

## The Circle of Lifestyle and Erectile Dysfunction

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### ABSTRACT

**Introduction.** Erectile dysfunction (ED) has been significantly associated with many chronic conditions including obesity, the metabolic syndrome, hypogonadism, diabetes mellitus, cardiovascular disease (CVD), lower urinary tract symptoms, and psychiatric/psychological disorders. ED is also a well-established predictor of CVD.

**Aim.** This review will focus on the association of ED with cardiovascular, metabolic, and cognitive conditions and discuss the effects of managing lifestyle factors in order to reduce the burden of ED and consequently outcomes in patients with chronic conditions.

**Methods.** A literature search using Medline, PubMed (U.S. National Library of Medicine and the National Institutes of Health), and abstracts from scientific meetings was performed from 1990.

**Main Outcome Measures.** Main outcome measures were improvements in sexual function.

**Results.** A total of 59 reviews on the topic were evaluated.

**Conclusions.** Targeting several lifestyle factors associated with CVD/metabolic/cognitive disorders, e.g., smoking, alcohol consumption, obesity, and physical activity, can have significant benefits, leading to an improvement in ED as well as testosterone levels and consequently CVD. Kirby M. The circle of lifestyle and erectile dysfunction. *Sex Med Rev* 2015;3:169–182.

**Key Words.** Erectile Dysfunction; Lifestyle; Cardiovascular

### Introduction

Erectile dysfunction (ED) is defined as the inability to attain or maintain a penile erection of sufficient quality to permit satisfactory sexual intercourse. ED affects ~20–50% of men aged 40–70 years [1]. The prevalence is less in younger men. Generally, ED will affect one third of men throughout their lives [2]. Despite the high prevalence, ED is frequently under-recognized and under-diagnosed in clinical practice [3], and opportunities to address adverse risk factors are missed.

ED presents a significant burden to quality of life. Many chronic conditions have been closely associated with ED, including obesity, the metabolic syndrome (METS), hypogonadism, diabetes mellitus (DM), cardiovascular disease (CVD), presence of other genitourinary disease, e.g., lower urinary tract symptoms, and psychiatric/

psychological disorders [4,5]. In an analysis investigating the impact of METS on ED in 107 men, the investigators found that METS could significantly contribute toward ED, suggesting that patients presenting with ED should be evaluated for the presence of METS [6]. CVD, in particular, shares risk factors linked to ED. Most of these conditions are strongly associated with a pro-inflammatory state, resulting in endothelial dysfunction and decrease in the availability and activity of nitric oxide (NO). Decreased vascular NO has been associated with abdominal obesity, smoking, and high intakes of fat and sugar, which all result in oxidative stress, leading to vascular disease [7]. Men with ED have decreased vascular NO as well as circulating and cellular antioxidants, and high levels of superoxide radicals [7]. Aging and poor lifestyle choices are associated with the reduced NO production [7], which in turn may lead to ED [7].

Improving lifestyle habits that modulate the risk factors may have a role in reducing the burden of sexual dysfunction [8]. Targeting several lifestyle factors associated with CVD/metabolic/cognitive disorders, e.g., smoking, alcohol consumption, obesity, and physical activity, can have significant benefits, leading to an improvement in ED as well as testosterone levels [9–14]. Conversely, reducing the burden of sexual dysfunction in men may reduce risk of cardiovascular (CV) events [15]. Phosphodiesterase type 5 inhibitors (PDE5-Is) are licensed for use in idiopathic pulmonary hypertension (sildenafil and tadalafil). In addition, these drugs have shown potential to be of benefit in several other conditions, such as coronary artery disease (CAD) and systolic heart failure [16]. The mechanisms of action through which PDE5-Is probably exert their benefits include pulmonary and systemic vasodilation; increased myocardial contractility; reduced large artery stiffness and wave reflections; improved endothelial function; and reduced apoptosis, fibrosis, and hypertrophy through mechanisms involving NO, cyclic guanosine monophosphate, protein kinase G, and Rho kinase [17]. PDE5-Is have demonstrated reductions in CV morbidity and mortality in diabetic patients with silent CAD and ED in addition to significant reductions in the relative risk CVD incidents among men with ED compared with healthy men [17,18]. This review will focus on the association of ED with CV, metabolic, and cognitive conditions and discuss the effects of managing lifestyle factors in order to reduce the burden of ED and consequently outcomes in patients with chronic conditions.

