

## INVITED REVIEW

# Erectile dysfunction, physical activity and physical exercise: Recommendations for clinical practice

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## Abstract

Erectile dysfunction could be an early sign of endothelial dysfunction and, therefore, of cardiovascular disease, with which it shares many risk factors. Among reversible risk factors, physical inactivity is one of the most important. Regular physical exercise has been shown to improve erectile function through different mechanisms involving glucose and lipid metabolism, regulation of arterial pressure, production of nitric oxide and hormonal modulation. Furthermore, exercise shows a synergistic effect with the drugs commonly used in the treatment of impotence. Since many patients with erectile dysfunction may have underlying cardiovascular disease, the evaluation of individual cardiovascular risk is mandatory before prescribing physical exercise. When exercise is not contraindicated, the most appropriate protocol must be chosen, considering the individual characteristics of the patient. Both aerobic and anaerobic/resistance protocols have proven effective. However, meta-analytic studies show that aerobic exercise with moderate-to-vigorous intensity is the most effective in improving erection. Testosterone is an important modulator of physical performance, and its blood levels must always be evaluated in patients with erectile dysfunction.

## KEYWORDS

erectile dysfunction, exercise, fitness, PDE5i, physical activity, testosterone

## 1 | INTRODUCTION

Erectile dysfunction (ED) is defined as the persistent inability to achieve and/or maintain a penile erection sufficient to perform a satisfying sexual intercourse (NIH Consensus Conference, 1993).

Mild ED has emerged as an important indicator of underlying cardiovascular disease (CVD) and may represent an early sign of endothelial dysfunction (Condorelli, Calogero, Vicari, Duca et al., 2013; Condorelli, Calogero, Vicari, Favilla et al., 2013). It has been demonstrated that ED severity correlates closely with increased cardiovascular risk and depends on the combined effect of hyperglycaemia, hypertension, arterial stiffness and hypogonadism (Isidori et al., 2014). Indeed, ED shares with CVD common

reversible and irreversible risk factors (obesity, diabetes mellitus, dyslipidemia, metabolic syndrome, physical inactivity and cigarette smoke). These risk factors decrease the antioxidant defences and the nitric oxide production in the systemic circulation and favour inflammation development (Meldrum et al., 2012). Similar to CVD patients, the first therapeutic step in the management of patients with ED is to identify reversible risk factors. Indeed, lifestyle changes have to precede or to be associated with a pharmacological treatment.

Among unhealthy lifestyle factors, physical inactivity is the most important risk factor for ED (Allen & Walter, 2018). Conversely, physical exercise improves sexual function and cardiovascular health (La Vignera, Condorelli, Vicari, D'Agata, & Calogero, 2012).

## 2 | PHYSICAL ACTIVITY AND PHYSICAL EXERCISE

It is noteworthy that “physical activity” (PA) is different from “physical exercise” (PE). The terms are often mistakenly used as synonyms, but express different concepts. PA is any active body movement resulting in energy expenditure. This energy expenditure can be measured in kilojoules (kJ) or kilocalories (kcal) per unit time (i.e., per day, per week) and depends on muscle mass, intensity, duration and frequency of muscular contractions (Caspersen, Powell, & Christenson, 1985). PE is a particular subset of PA. It indicates a planned, structured and repetitive PA aimed at improving or maintaining physical fitness (Caspersen et al., 1985). For example, a storekeeper who raises and carries loads makes a PA but not a PE, because the movement causes an energy expenditure but is not aimed at improving or maintaining fitness. Physical fitness indicates the physical well-being of an individual. It has five health-related components: cardiorespiratory endurance, muscular endurance, muscular strength, body composition and flexibility, each of which can be measured. For example, cardiorespiratory endurance can be evaluated by maximum oxygen uptake ( $\text{VO}_2\text{max}$ ) on treadmill or cycle ergometer (Caspersen et al., 1985).

Both PA and PE can improve sexual function and cardiovascular health. A recent meta-analysis of seven trials showed that the increase in total PA is associated with a significant improvement of erectile function scores (Silva, Sousa, Azevedo, & Martins, 2017). As far as PE, both short- and long-term protocols are beneficial. Aerobic exercise with moderate-to-vigorous intensity showed the greatest effectiveness, especially in patients with cardiovascular risk factors, while pelvic floor muscle-specific exercises resulted in no significant increase in the international index of erectile function (IIEF) score. PA and PE showed to be more effective in combination with pharmacological therapy (Silva et al., 2017). Another recent meta-analysis confirmed that PA is associated with a lower risk of ED, with a dose-dependent effect: high levels of PA (e.g., 30' of moderate- or high-intensity activity five times per week) were associated with a lower risk of ED compared with moderate levels of PA (e.g., 20' of moderate-intensity activity three times per week; Allen & Walter, 2018).

