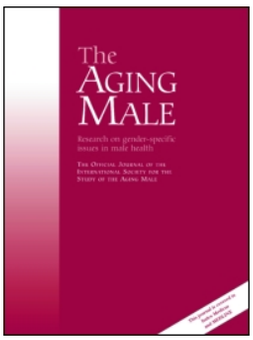

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REVIEW ARTICLE

Aging and erectile function

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ABSTRACT

The authors review and discuss numerous factors that influence erectile function and their interactions, based on the published literature. Of critical importance are vascular nitric oxide; nutrition; exercise; weight control and maintaining insulin sensitivity; early treatment of hypertension with attention to effects on erectile function; avoiding sources of oxidative stress such as obesity and smoking; reducing inflammation (e.g. from gingivitis); improving pelvic floor muscle strength; and inhibiting cyclic GMP break-down. The described interventions act on different aspects of erectile biochemistry and physiology. Therefore, combining multiple therapeutic approaches will yield maximum benefits for erectile and vascular and general health.

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Erectile dysfunction; nitric oxide; oxidative stress; obesity; insulin resistance; pelvic floor exercises

Multiple factors influencing erectile potency

Aging, vascular health, and erectile function are inextricably linked [1]. Abnormalities of vascular function have allowed a view into the mechanisms of aging for many years. More recently, decreased erectile function has been identified as an early warning sign of impending vascular diseases, which we analogized as "the canary in the coal mine" in the American Journal of Cardiology [2]. In one study, two-thirds of men with angiographically proved cardiac artery disease (CAD) had symptoms of reduced erectile function ("erectile dysfunction or ED"), an average of 39 months earlier [3]. In a study of men with ED and no CAD, flow mediated dilation (FMD), a manifestation of vascular endothelial nitric oxide (NO) release, was reduced by almost half (p=.014) but the mean coronary artery risk score and lipid profile were not different from control men [4]. Although ED has been reported to affect 10% of men at age 40 and 80% over age 70 [5], in men without CAD the incidence is much lower (2% from age 40 to 49, rising to only 39% for men over 70) [6]. ED and vascular health are closely connected because the underlying biochemical mechanisms are the same. Oxidative stress (OS), inflammation, insulin resistance (caused in part by OS), and decreased physical activity all lead to decreased vascular NO. In this review, we will discuss age-related ED in the context of these interrelated mechanisms, and the resulting insights gained regarding maintenance or improvement of erectile and vascular health. Methods to improve erectile function are not competitive (e.g. medical versus lifestyle approaches). They are complementary, as they operate on entirely different aspects of erectile biochemistry and physiology [1]. Each of those approaches leads to definite but relatively limited improvements in erectile performance. Therefore, combining multiple or ideally all interventions will have maximal impact. Viagra-like drugs that decrease breakdown of cyclic GMP had been considered as only directly inducing smooth muscle relaxation. However, even those are now recognized to reduce OS and improve vascular function. Figure 1 illustrates some of these interrelating and additive effects that will be discussed below.

NO is the most important mediator of penile vascular and sinusoidal smooth muscle relaxation and its action is mediated by cyclic GMP. Various neural pathways activated by sexual arousal stimulate non-adrenergic, non-cholinergic penile nerves to increase neural NO synthase (nNOS) resulting in dilation of penile vessels, marked inflow of blood, and engorgement of penile sinusoids. Shear stress caused by the very large increase in penile blood flow then increases

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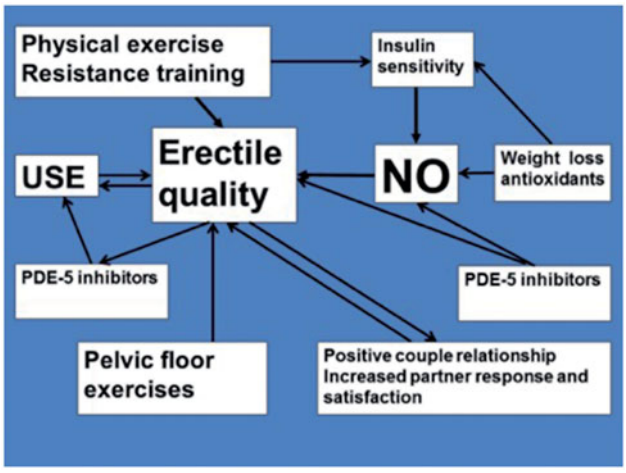

Figure 1. Factors affecting nitric oxide (NO) and erectile quality and their interactions [7].