### Chronic Conditions Associated with ED

#### CVD

ED is common in patients with CVD as well as being an independent risk factor for future CV events in patients with diseases such as diabetes, pre-existing CVD, etc. [2,15,19,20]. Moreover, ED is a predictor of CVD. The symptoms of ED present on average 3–5 years earlier than symptoms of CVD [10,21]. This has been shown in multiple studies. Hodges et al. assessed the temporal relationship between ED and CVD in 207 patients with CVD vs. 165 control subjects [21]. In this study, ED was reported by 66% of individuals with CVD and 37% of the control group, with a mean duration of 5 years for CVD patients and 6.6 years for controls ( $P < 0.05$  for both outcomes), suggesting that ED may precede a CV event by as

much as 5 years. Only 53% of the CVD group and 43% of the control group had discussed their symptoms of ED with a healthcare professional and hence their CVD risk was not assessed. Gupta et al. further confirmed that ED is an early marker of CAD in a meta-analysis, demonstrating an average lead time between manifestation of ED and CAD presentation of 2–5 years [1]. Therefore, men with ED should be specifically targeted for CVD preventive strategies including lifestyle changes.

In men less than 40 years of age, conflicting results have been obtained regarding CV risk. In a Brazilian study of men under 40 years of age, ED was not associated with CV risk factors, but it led to negative impact in men's self-esteem, interpersonal relationships, work and leisure activities, and in sexual life satisfaction [22]. However, a more recent study of 965 men in the United States ( $\geq$ / $<$ 50 years) investigated the association between change in ED status and Framingham CVD risk, as well as change in Framingham risk. This study demonstrated that after taking into account other CVD risk factors, transient and persistent ED is associated with Framingham CVD risk and a greater increase in Framingham risk over time, particularly in younger men [23]. Inman et al. assessed the association between ED, the long-term risk of CAD, and the role of age as a modifier of this association in 1,402 men without known CAD [24]. The results demonstrated that ED in men aged 40–49 years was associated with a 50-fold risk of CAD [24]. These data suggest that ED and CAD may be differing manifestations of a common underlying vascular pathology. Together, current evidence base supports the need for clinical assessment of CVD risk in men presenting with ED regardless of age.

Early intervention in men with sexual dysfunction, who may be at risk of CV disease, will help prevent future events [15]. Lifestyle modification that targets CVD risk factors may also lead to improvement in ED and vice versa. A systematic review evaluating the effect of lifestyle interventions and pharmacotherapy for CV risk factors on the severity of ED demonstrated that lifestyle modifications and pharmacotherapy were associated with statistically significant improvement in sexual function [1].

#### Diabetes

ED affects at least 50% of men with DM [25–27]. Hypogonadism is commonly found in men with diabetes, which must be identified and managed to

prevent progressive ED [28–30]. A case–control survey of 335 men demonstrated that diabetes was associated with doubling the risk of ED [29]. Screening men with type 2 diabetes mellitus (T2DM) for testosterone deficiency has been recommended [28,31].

In addition, ED and diabetes negatively affect male self-esteem and lead to depression and anxiety. Therefore, managing the psychological impact on patients is also likely to be beneficial [30]. ED is also a strong predictor of poor quality of life in men with diabetes [28,32].

The pathologic mechanisms associated with diabetes such as neuropathy, endothelial dysfunction, cavernosal smooth muscle structural/functional changes, and hormonal changes are all involved in the development of ED [25].

### *Hyperlipidemia*

Population-based studies demonstrate that dyslipidemia and obesity are major risk factors for ED [10]. Approximately 26–70% of men with ED have been found to have elevated serum cholesterol levels [26–35]. Indeed, hypercholesterolemia has been found to be an independent predictor of increased ED severity [36]. Moreover, significant improvements in sexual health-related quality of life in men with untreated ED have been observed with 40 mg simvastatin treatment for 6 months [37]. Similar results have been observed with atorvastatin [38]. A recent systematic review has demonstrated that statins are associated with a significant increase in International Index of Erectile Function-5 (IIEF-5) scores, suggesting that modifying lipid levels improves sexual function [39].

In the original Massachusetts Male Aging Study (MMAS), having any degree of ED was inversely related to the high-density lipoprotein levels [40]. Nikoobakht et al. found that mean plasma cholesterol and low-density lipoprotein (LDL) levels in men with ED were significantly higher than controls [41].