## 3 | EFFECT OF AEROBIC, RESISTANCE, AND PELVIC FLOOR MUSCLE-SPECIFIC EXERCISE ON ERECTILE FUNCTION

Exercise increases systemic endothelial nitric oxide (NO) production through shear stress caused by the mechanical effect of increased blood flow. Furthermore, it improves systemic sensitivity to insulin which is another important stimulator of vascular NO release (Meldrum et al., 2012).

Aerobic exercise has positive effects on cardiovascular risk factors such as hyperlipidemia and glycemic profile, and improves cardiac output and exercise tolerance. A meta-analysis showed that training targeted at maximal fat oxidation is effective in decreasing fat mass, body weight and blood cholesterol levels (Romain et al.,

2012). This type of protocol consists in very low-intensity training, usually subdivided in three section of 45' per week, and is based on the theory that at low intensities of exercise lipids are preferentially oxidised, whereas at the highest intensities, the main source of energy is carbohydrates (Romain et al., 2012).

In addition to acting on the classic risk factors (weight and cholesterol levels), regular aerobic PE has been shown to increase the number of circulating endothelial progenitor cells (EPC) in patients with cardiovascular risk factors and coronary disease by improving nitric oxide bioavailability, lowering insulin-resistance, serum pro-inflammatory cytokines and C-reactive protein levels. In contrast, drastic physical inactivity brings to vascular damage, as suggested by increased amount of circulating endothelial microparticles (EMP; La Vignera, Condorelli, Vicari, D'Agata, & Calogero, 2011).

Resistance exercise could also be beneficial. A higher muscular strength is associated with better cardiometabolic risk factor profile, lower risk of all-cause mortality, and fewer CVD events (Garber et al., 2011). Furthermore, resistance training may be effective in preventing and treating metabolic syndrome, thanks to its positive effects on body composition, insulin sensitivity, blood glucose levels and blood pressure levels (Garber et al., 2011). A recent study demonstrated that greater handgrip strength and higher levels of PA are associated with a lower risk of ED in older man (Chung, Shin, & Park, 2018). The Authors postulated that reduced physical functioning may contribute to ED; however, further investigations are needed to clarify the biological mechanisms linking handgrip strength and ED.

The meta-analysis by Silva and colleagues reported no efficacy of pelvic floor muscle-specific exercises in improving erectile function, but trials included in the analysis were conducted on patients with the most severe grade of ED and with a low intensity/timing of training (Silva et al., 2017). Pelvic floor muscles participate in an important way in the mechanics of the penile erection. In fact, the superficial pelvic floor muscles (bulbocavernosus, ischiocavernosus and transverse perineal muscles) maintain erectile rigidity, increase pressure in corpora cavernosa, prevent the return of the venous blood from the penis and promote the expulsion of semen from the urethra during orgasm (Siegel, 2014). Colpi and colleagues reported that perineal floor muscle contraction, evaluated by electromyography, is significantly higher in potent men than in patients with ED matched by age and that perineal floor efficiency gets worse with age (Colpi, Negri, Nappi, Chinea, & Colpi, 1999). Thus, it is plausible that pelvic floor muscle-specific exercise can improve erection. There is evidence that pelvic muscles training is more effective in the subset of patients with venous-occlusive deficit and in those with ED post-radical prostatectomy (Siegel, 2014).

## 4 | INFLUENCE OF TESTOSTERONE AND PDE5I ON PHYSICAL PERFORMANCE

Exercise induces acute testosterone increase and blood testosterone, in turn, is an important modulator of physical performance.