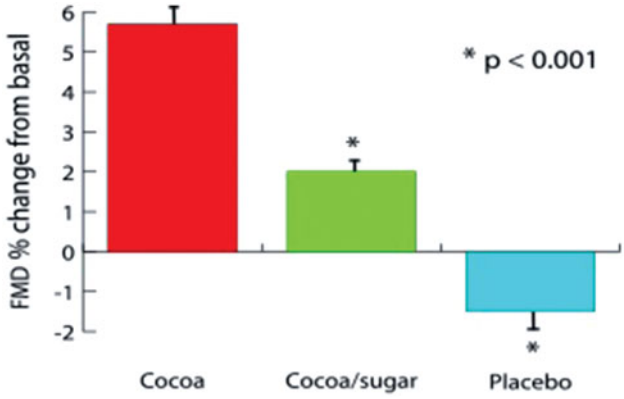

Figure 2. FMD is markedly increased by an amount of cocoa equivalent to that contained in a 40-g portion of chocolate containing 55% cocoa. An amount of sugar contained in many full sugar sodas blocked about two-thirds of that increase [2].

endothelial NOS (eNOS) that relaxes smooth muscle of the penile arteries and surrounding the sinusoids of the corpora cavernosa (CC). Resulting distention of the CC together with muscular pressure from surrounding pelvic floor (PF) muscles then maintain the erection by occluding penile veins adjacent to and within the penile tunica. Continued sexual arousal and more extended activation of nNOS by a cyclic AMP mediated mechanism together prolong neural NO release. More prolonged endothelial NO release occurs due to increased eNOS messenger RNA transcription and stability. Muscular contractions of the PF muscles are required to raise intracorporeal pressure (ICP) above vascular inflow pressure to maximize penile rigidity.

Oxidative stress and obesity

Oxidative stress is considered to be a central cause of aging. Generation of reactive oxygen species (ROS) is an integral part of metabolism for any organism living in an aerobic environment, but numerous protective mechanisms exist to counter adverse effects of ROS on cellular metabolism and structure. The most well-defined model of OS which impacts vascular and erectile health and aging is obesity [8]. Mitochondria are the cells' furnaces producing energy, which is normally accompanied by ROS generation. Excessive substrates associated with obesity (glucose and fatty acids) cause greater generation of ROS. In addition to increasing OS, adipose tissue also increases circulating inflammatory molecules that in turn further increase OS. OS increases pro-inflammatory cytokines, thus producing a "vicious cycle" [8]. Fat accumulation increases with age due to reduced physical activity and lean muscle mass (see below), and simply as time passes. Only an extra 10 calories intake per day (e.g. a small lifesaver candy) translates to a pound per year and 30 pounds in 30 years. Men with ED averaging 53.5 years of age had higher BMI, serum triglyceride levels, and waist circumference and lower high-density lipoprotein (HDL) cholesterol than men without ED. Their mean visceral adipose index, a mathematical calculation using these measurements, was significantly higher ($p<.001$) than in the men without ED [9]. Visceral fat accumulation, which can be excessive with and without an elevated body mass index (BMI) [10], causes insulin resistance and elevated circulating glucose. Insulin resistance blocks insulin stimulation of NO and higher glucose levels increase OS. Production of NO and its stability are highly dependent on antioxidants [11]. This is illustrated by the very marked increase of FMD by an antioxidant challenge equivalent to a 40-g portion of chocolate containing 55% cocoa (Figure 2). Cocoa is a very strong antioxidant well documented to improve vascular function and reduce mortality following myocardial infarction [12,13]. The OS caused by an amount of sugar contained in many 12 ounce sodas blocked about two-thirds of that increase [2], but even with this strong induction of OS, the modest amount of cocoa maintained a positive effect.