Hyperlipidemia probably contributes toward ED through endothelial dysfunction, which interferes with cavernous smooth muscle relaxation. Impairment of endothelium-dependent relaxation in various vascular beds of men with hypercholesterolemia has been well characterized [10,42]. Oxidized LDL along with the production of superoxide radicals, and functional impairment of endothelial NO, are probably the main causes of impaired endothelial relaxation and the development of ED [10,43]. In addition, dyslipidemia pro-

motes atherosclerosis, which is an independent risk factor for development of ED [10].

### *Hypertension*

In addition to dyslipidemia, hypertension significantly correlated with ED in the MMAS [40]. Curkendall and Glasser found that up to 18% of patients seeking treatment for ED from their general practitioner were also suffering from undiagnosed hypertension [44]. The incidence of hypertension among men with ED is approximately 17–25% [45,46]. Generally, ED is twice as frequent in hypertensive vs. normotensive men and appears to be more severe [19].

Hypertension and ED may be markers of generalized vascular disease or vascular dysfunction [15]. Indeed, studies of PDE5-Is have demonstrated beneficial effects of these agents on the reduction of blood pressure [15]. PDE5-Is lead to pulmonary and systemic vasodilation, increased myocardial contractility, reduced large artery stiffness and wave reflections, improved endothelial function, and reduced apoptosis, fibrosis, and hypertrophy through mechanisms involving NO, cyclic guanosine monophosphate, protein kinase G, and Rho kinase [16].

Certain antihypertensive medications have also been shown to contribute toward ED [15]. Thiazide diuretics and beta-blockers (except nebivolol) can adversely influence erectile function, whereas angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blocker (ARB), and calcium channel blockers appear to have no effects on erectile function [15]. PDE5-Is can be safely co-administered with antihypertensive medication to counteract their sexual side effects [19]. Hence, hypertension and its treatment may contribute toward ED, and conversely, ED can contribute toward development of hypertension, emphasizing the importance of holistic assessment and management of ED [15]. The drugs of choice in hypertension for men with ED are generally ARB, as opposed to ACE inhibitors [47,48].

### *Psychological/Psychiatric Factors*

ED is associated with a wide array of psychiatric and psychological symptoms [49,50]. A study evaluating the relationship between ED and different psychopathological symptoms in 1,388 men (mean age 51 years) demonstrated that depressive symptomatology was associated with hypogonadism, the presence of low frequency of intercourse, and hypoactive sexual desire [49]. ED is associated

with psychopathological distresses that can exacerbate ED [48]. Severe ED has been significantly associated with not having a regular sex partner; and worse scores on measures of positive affect, belonging/loneliness, sexual self-efficacy-strength, psychological adjustment, marital happiness, anxiety at last intercourse, and depression [51].

ED has been shown to cause depression, and depression and its treatment can cause ED [51]. A population survey of men aged 40–70 years carried out in Brazil, Italy, Japan, and Malaysia in 1997–1998 showed a prevalence of ~18% of moderate or complete ED in men with depression. Furthermore, depressive symptoms were negatively associated with physical activity [52].

ED is a well-reported side effect of antidepressant medication [53]. Over one third of patients on serotonin reuptake inhibitors (SSRIs) report sexual dysfunction; bupropion (a norepinephrine-dopamine reuptake inhibitor) has been associated with less sexual dysfunction than the SSRIs, sertraline, etc.; reboxetine (a norepinephrine reuptake inhibitor) has been associated with greater sexual satisfaction than the SSRI fluoxetine; moclobemide, a monoamine oxidase inhibitor, has been associated with increased sexual desire compared with the tricyclic antidepressant doxepin [53]. A Cochrane review published in 2013 stated that there is a paucity of randomized trials assessing the effects of switching to currently available antidepressant agents on ED [53]. However, treatment of ED with PDE5-Is has demonstrated significant improvements in self-esteem, confidence, and relationship satisfaction, which has shown moderate to high positive correlations with IIEF scores [53,54]. Furthermore, men who seek help for ED have lower satisfaction with sexual life and lower satisfaction with their overall life compared with healthy people regardless of severity of ED [55]. Treating ED effectively therefore may allow the antidepressant medication to be withdrawn.

The European Male Ageing Study demonstrated that low prolactin is associated with sexual dysfunction and psychological changes together with metabolic disturbances in middle-aged and elderly men [56].

### Lifestyle Risk Factors

#### Obesity

Many studies have linked ED to obesity [55–57]. Overweight and obesity may increase the risk of

ED by 30–90% [58]. Obesity has also been associated with reduced testosterone (T) levels [58].

The nature of the links between these conditions is probably multifactorial and likely to differ between individuals. Increased visceral adiposity is associated with endothelial dysfunction, which is a common feature of ED [59].