Exercise-mediated testosterone production is aimed at regulating central nervous system response, metabolism, neuro-muscular activity, and muscle growth (Sgrò & Di Luigi, 2017). It has been shown that the age-related decline in bioavailable and free testosterone levels is significantly associated with handgrip strength decrease (Chin et al., 2012) and that testosterone replacement therapy enhances physical performance and handgrip strength (Page et al., 2005). Page and colleagues evaluated through a shortened version of the physical performance test and a dynamometer the physical function and the handgrip strength of men with testosterone levels <350 ng/dl, at baseline and 12, 24, and 36 months after the introduction of testosterone replacement therapy. They compared the obtained performances with those of a group of untreated hypogonadal patients (control group). The patients receiving testosterone showed a significantly improved performance after 36 months of treatment, while control group showed a deterioration in physical performance over time (Page et al., 2005). The Author hypothesised that the effect of testosterone replacement therapy is due to the increase in lean body mass and in oxygen-carrying capacity, even if they do not exclude a contribute of mood and energy levels improvement (Page et al., 2005). These data indicate a mutual relationship between testosterone, ED and physical performance: regular exercise is important for maintaining a good erection but if testosterone levels are not adequate the patient may not be able to reach appropriate fitness levels. Furthermore, decreased testosterone levels could make less effective the action of the drugs used for ED treatment, such as phosphodiesterase-5 inhibitors (PDE5i; Aversa, Francomano, & Lenzi, 2015).

PDE5i are the first choice drugs for the treatment of ED. PDE5i and PE could act synergistically to improve penile erection (Silva et al., 2017): the first ones acting mainly in the short term, the latter modulating in the long-term the risk factors for endothelial dysfunction (Gerbold, Larsen, Graugaard, & Areskoug Josefsson, 2018). Therefore, they could be prescribed together. The interaction between PDE5i and exercise has been studied. PDE5i have been shown to increase exercise capacity during hypoxia in the course of aerobic

performance (Guidetti et al., 2008). In normoxia, a single tadalafil administration does not significantly modify anaerobic thresholds in healthy athletes (Di Luigi et al., 2008). Instead, administered before an anaerobic exercise, PDE5i decrease the time to peak power, probably by improving muscular creatine kinase activity, enhancing glycogenolysis, and increasing blood lactate production (Guidetti et al., 2007).

## 5 | SEXUAL/PHYSICAL ACTIVITY AND CARDIOVASCULAR RISK

Since CVDs underlie many patients with ED, before prescribing PE to restore sexual activity, the evaluation of individual cardiovascular risk is mandatory. Indeed, sexual activity is comparable to a low-moderate intensity exercise, being equivalent to walking for a mile in the plains in 20', walking up two flights of stairs in 10" or to 4' of the Bruce Treadmill test (Nehra et al., 2012). Sudden cardiac death during sexual activity is very rare, accounting for around 2% of all exercise-related death (Stein, Sardinha, & Araújo, 2016). However, the relative risk of myocardial infarction during sexual intercourse is about 2.5 and is lower in people who practise regular PE (Muller, Mittleman, Maclure, Sherwood, & Tofler, 1996). Myers and colleagues demonstrated that men, both healthy and cardiopathic, with higher peak exercise capacity during treadmill test have lower risk of death (Myers et al., 2002). These and many other evidences (Stein et al., 2016) suggest to prescribe exercise (and sexual activity) to almost all patients.

However, for practical purposes, in order to define the indication to resume or not sexual/physical activity, patients with ED can be stratified in three cardiovascular risk classes (low, moderate and high) according with the Princeton Consensus (Nehra et al., 2012; Table 1). The low-risk category includes patients without significant cardiovascular risk related to PE who do not need further evaluation before starting or resuming sexual activity. The moderate-indeterminate risk category is made up of patients with

**TABLE 1** Cardiovascular risk stratification according to the Princeton Consensus

Low risk	Moderate risk	High risk
Symptomless patients with <3 cardiovascular risk factors (gender excluded)	Patients with more than 3 cardiovascular risk factors (gender excluded)	Patients with arrhythmia at high risk
Mild or stable angina	Moderate or stable angina	Not-responding or unstable angina
Clinical history positive for noncomplicated acute myocardial infarction	Recent acute myocardial infarction (2–6 weeks before)	Recent acute myocardial infarction (<2 weeks before)
Left ventricular dysfunction or heart failure (NYHA I or II)	Left ventricular dysfunction or heart failure (NYHA II or III)	Left ventricular dysfunction or heart failure (NYHA IV)
Clinical history positive for coronary revascularization	Cardiologic sequels of atherosclerosis (ictus, peripheral vasculopathy)	Hypertrophic obstructive cardiomyopathy or other cardiomyopathies
Controlled hypertension		Not-controlled hypertension
Mild valvulopathy		Moderate-to-severe valvulopathy