In a study of 110 obese men without diabetes, hypertension (HTN), or dyslipidemia, ED was strongly correlated with waist/hip ratio [14]. Obese individuals need to consume more calories just to maintain their weight and resulting higher glucose levels further increase OS both directly and by increasing formation of advanced glycation endproducts (AGEs), which further increase OS. AGEs accumulate with age due to higher glucose levels and by consuming foods cooked at a high temperature, such as with grilling and barbequing. Obesity, through OS, is correlated with

endothelial dysfunction and thereby vascular disease by reducing endothelial antioxidant capacity that normally maintains NO production and stability [2]. In the case of extreme OS, as with smoking, uncoupling of NO synthase leads to production of superoxide and conversion of NO to peroxynitrite [15], a potent pro-oxidant that reduces endothelial NO synthase bioactivity [16].

OS can be counteracted by endogenous mechanisms or by exogenous ingestion of antioxidants. The principal intracellular antioxidant, glutathione, is reduced in men with ED [17], and its synthesis decreases with age [18]. A key circulating antioxidant, paraoxinas-1 (PON-1), is reduced with ED [19]. PON-1 is an HDL associated antioxidant and as with HDL, is reduced with physical inactivity, which becomes increasingly more common with age. In men with ED, pycnogenol, a well characterized and standardized preparation of polyphenolic antioxidants, has been shown to improve ED in a double-blind, placebo-controlled, crossover study [19,20]. Flavinol-rich cocoa increases NO and peripheral blood flow in healthy individuals after five days of administration and also 90 min after a dose, suggesting that vascular and erectile function could be improved in healthy men not suffering from ED [21,22]. With a 20 mg dose of Tadalafil (a phosphodiesterase 5 (PDE5) inhibitor) given to men with ED, serum total antioxidant status increased 45%, total serum oxidant status decreased 33% and serum PON-1 activity increased 50% (all $p<.0001$) [23]. However, smaller doses were not studied. Cyclic GMP reduces levels of superoxide and NADPH oxidase expression, which could explain these effects of medications that increase cyclic GMP levels. In the most severe example of OS, FMD in smokers given 1000 mg of vitamin C and 800 IU of vitamin E dramatically increased from the marked suppression in smokers to a level above that observed in non-smokers [11,15].

Insulin resistance

Insulin resistance increases with age and has been implicated in aging, including development of Alzheimer's disease [24]. Insulin is a prime stimulator of NO and skeletal muscle glucose disposal. Inflammatory molecules and OS cause insulin resistance and antioxidants such as cocoa have been shown to increase insulin sensitivity in various animal and human studies [11]. In obese men, increased insulin sensitivity induced by diet and vigorous activity was strongly correlated with increased NO production [25].

The increased insulin resistance with age is due in part to increasing body fat and decreasing physical activity and muscle mass. Skeletal muscle is a primary determinant of clearance of circulating glucose. Both regular exercise and resistance (weight) training can increase lean muscle mass and insulin sensitivity and reduce the onset of type II diabetes [26,27]. Regular exercise and resistance training also increase insulin sensitivity by reducing visceral fat [28].

Inflammation

Inflammatory markers such as C-reactive protein are increased in men with ED [29]. Circulating pro-inflammatory cytokines increase OS and insulin resistance. Vascular NO is reduced and ED is increased in chronic inflammatory diseases [1], which increase with age and are associated with increased vascular disease. Aggressive treatment of gingivitis (which becomes more prevalent with age and is associated with the risk of myocardial infarction) increased circulating inflammatory markers and decreased FMD in humans. After 6 months, the periodontal disease and FMD ($p<.001$) were significantly improved compared to control subjects [30]. Induced gingivitis in an animal model increased inflammatory markers and decreased intracorporeal pressure and penile NOS activity [31]. CC strips from mice infused with tumor necrosis factor-alpha (TNF-α) had decreased NO-dependent relaxation and reduced eNOS and nNOS gene expression [32]. Omega-3 fatty acid supplements should be considered for men living with chronic inflammation, including obesity, due to their prominent anti-inflammatory effects [33].