The low-grade inflammatory state known to occur in the METS may lead to reduced testosterone synthesis. Between 20–64% of men with diabetes have hypogonadism, with higher prevalence rates found in the elderly. Hypogonadism can be a cause and a consequence of diabetes and the METS [60,61]. Increased visceral fat may contribute toward hypogonadism through activity of the enzyme aromatase, which converts testosterone to estrogen [62], and/or contributes toward the synthesis of the protein leptin, which has been inversely associated with testosterone levels [63,64]. Androgen deficiency promotes the production of fat cells, contributing to obesity and the METS [59], and it also results in impaired glucose metabolism [65]. The reduced testosterone levels associated with obesity and the METS contribute further toward ED [66].

Weight loss after bariatric surgery has demonstrated significant improvements in erectile function (IIEF-5 scores), and increased total testosterone, free testosterone, and reduced prolactin levels [67]. Moreover, in a study of 95 patients undergoing bariatric surgery for weight loss, improvements were observed in sexual drive, erectile function, ejaculatory function, problem assessment, and sexual satisfaction. The amount of weight lost predicted the degree of improvement in all areas of the survey [68].

Weight loss produced by lifestyle interventions has also been associated with an increase in testosterone levels [69]. Weight management is an important factor in maintaining circulating testosterone in aging men. Weight gain has been associated with falls in testosterone levels [70]. The prevalence of low-testosterone levels in obese men varies from 20% to 64% depending on the population and on whether total or free testosterone is being measured [61].

Low testosterone predicts mortality from CVD [71,72]. Therefore, CVD risk factors should be assessed in patients with low testosterone, and testosterone replacement therapy or drugs that stimulate endogenous testosterone production initiated when the diagnosis is appropriately confirmed, in symptomatic hypogonadal patients.

Corona et al. suggest using improvement in sexual function as motivation to reduce weight in obese subjects, thereby reducing their risk of other CV comorbidities and diabetes [58].

### Smoking

A case-control survey of 335 men aged 50–80 years in Canada demonstrated that ED was twice as likely to occur in former smokers and cumulative smoking in pack-years, suggesting a dose-response pattern with the risk of ED [29]. The Health Professionals Follow-Up Study, a large cross-sectional study including 31,742 men, aged 53–90 years, found that smoking was associated with the risk of ED [73]. A further survey of 10,458 men living in Gothenburg, Sweden, in 1992 revealed that smoking most significantly affected the risk of ED along with concomitant medication use [74]. Cao et al. conducted a meta-analysis involving 28,586 participants to evaluate the association between smoking and the risk of ED [75]. The results demonstrated that current smoking significantly increases the risk of ED [75].

Second-hand tobacco use has also been associated with ED [29,76]. The Boston Area Community Health survey assessed 2,301 men, aged 30–79 years, in order to examine the association of active and passive smoking and ED [76]. The results demonstrated a significant trend in increased risk of ED with cumulative pack-years of smoking. In addition, compared with never smokers not exposed to passive smoking, men who never smoked but were exposed to passive smoking had a moderate, statistically non-significant, increase in risk of ED [76].

### Alcohol Abuse/Drug Use

Alcohol consumption has also been associated with increased prevalence of ED [73]. Indeed, alcohol intake has been established as a predictor of ED over 5 years [77]. However, consumption of moderate amounts of alcohol may exert a protective effect on ED in both the general population and in diabetic men [73,78]. An Australian study conducted to examine the association between alcohol consumption and ED found that among current drinkers, the odds for ED were lowest for consumption of between 1 and 20 standard drinks a week [11]. Another meta-analysis demonstrated that consumption of eight or more drinks/week significantly reduced the risk of ED, but consumption of less alcohol (1–7 drinks/week) was not significant [79]. A Chinese study suggested that

alcohol drinking of three or more drinks per week might reduce sexual satisfaction and impair erectile function in current smokers, but not in men who never smoked [80].

### Assessment of ED with Lifestyle Risk Factors

Risk factors for ED include hypertension, diabetes, dyslipidemia, cigarette smoking, METS, and sedentary behavior [1,10,81]. Modifying these risk factors can reduce future CV risk [7]. ED is an independent risk factor for future CVD events; therefore, sexual function should be incorporated into CVD risk assessment for all men. Moreover, CV risk reduction potentially improves sexual function [15,82]. Early diagnosis of ED, CV assessment, and aggressive treatment of CV risk factors might contribute to prevention of acute events [83]. In addition to this, simvastatin has been shown in a 6-month placebo-controlled trial to improve sexual health-related quality of life and reduced LDL cholesterol, thereby reducing future CV risk [37,84].