Intensity	Relative measures		Absolute measures			
	%HRmax	%VO <sub>2</sub> max	MET	MET by age		
				20–39 years	40–64 years	≥65 years
Very low	<57	<37	<2	<2.4	<2	<1.6
Low	57–63	37–45	2–3.9	2.4–4.7	2–3.9	1.6–3.1
Moderate	64–76	46–63	4–5.9	4.8–7.1	4–5.9	3.2–4.7
Vigorous	77–95	64–90	6–8.4	7.2–10.1	6–8.4	4.8–6.7

**TABLE 2** Units of measure of exercise intensity (Garber et al., 2011)

uncertain cardiovascular risk. These patients need to undergo cardiologic tests or specialist's counselling to be more properly classified. Patients belonging to the high-risk category show unstable or dangerous cardiologic conditions that contraindicate sexual activity unless cardiologic conditions are stabilized with appropriate treatment (Table 1).

## 6 | HOW TO PRESCRIBE PHYSICAL EXERCISE TO PATIENTS WITH ERECTILE DYSFUNCTION

When PA is not contraindicated, the right training protocol for the individual patient must be chosen. Aerobic exercise with moderate-to-vigorous intensity has been shown to be the most effective in improving ED (Silva et al., 2017). However, intensive trainings induce carbohydrate rather than lipids oxidation, are orexigenic and can paradoxically lead to weight gain. Furthermore, patients have worse compliance to intensive protocols (Garber et al., 2011). For these reasons, especially in obese patients, a low-intensity endurance training targeted at maximal muscular lipid oxidation could be prescribed (Drapiere et al., 2018).

Generally, aerobic training is recommended with an energy expenditure of at least 800–1,200 Kcal a week, corresponding to aerobic PA of moderate intensity for 150' a week or of vigorous intensity for 75' a week, divided into 2–3 session per week (Garber et al., 2011). Both protocols have shown a positive impact on blood pressure, lipid profile, inflammatory markers and insulin sensitivity (Nehra et al., 2012). A recent systematic review aimed at assessing the quality and quantity of PA needed (i.e., modalities, duration, intensity, and frequency), showed that 40' of aerobic PA of moderate intensity four times weekly (160' a week) for 6 months are effective in improving erectile function. Short sessions of vigorous intensity PA and resistance exercises can be further added to optimise the training (Gerbold et al., 2018). The absolute intensity of exercise is measured in MET (metabolic equivalents): 1 MET is the energy spent at rest, 4–6 METs correspond to PA of moderate intensity, >6 METs to activity of vigorous intensity. The target to achieve is a total energy expenditure of ≥500–1,000 METs-minutes per week (Garber et al., 2011). However, the use of MET to calculate exercise intensity can be inaccurate because it does not consider individual factors such as body weight, sex

and fitness level. Therefore, for individual exercise prescription, relative measures of intensity, such as per cent of maximal heart rate (%HRmax) or per cent of maximal oxygen uptake (%VO<sub>2</sub>max), could be more appropriate (Garber et al., 2011). For improving the accuracy of MET, specific cut-off by age can be applied (Garber et al., 2011). For example, for a 55 years old man a PE of moderate intensity corresponds to 4–5.9 METs, 64%–76%HRmax, or 46%–63%VO<sub>2</sub>max (Table 2).

## 7 | CONCLUSIONS

Meta-analyses have shown that physical inactivity is the most important risk factor for ED (Allen & Walter, 2018) and that PA and PE are effective in improving erection (Silva et al., 2017). The protocol mostly prescribed consists in 150–160 min/week of aerobic PA of moderate intensity. Vigorous intensity PA and resistance exercise could represent a valid supplement, as well as pelvic floor muscle-specific exercise (Gerbold et al., 2018; Siegel, 2014). PA is more effective if prescribed together with PDE5i (Silva et al., 2017), drugs that exert little effect on physical performance (Guidetti et al., 2007). Blood testosterone levels are essential for achieving a good physical fitness. In hypogonadal patients, in absence of contraindications, testosterone replacement therapy should be prescribed to maximise individual well-being and performance (Page et al., 2005). Before resuming physical and sexual activity, it is mandatory to evaluate cardiovascular risk: patients with high cardiovascular risk, according to the Princeton Consensus classification, must be first stabilized with appropriate pharmacological treatment (Nehra et al., 2012).

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## CONFLICT OF INTEREST

The authors declare no conflict of interests.

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