension and blood clotting
- Increased reactive oxygen species (ROS) produced by mitochondria, NADPH oxidase (NOX) and xanthine oxidase. This increases oxidative stress thereby decreasing the production of NO
- Decreased synthesis of BH4 which increases NOS uncoupling, resulting in increased oxidative stress and decreasing the production of NO
- Decreased membrane transport of L-arginine thus decreasing the substrate for NOS
- DHEA is a prohormone which can be metabolized into other estrogens and testosterone. It is synthesized in the adrenal cortex, gonads, adipose tissue, brain and skin. It directly increased NO production by the activation of eNOS.

Low **DHEA** levels are associated with higher risk of ED in men and low sexual responsiveness in women.

Growth Hormone (GH) and IGFI stimulate eNOS. Adult hypo-pituitarism and untreated GH deficiency is associated with endothelial dysfunction, decreased NO production, increased peripheral resistance and increased cardiovascular mortality and morbidity.

OXYTOCIN:

Oxytocin affects sexual health. Oxytocin induces penile erection by increasing NOS activity in the cell bodies of oxytocinergic neurons, projecting to extra-hypothalamic brain areas and mediating the behavioral responses. Oxytocin, the 'love hormone,' increases NO production through the NOS enzyme system and levels are greatly increased after orgasm in both men and women.

Nitric Oxide could extend fertility. NO appears to slow or reverse the aging of eggs in mouse ovaries. This finding suggests NO may help women in their 30s and 40s remain fertile longer and increase their chances of having healthy babies.

Thyroid:

Cold extremities as a symptom in individuals with thyroid imbalance may be a result of NO deficiency. In the thyroid, NADPH oxidase {NOX) enzymes called DYOX1 and DYOX2 increase the generation of ROS (reactive oxygen species), such as superoxide and hydrogen peroxide. This is important because a precise amount of hydrogen peroxide is required for thyroid peroxidase (TPO) to function optimally. Increased DUOX activity, along with reduced TPO activity, has deleterious effecs on the thyroid tissue caused by oxidative stress. Several factors such as environmental toxicities, mast cell activation, stress, chronic infections or inflammation contribute to the upregulation of NOX and DUOX, which increases ROS.

However, NO and nitrites inhibits NOX and the DUOX enzymes. Supporting the nitrate to nitrite to NO pathway may be an underutilized thyroid therapy due to its role in decreasing the production of superoxide and other ROS by optimizing NO levels. ScavengingROS, and supporting healthy circulation/ microcirculation.

Your Metabolic System:

NO regulates carbohydrate metabolism and insulin production. NO is also emerging as a central regulator of energy metabolism and body composition. Impairment of NO synthesis is a central defect causing metabolic abnormalities associated with insulin resistance. Appropriate amounts of insulin will stimulate NOS activity. Increasing NO output has remarkable effects on obesity and insulin resistance. For example, NO helps activate GLUT4 receptors for transport of glucose into the cells.

Circadian Rhythm:

Decreased NO from aging is linked to impaired circadian rhythm. Reduced NO production contributes to age associated impairment of clock gene expression. Basically, impairment of NO production results in a phase shift of the circadian clock. When circadian rhythmicity is impaired, a condition called non-dipper hypertension can occur. This refers to when blood pressure does not decrease nocturnally as it should. Non- dippers experience impaired endothelial- dependent vasodilation, attributed to a decrease of NO production. This increases the risk for cardiovascular disease.

NO and Mental Health:

Nitric oxide {NO) influences mental health in several ways. In fact, studies have shown that restoring NO production will help an individual feel better, think better, sleep better, have less anxiety and experience less symptoms of depression.

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NO and Gut Health:

Nitric oxide helps prevent inflammation from proinflammatory cytokines and helps protect from leaky gut.

NO and Nutrition:

Vitamin C boosts NO levels. Consider taking the Nitric Oxide capsules with Vitamin C.

E Lbban, et al. Is vitamin C a booster of the effects of dietary nitrate on endothelial function? Physiologic rationale and implications for research. Nutrition May2023, Vol 109, 1119995.

NO for Females

Sexual Dysfunction is a common medical issue that adversely affects a person's health, quality of life, and interpersonal relationships. Female Sexual Arousal Disorder (FSAD) affects up to 70% of women with at least 25% of women unable to reach an orgasm. These incidences increase with age, however it does not have to be an inevitable symptom of aging. How does nitric oxide (NO} impact female sexual behavior? Sexual responsiveness in women requires adequate blood flow to the vagina and clitoris. NO being an important signaling molecule in vasodilation supports improved circulation throughout the body. NO plays an important role in female sexual response to arousal most importantly engorgement and lubrication. The advantage of supplementing with nitrates to enhance the production of NO, is that it allows us to bypass the dysfunctional NOS enzyme system and therefore support healthy female sexual function.

1. Women suffer from the same type of insufficient blood flow that causes impotence in men. The female genital arousal response is manifested by attaining and maintaining sufficient sexual excitement leading to genital engorgement, swelling and lubrication. All of this is mediated by NO.
2. NO is a potent vasodilator of clitoral tissue. If functions as a non-adrenergic, non-cholinergic (NANC) neurotransmitter in the clitoral corpus cavernous and is responsible for the relaxation response of the non-vascular smooth muscle. Sexual stimulation leads to NO production and stimulates the release of Guanylate Cyclase (GC) which converts Guanosine Triphosphate (GT) to Cyclic Guanosine Monophosphate (cGMP). cGMP then relaxes smooth muscles in the clitoral corpus cavernous to increase blood flow. Improved blood flow means better orgasms.
3. NO acts as a neurotransmitter in the brain affecting the release of oxytocin and luteinizing hormone releasing hormones (LHRH) which are central in the modulation of sexual behavior.
4. Oxytocin is called the ‘Love Hormone’ or the ‘Cuddle Chemical’. Oxytocin increases NO production through the NOS enzyme system ad levels are greatly increased after orgasm. The thing is, this NOS enzyme system functions at around 50% of capacity by

the time we are 40 and it is therefore important to maintain NO levels through the nitrate pathway (intake of dietary nitrate through diet or supplementation).

5. Following sexual stimulation, neurotransmitters, including NO and Vasoactive intestinal peptide (VIP) are released, modulating vaginal vascular and nonvascular smooth muscle relaxation. This leads to 3-5ml vaginal transudate while also enhancing lubrication, essential for pleasurable coitus.
6. NO is an important neurotransmitter in decreasing anxiety which increases sexual pleasure. NO is involved in the creation of long-term memory, with studies having shown that memory and libido are connected. Other research indicates that NO enhances the ability to remember sex scents (pheromones) which are intimately related to libido.
7. Selective Serotonin Reuptake Inhibitors (SSRIs) inhibit Nitric Oxide Synthase (NOS) thus decreasing NO production and blocking arousal. SSRIs can produce sexual anhedonia- an absence of any feeling of pleasure from sex or even from orgasm.

NO for MEN, Practitioner Edition: Nitric Oxide and Erectile Dysfunction

Erectile dysfunction (ED) is a common and complex disorder that significantly impacts quality of life 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). 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 int ra-cavernous pressure and penile erection. NO activates soluble guanyl cyclase 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 PDES 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 PDES 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.

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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 thereby 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.

Source: **Beth Shirley RPh CCN - 2020**

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