Decreased physical activity

Physical activity progressively decreases as men age. ED affects 10% of men at age 40 and 80% over age 70 [5]. Using daily hours of TV viewing as a strong indicator of inactivity, ED was increased 2- to 3-fold [34]. Mild to severe erectile difficulties are 10-fold higher in sedentary men [35]. Moderate exercise is associated with a two-thirds, and a high degree of physical activity with over 80% reduction of the incidence of ED [36]. Exercise increases lean muscle mass, insulin sensitivity and PON-1 and decreases OS, all of which increase NO [1]. Strength training also increases resting metabolic rate in aging men [37], due to an increase in lean muscle mass [38]. Exercise and strength training therefore help to mitigate the

substantial increase in weight and visceral fat that commonly accompanies aging.

Decreased bulk and strength of pelvic floor muscles

ICP up to 2–4 times systolic levels has been recorded in the human male [39], but pressure within the CC (and therefore penile rigidity) solely from inflow of blood cannot exceed systolic blood pressure. The bulbocavernosal muscles augment erectile potency by partially surrounding the CC to constrict venous outflow and directly increase ICP [39]. Reflex contractions of the PF muscles have been shown to occur due to distention of the CC [40] and pressure on the glans penis [41], resulting in increased ICP with coital thrusting. The ischiocavernosal muscles also overlie and insert onto the penile tunica to allow their contractions to improve erectile quality. In a study of six cadavers of relatively young, sexually active men [42], the bulbocavernosus muscles were described as partially encircling the CC and mostly inserting into the ventral thickening of the tunica. The CC was described as entrapped in the ischiocavernosus muscle with its muscle fibers aligned in a longitudinal direction and inserting into the outer longitudinal collagen bundles of the tunica. The PF muscles were less developed and their points of attachment to the tunica were thinner ($p<.01$) in the older sexually less active men.

In a randomized, controlled crossover trial, PF exercises (PFEs) significantly improved erectile function in a series of 55 men with a median age of 59.2 years [43,44]. At the end of three months, the International Index of Erectile Function (IIEF) score ($p=.004$) and overall satisfaction ($p=.008$) were significantly increased but were essentially unchanged in controls (Figure 3). IIEF scores were significantly increased when the control group was crossed over to PFEs ($p<.001$). Partners' intercourse satisfaction ($p=.02$) and sexual desire ($p=.01$) also increased. With a further 3 months of PFEs at home, the improved erectile function was maintained. Analysis by intention to treat showed erectile function normalized in 40% of subjects and another 35% experienced improved function. Results were further validated with digital assessments and manometric measurements of anal pressure.

In the above study, a trained physiotherapist used a rectal probe with pressure recording to instruct the subjects in proper technique using biofeedback. Similar improvements may be achieved in a less structured setting in clinical practice, as suggested in uncontrolled studies. The younger these exercises can

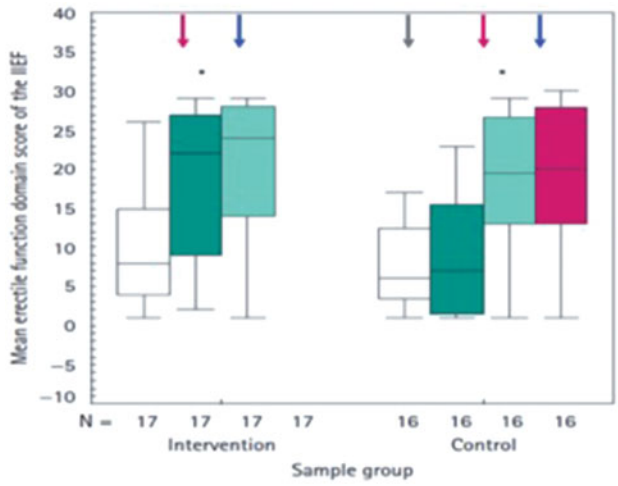

Figure 3. The International Index of Erectile Function (IIEF) increased two- to three-fold after 3 months of pelvic floor exercises (PFEs), whereas it remained unchanged in controls. When control men were changed to PFEs, a similar increase was observed. The improvement was maintained with PFEs done at home [43].

be started, the easier the man can initiate them. Although at first it may seem that it takes a great deal of concentration to imagine muscles are actually being commanded to contract, with persistence and time a very strong PF can be regained. It is recommended that the PFEs should be performed in various positions such as standing, lying, sitting, and walking in order to exercise all parts of the PF. Performing them during walking is particularly important, because a recent study found a negative correlation between walking and PF strength [45] (suggesting that walking is normally accompanied by relaxation of the PF). Most can be done during normal activities and no one need know they are being performed. As the PF redevelops, the man will be aware of contractions occurring during intercourse and the resulting increased rigidity, which in turn further exercises those muscles. He will also become aware of the well documented increase in satisfaction of his sexual partner with improved erectile hardness [46]. When compared to use of sildenafil [47] in men having a similar degree of ED, effectiveness of the two treatments was similar (Figure 4) [43].