Initial diagnostic workup should include assessment severity and duration of ED, measuring fasting serum glucose level and lipid panel, thyroid-stimulating hormone test, resting electrocardiogram, morning total testosterone levels, serum creatinine (estimated glomerular filtration rate) and albumin : creatinine ratio, and determination of the presence or absence of the METS [2,85]. Hypogonadism is generally suspected when morning levels for total testosterone are <300 ng/dL, and clinical signs and symptoms typically associated with androgen deficiency are present [31]. Hypogonadism should be particularly considered and assessed for all men especially the ones with T2DM [31].

In patients with ED and CV risk, drugs such as statins, diuretics, etc., can impact on sexual function [15,20]. Therefore, recording full patient history and medication use is important to allow for informed prescribing. Lifestyle changes should be discussed with any man concerned about ED [86].

### Managing Lifestyle Factors Associated with ED

The development of ED is linked to CVD, hypertension, hyperlipidemia, and METS, all of which are largely preventable with an intervention strategy based on lifestyle changes. Modifiable lifestyle risk factors for these conditions and ED include

smoking, lack of physical activity, obesity, and excessive alcohol consumption [87].

### *Lifestyle Changes*

Interventional studies demonstrate that lifestyle modifications for CV risk factors are associated with improvements in ED [1,88]. Indeed, it has been suggested that physicians managing ED should adhere to the same guidelines that are observed in CV medicine [86]. Improved nutrition, weight control, and replacement of any testosterone deficiency will all improve vascular and erectile function [1,7]. A systematic review evaluating the effect of lifestyle interventions and pharmacotherapy for CV risk factors on the severity of ED, in 740 men, demonstrated that lifestyle modifications and pharmacotherapy for CV risk factors were associated with statistically significant improvement in sexual function [1]. These included losing 10% of body weight, eating five fruits and vegetables a day, and smoking cessation. Exercising for 20–30 minutes five times a week demonstrated a significant effect; however, even just 10 minutes of vigorous exercise three times a week demonstrated benefits [1]. Furthermore, CV risk factor reduction improved ED even in men who were initially not responsive to PDE5-Is [1].

A study carried out to analyze the effect of changing lifestyle factors on 209 men with or at risk of ED demonstrated improved erection scores (IIEF-5) in men who were given detailed advice about how to reduce body weight, improve quality of diet, and increase physical activity vs. control group who were given general information about healthy food choices, and general guidance on increasing their level of physical activity [12].

Whether this is practical in everyday general practice is debatable, but the discussion of lifestyle should take place at every consultation and motivational interviewing techniques used to encourage and support the appropriate lifestyle changes. Most patients are aware of the benefits of exercise and a healthy diet. We need to take every opportunity to move them from contemplation to the action phase. Even with the short time we have with the patient, it is our attitude and our commitment toward emphasizing the importance of diet and exercise and the risks associated with inactivity on erectile function that may encourage change. It is a simple and important message, and it should be delivered at every contact with sincerity and in a non-judgmental way.

The mechanisms by which lifestyle interventions affect ED are not clear. For example, weight loss may improve ED through reducing inflammation, increasing serum testosterone levels, and improving mood and self-esteem [89], supporting the concept that the patient should achieve a body mass index (BMI)  $\leq 30$  kg/m<sup>2</sup> [89].

### *Physical Activity*

A meta-analysis of exercise and ED showed that moderate and high physical activities were associated with a lower risk of ED, with odds ratios at 0.63 (95% confidence interval [CI]: 0.43–0.93) and 0.42 (95% CI: 0.22–0.82), respectively [79]. Other studies have also shown that physical activity has a beneficial effect on prevention and/or improvements of ED [72]. In a prospective study of risk factors for ED, the authors found that physical activity was inversely associated with the risk of developing ED during the 14-year follow-up [57]. Another prospective study of men aged 20–80 years demonstrated that low physical activity is a significant predictor for the development of ED [88]. A study of hypertensive patients with ED demonstrated that an 8-week exercise training (duration of 45–60 minutes per day) improved ED compared with sedentary controls [90].

A randomized, open-label study a total of 60 patients with ED on PDE5-I vs. PDE5-I + aerobic exercise for 3 months demonstrated significantly improved IIEF restoration of ED in the aerobic exercise group vs. control group (77.8% vs. 39.3% [ $P < 0.004$ ]) [91]. A study evaluating a standard protocol of 3 months of aerobic physical activity (150 minutes per week) in middle-aged patients with ED demonstrated significantly higher International Index of Erectile Function 5 (IIEF-5) scores in the intervention group compared with controls as well as reduction of apoptotic circulating endothelial progenitor cells (EPCs) and endothelial microparticles [92].

Moreover, exercise has also been associated with better erectile function in men under 40 years old. Hsiao et al. recruited men aged between 18 and 40 years to complete self-administered Paffenbarger Physical Activity Questionnaire and the IIEF. Sedentary lifestyle was associated with significantly increased ED, and increased physical activity was associated with better sexual function in this group of men [93].

Similar results have been seen for men with diabetes. Wing et al. evaluated 1-year changes in erectile function in overweight/obese men with

type 2 diabetes participating in the Look AHEAD (Action for Health in Diabetes) trial [94]. Men were randomized to diabetes support and education or to intensive lifestyle intervention group (active weight loss and exercise group). At 1 year, erectile function improved more in intensive lifestyle intervention group than in the diabetes support and education group vs. baseline levels [92].

A study examined 674 men aged 45–60 years to determine the amount of physical activity needed to maintain erectile function [94]. The men were assessed using physical examination, medical history, testosterone levels, and sex hormone binding globulin. In addition, IIEF-5 and Paffenbarger scores were obtained for these men. The results demonstrated a significant positive correlation between the sexual function and physical activity. The risk of severe ED was decreased by 82.9% for males with physical activity of at least 3,000 kcal/week compared with males with physical activity under 3,000 kcal/week (OR = 0.171,  $P = 0.018$ ) [95].

Physical activity improves ED by improving endothelial dysfunction, through increases in vascular NO [96,97] and decreases in oxidative stress [12]. Exercise and weight loss also increase insulin sensitivity [94]. The increase in EPCs attributed to exercise may further contribute toward preservation of a structurally and functionally intact endothelium [98]. Mild-to-moderate resistance training can provide an effective method for improving muscular strength and endurance, preventing and managing a variety of chronic medical conditions, modifying coronary risk factors, and enhancing psychosocial well-being [99].

There is evidence that pelvic floor muscles (PFMs) maintain erections [97]. An observational study of 122 men with ED who participated in 30-minute sessions of PFM exercises coupled with electrical stimulation demonstrated non-significant improvements of ED with PFM exercises [100]. PFMs exercises also result in an improved erectile function after radical prostatectomy [101].

### Nutrition

A dietary pattern high in fruit, vegetables, nuts, whole grains, and fish, but low in red and processed meat and refined grains, has been associated in subjects without ED in a review summarizing clinical evidence for the role of dietary factors in ED [102]. Omega-3 fatty acids reduce inflammatory markers and increase endothelial NO production [96]. Therefore, these should be consumed by

men with ED, especially if they are at increased risk of serious or even fatal cardiac events [96].

Nutrition is an important factor for the management of ED in men with diabetes [25]. In a survey carried out to evaluate the association between fruit/vegetable consumption and ED among Canadian men with diabetes, a 10% risk reduction of ED was found with each additional daily serving of fruit/vegetable consumed [103]. The effect of 8 weeks of low-calorie diet, using meal replacements (KicStart), was measured on insulin sensitivity, plasma testosterone levels, erectile function, and sexual desire in diabetic vs. non-diabetic men of similar BMI and waist circumference [14]. The results demonstrated that weight loss of ~10% was significantly associated with increased insulin sensitivity, plasma testosterone levels, sexual function, and sexual desire improvement scores, in diabetic as well as non-diabetic men. The degree of weight loss was significantly associated with improvements in plasma testosterone levels and erectile function [14]. Another study evaluated the effects of diet-induced weight loss and maintenance on sexual and endothelial function and inflammatory markers in 31 obese diabetic men over 8 weeks [104]. Both low-calorie and low-fat, high-protein, reduced-carbohydrate diets investigated, improved plasma glucose, LDL levels, sexual function, and sexual desire scores, as well as endothelial function. Inflammatory markers decreased with the high-protein diet, but not the low-calorie diet. At 52 weeks, reductions in weight, and inflammatory markers, were maintained and the sexual function and desire scores improved further [104]. The authors concluded that a high-protein, low-carbohydrate, low-fat diet also reduces systemic inflammation and sustains these beneficial effects for up to 1 year [104].