Decreased use

Virtually every organ in the body benefits from increased use, including the brain, and it would be very surprising if the penis was an exception. The frequency of coitus decreases with age [48]. The incidence of ED has been reported to be twofold higher in men with a coital frequency of less than once per

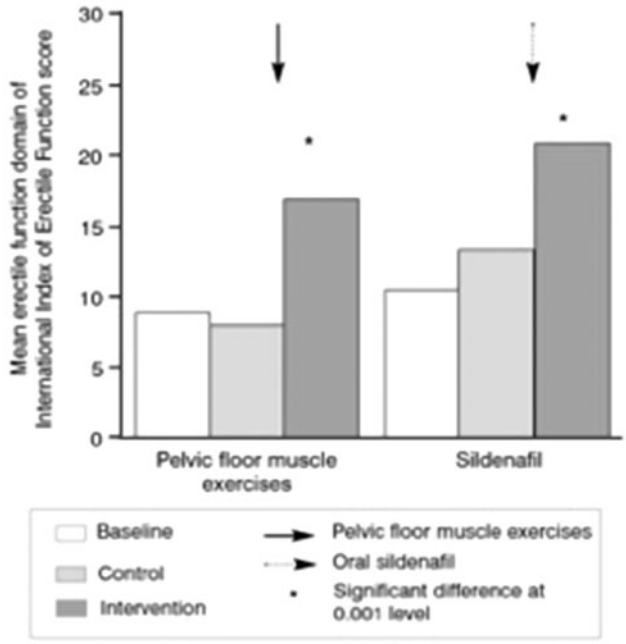

Figure 4. Comparison of pelvic floor muscle exercises [43] and sildenafil [47] at 3 months using the erectile function domain of the IIEF [43].

week [49]. The increase in blood flow with erection and resulting sheer stress and NO release from the endothelium is much greater than in systemic vessels with exercise [2]. Using an animal model, in large vessels acute exercise increased vascular NO for 48 h, but daily exercise increased NO fourfold, lasting for a week [50]. Following radical prostatectomy, men whose erectile function was satisfactory before surgery were less likely to suffer ED [51], and use of vacuum devices to increase blood flow following prostate surgery have been associated with improved erectile function [52]. These studies support the hypothesis that erections promote subsequent erectile function. Consequently, all measures that improve erectile function, including PDE5 inhibitors, have a secondary benefit by allowing more frequent, improved, and more prolonged erections.

Anatomic changes in penile structure with age

Decreased corporal smooth muscle and increased fibrosis have been observed in animal models of aging, which prevents sufficient engorgement of penile tissue that in younger animals exerts pressure on veins within the penile tunica to trap blood within the CC. These changes were shown to be largely reversed by chronic ingestion of sildenafil, without affecting indices of OS [53]. The observation that penile gene transfer of eNOS increased erectile function in the aged rat also suggests that increased NO (and therefore better erections) may help to prevent anatomic penile aging [54].

Prostatic hyperplasia/hypertrophy

Lower urinary tract symptoms (LUTSs)/benign prostatic hypertrophy (BPH) is linked to ED, likely due to associated factors of obesity, poor diet, dyslipidemia, HTN, metabolic syndrome, alcohol, and smoking [55]. Prostatic enlargement does not appear to directly play a role. In a systematic review, the majority of studies showed no change of erectile function with surgical intervention [56].