The Mediterranean-style diet has been associated with a lower prevalence of ED in both diabetic and non-diabetic men [105,106]. In addition, in non-diabetic subjects with METS, 2 years of the Mediterranean-style diet has demonstrated improved endothelial function scores, reduced inflammatory markers as well as significantly improved erectile function [107]. Components of the Mediterranean diet are shown in Table 1 [108,109].

Furthermore, the Mediterranean-style diet has demonstrated significant reduction of the risk for CVD [110–112]. The Mediterranean diet reduces ED and CVD risk through its beneficial effect on endothelial dysfunction [113]. Adherence to

**Table 1** Mediterranean diet [108,109]

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There are several variants of the Mediterranean diet, but some common components can be identified:

- High monounsaturated/saturated fat ratio
- Ethanol consumption at moderate levels and mainly in the form of wine
- High consumption of vegetables, fruits, legumes, and grains
- Moderate consumption of milk and dairy products, mostly in the form of cheese
- Low consumption of meat and meat products
- Moderate to high consumption of fish

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the Mediterranean diet has also been associated with lower all-cause and disease-specific survival in men with chronic conditions [102]. In clinical trials, Mediterranean diet was more effective than a control diet in improving ED or restoring absent ED in men with obesity or METS [102].

A systematic review and meta-analysis of trials on the effect of body weight loss on sex hormone levels revealed that low-calorie diet is associated with a significant ( $P < 0.0001$ ) increase in plasma total testosterone levels. Multiple regression analysis showed that the degree of body weight loss was the best determinant of total testosterone rise [69].

Antioxidants, such as omega-3 fatty acids, increase vascular NO and improve vascular and erectile function and are especially important in men with ED who smoke, are obese, or have diabetes [96]. The use of folic acid with PDE5-Is has demonstrated improvements in sexual function of diabetic patients with ED [114].

### Smoking Cessation

Stopping cigarette smoking can improve ED in a considerable proportion of smokers [115]. An 8-week smoking cessation program of 65 men showed that successful quitters ( $n = 20$ ), compared with those who relapsed ( $n = 45$ ), showed enhanced erectile tumescence responses and faster onset to reach maximum subjective sexual arousal [115]. In a prospective study, the ED status between patients who stopped smoking after nicotine replacement treatment and those who continued was compared before and after a 1-year follow-up [116]. At baseline, the severity of ED correlated significantly with the level of exposure to smoking. After 1 year, the ex-smokers had a significantly better ED status than current smokers ( $P = 0.009$ ). Among ex-smokers, patients with advanced ED and those who were older had less improvement [116].

### Alcohol Intake Management

Alcohol has long been regarded as a risk factor ED, and although excess alcohol consumption should undoubtedly be avoided for various health reasons, light or moderate alcohol consumption may actually have beneficial effects on erectile function. The association between usual alcohol consumption and ED was assessed via data obtained from an Australian population-based cross-sectional study of men's health [11]. As compared with never-drinkers, the age-adjusted odds of ED were lower in current, weekend, and binge drinkers and higher in ex-drinkers. Regarding current drinkers, the odds were lowest for consumption within the National Health and Research Council (NHMRC) guidelines of between 1 and 20 standard drinks a week. After further adjustment for CVD or cigarette smoking, the age-adjusted odds of ED were reduced by 25–30% among alcohol drinkers. This suggests a modest negative association between alcohol consumption and ED and confounding of the association by CVD and cigarette smoking. The study authors concluded that these results provide no justification for advising men with ED whose drinking habits are consistent with the Australian NHMRC guidelines to cease or reduce their consumption of alcohol [11].

### Psychological Management

The American Heart Association and the European Society of Cardiology (ESC) Council on Cardiovascular Nursing and Allied Professions recommend routine assessment of sexual problems and sexual counselling as part of effective management by physicians, nurses, and other health-care providers for patients who have had a CVD event [117].

Sexual dysfunction induced by antidepressant medication is generally managed by adding PDE5-Is; however, there is no evidence so far of managing ED in these patients using lifestyle factors [118]. Two systematic reviews have demonstrated evidence for group therapy to improve ED [119,120]. Treatment response can vary between patient subgroups, but focused sex-group therapy has shown greater efficacy than control groups (no treatment). In addition, psychotherapy plus PDE5-Is has shown significant improvements in ED and compliance with PDE5-I use vs. PDE5-I alone [120]. Obsessive-compulsive dimension, depression, anxiety, and psychoticism have all been improved significantly with PDE5-Is [121]. In a meta-analysis that compared group therapy plus



sildenafil citrate vs. sildenafil, men randomized to receive group therapy plus sildenafil showed significant improvement of successful intercourse and were less likely to drop out than those receiving only sildenafil [120].