Atherosclerosis

Due to the small diameter of the penile arteries and the very large increase in blood flow required to distend the penis, it has been speculated that even early atherosclerotic changes in the walls of those vessels could narrow their lumens and/or reduce their ability to dilate [57]. Whereas large arterial vessels dilate only about 10–20%, in young potent men vessel diameter increased by 72% and flow velocity increased approximately 200% in response to visual sexual stimulation [58]. Some degree of atherosclerotic change in arterial vessel walls is a virtually universal accompaniment of aging. In a study of 122 men with ED under age 40 without evident cardiovascular disease and control men without ED, multivariate logistic regression showed significant relationships of systolic blood pressure, C-reactive protein, and Framingham risk score to ED, despite mean levels of each being within the normal range. FMD was significantly lower and correlated with the severity of ED ($p<.001$). Those findings argue strongly for an effect of these subclinical changes on the ability of the penile arteries to increase their diameter to allow adequate blood flow into the CC.

Other factors reported to increase vascular NO

Omega-3 fatty acids have been shown to markedly increase NO using human endothelial cells [2]. Folic acid increases vascular NO and may act directly rather than primarily by decreasing levels of homocysteine [59]. Both have been shown to reduce blood pressure, and omega-3 fatty acids help to prevent arrhythmias by stabilizing the myocardium [2]. As men with ED may have unrecognized CAD, omega-3 fatty acids may help to prevent sudden cardiac deaths. There has been no study of omega-3 fatty acids alone but with intake doubling from 0.6 to 1.3 g per day with the

Mediterranean diet, the IIEF increased by 19% ($p<.01$) [60]. However, antioxidant intake also improved.

L-Arginine is the raw material from which NO is produced. The average daily intake of L-arginine in the diet is about 5 g. Increasing arginase levels with age [61] may play a small role in increasing ED in older men by increasing metabolism of L-arginine by the gut and liver during absorption. Although some studies have suggested a small improvement of ED with 5 g supplements of L-arginine, use of smaller amounts like 1 g, although frequently promoted, appears to be ineffective [21]. However, in men with low protein intake, particularly with advancing age, augmenting oral L-arginine may logically be of benefit.

Early treatment of hypertension

The incidence of HTN increases with age. The prevalence of ED in men suffering from HTN is increased 2–3-fold and increases with its duration and severity [62]. Antihypertensive medications generally adversely affect erectile function [62] with the prominent exception of short acting angiotensin II receptor blockers. In a randomized trial, Irbesartan increased the IIEF score by 3.7 (22%) [63]. Exercise, weight loss, antioxidants, omega-3 fatty acids, a low-carbohydrate diet, and adequate folic acid and calcium intake have all been shown to reduce blood pressure or prevent HTN [2].

Testosterone

Circulating testosterone (T) decreases with age [64]. Low and low normal levels have been associated with ED and vascular NO production correlates with serum T [65]. T supplementation improves erectile function and response to PDE5 inhibitors in hypogonadal men and improves sensitivity to insulin and reduces central body fat distribution. Treatment of hypogonadal men with injections of T undecanoate for up to 12 years improved erectile function, cardiometabolic risk factors, and reduced prostate cancer [66]. Testosterone treatment is discussed in detail in a comprehensive review by Buvat et al. [67]. T treatment improves erectile function more consistently in younger than in older hypogonadal men [67], possibly due to the numerous age-related impediments to NO production being discussed. T levels may increase with exercise and weight loss [67] and with agents that increase vascular NO [21]. It may be logical to concentrate on measures to improve vascular health and NO production before measuring circulating T levels [1].

Inhibitors of cyclic GMP degradation

PDE5 inhibitors raise cyclic GMP in penile tissues [68], but also can improve antioxidant status (see "oxidative stress" above). With 20 mg of tadalafil, the increase of PON-1 was sufficient to counterbalance the low levels observed in men with ED. That dose also increased vascular NO [2], possibly secondary to improved antioxidant status. PDE5 inhibitors may contribute to blood pressure control. In a study of untreated hypertensive subjects given 50 mg of sildenafil three times daily, systolic and diastolic blood pressure decreased 10 and 6 mm, respectively ($p<.01$) [69]. Regular use of PDE5 inhibitors may further increase erectile function by increasing the frequency, duration, and quality of erections (see "decreased use" above). In turn, maximizing all efforts to improve erectile function as outlined here and in our cited reviews will increase satisfaction with and use of PDE5 inhibitors, as erection hardness is a predictor of their continued use [70]. PDE5 inhibitors also have an important role in preserving erectile function following radical prostatectomy for prostate cancer, the potential need for which increases with age [1].