Psychological and sexual counselling is also of major importance in order to improve erectile function in individuals after surgery for pelvic cancers [122].

### Testosterone Replacement

Testosterone replacement therapy has demonstrated improvements in the METS, mood, and sexual function, suggesting that testosterone therapy in hypogonadal men may be a powerful tool in reducing the risk associated with cardio-metabolic diseases [123].

Testosterone replacement has been associated with improvements in IIEF and patient reported quality of life in patients with diabetes as well as improvements in insulin resistance, total and LDL-cholesterol levels, lipoprotein a, weight, BMI, and waist circumference [124–126]. In one study, the improvements were mostly marked in less obese patient and those without coexisting depression [123]. Data also suggest that the improvements may be dependent on baseline tes-

tosterone levels, i.e., there are threshold levels for response to testosterone replacement therapy [124]. Furthermore, addition of testosterone to PDE5-I regimen has been associated with benefits in terms of response to PDE5-I treatment, with significant changes in hypogonadal men with low baseline T levels  $\leq 3$  ng/mL [127].

Hypogonadism should always be sought in men failing to respond to PDE5-I therapy and should be a routine screening test for all men with ED.

### Recommendations

The European Association of Urology (EAU) recommends routine laboratory tests, including glucose-lipid profile and total testosterone to identify and treat any reversible risk factors and modifiable lifestyle factors [126]. The EAU further recommend “lifestyle changes and risk factor modification must precede or accompany ED treatment” and has classified the level of evidence for this recommendation as 1b with a Grade A [128].

Table 2 provides a set of recommendations for a holistic approach to management of men with ED. Improved antioxidant status through diet and/or

**Table 2** Recommendations for managing lifestyle factors in men with ED

#### Recommendations for the holistic management of ED

##### Assessment

Assessment of ED severity and duration

Assessment of fasting plasma glucose, lipids, blood pressure, resting electrocardiogram, thyroid-stimulating hormone test, morning total testosterone levels, serum creatinine (estimated glomerular filtration rate) and albumin : creatinine ratio, and determine the presence or absence of the features of the metabolic syndrome

Evaluation of any underlying risk factors, e.g., cholesterol levels, insulin resistance, hypertension, blood glucose or HbA1c, and exclude any end organ damage

Monitor and manage any comorbidities, e.g., CVD, diabetes, hypertension, and hypogonadism with appropriate medical therapy

Full patient history, current medication use, and use of medications that may interfere with erectile function (recommend to avoid these)

##### Testosterone levels

Replacement of testosterone deficiency if hypogonadism confirmed appropriately

##### Nutrition

Adequate intake of omega-3 fatty acids, antioxidants, calcium, and folic acid and other important nutrients through a healthy diet

The strongest evidence is for Mediterranean diet.

High-protein, low-carbohydrate, low-fat diet have been associated with an improvement of erectile dysfunction and CV risk factors by promoting weight loss

##### Physical exercise

Ideally daily, but advised to exercise 20–30 minutes five times a week and advised 45–60 minutes in patients with pre-existing CVD risk factors such as diabetes and hypertension. The aim should be to achieve at least 150 minutes/week. The combination of resistance and aerobic exercise is beneficial

Pelvic floor muscle exercises

##### Weight loss

Recommend losing at least ~10% of body weight, if overweight

##### Smoking

Advise smoking cessation support for all smokers

##### Alcohol intake

Alcohol intake should be moderate—Between 1–20 standard drinks/week; if intake is moderate, there is no need to adjust unless weight loss is needed. Excessive alcohol intake should be avoided

CV = cardiovascular; CVD = cardiovascular disease; ED = erectile dysfunction.

supplements should be integrated into any comprehensive approach for maximizing erectile function [96].

## Conclusions

In conclusion, first-line therapy for ED should consist of lifestyle changes. ED predicts future CV events; hence, its presentation provides the clinician with an opportunity to proactively assess and minimize CV risk. The emergence of evidence supporting the association between CVD, ED, and psychological disorders emphasizes the importance of a holistic approach, which may optimize management of these conditions. Lifestyle factors can impact erectile function, testosterone levels as well as future risk of CVD. Adoption of a healthy lifestyle should be actively encouraged by health-care professionals to patients with ED.

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