A multi-faceted approach to the ED which accompanies aging

As the interventions described above act on different aspects of erectile biochemistry and physiology, combining multiple interventions will have the maximum benefit for erectile and vascular health and will also help to prevent or delay many age-related diseases. Table 1 outlines key steps a man can take to preserve or improve his erectile potency, the mechanisms involved when known, and the reported effect size with each intervention where studied. Although measures differ, they have been listed in approximate order of their effectiveness as surmised to date. The lesser effect of weight loss is due to limited change of weight achieved. The lack of inclusion of stress reduction and sexual arousal is not to minimize their key roles, but they are beyond the scope of this review. Low sexual desire is complex and although some association with low T levels has been demonstrated, psychological health and the quality of the man's relationship with his partner and perception of the partner's response and satisfaction are clearly important variables [71]. As improvement of erectile function has been shown to improve female arousal and satisfaction [46,59], there is a positive reinforcing feedback that will further improve the couple's sexual enjoyment. Figure 1 shows the interaction of many of the

Table 1. Ten interventions to improve erectile potency, their mechanisms were defined, and in approximate order of their effect sizes was reported.

Intervention	Mechanism	Effect size (ref)
Exercise	Increased insulin sensitivity; decreased oxidative stress; increased lean muscle mass	2–3-fold (Selvin, [34])
Pelvic floor exercises	Decreased penile venous outflow; increased penile rigidity	2–3-fold (Dorey, [43])
PDE5 inhibitors	Increased cyclic GMP, improved antioxidant status, increased use	2–3-fold (Goldstein, [47])
Increased use	Increased NO release	2-fold (Koskimaki, [49])
Antioxidant supplement	Increased NO production, decreased NO breakdown, increased insulin sensitivity	Pycnogenol 1.8-fold (Stanislavov, [20])
Weight loss or maintenance of normal weight	Decreased oxidative stress, increased insulin sensitivity, decreased inflammation, improved exercise tolerance	1.25-fold (Esposito, [14])
Treat hypertension	Angiotensin II inhibitors	1.22-fold (Irbesartan), (Baumhakel, [63])
Omega3/anti-oxidant intake	Increased NO, decreased inflammation, improved antioxidant status	Mediterranean diet 1.2-fold (Esposito, [60])
Decreased inflammation	Targeted treatment and prevention (e.g. gingivitis), weight loss, omega-3 fatty acids	Not defined
Testosterone (for hypogonadism)	Increased NO, increased libido, increased insulin sensitivity and response to PDE5 inhibition	Uncertain for aging men (Buvat, [67])

factors discussed here, some of which also have this positive feedback loop. Further information can be found at www.erectile-function.com.

The limits of male penile aging

Presumably, "all good things must come to an end". However, on the Greek island of Ikaria, one of the "Blue Zones" where an unusual proportion of individuals live to over 90 years of age, a preliminary study of Ikarian men between 65 and 100 years old found that 80% of them claimed to have sexual relations on a regular basis; about 25% of them reported "good duration" and "achievement" [72]. Their responses were subjective, but the IIEF, on which the majority of ED studies are based, is also entirely subjective. On that hilly island, vigorous exercise is just part of daily life, stress is minimal, the men remain normal in weight and inhabitants enjoy a healthful, Mediterranean diet. It should hardly be surprising that the mechanisms of erectile function are so resilient and redundant, as the very survival of our species depends on it. Fortunately, that allows sufficiently motivated men to forestall this "normal" consequence of aging.

Disclosure statement

The authors report no conflict of interest. David R. Meldrum maintains a website, erectile-function.com as a service to infertile couples that does not generate any profit for the website or the authors' books.

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Marge A. Morris earned a Master's degree in education from Vanderbilt University, a postgraduate degree in nutrition and training in exercise and physical fitness from UCLA, is a registered dietician and is certified as a Diabetes Educator. She has worked at UCLA Medical Center as a clinical dietitian, counsels patients with diabetes, and has taught nutrition online.

Joseph C. Gambone is a reproductive endocrinologist and professor emeritus at the David Geffen School of Medicine at UCLA. He was awarded a Masters of Public Health degree from the UCLA School of Public Health in 1999. He is the author of over 100 scientific articles and book chapters and was executive editor of *Essentials of Obstetrics and Gynecology*.

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