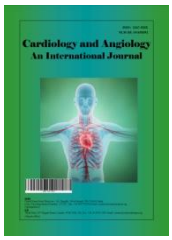

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The Role of Diet in the Pathogenesis of Erectile Dysfunction

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Authors' contributions

The sole author designed, analysed, interpreted and prepared the manuscript.

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ABSTRACT

Erectile dysfunction (ED), characterized by a man's constant or recurrent disability to obtain and/or maintain penile erection sufficient to achieve and complete satisfactory sexual intercourse, is a common ailment. Its incidence and prevalence increases with age. ED is caused by several factors -psychological factors, organic factors, and metabolic factors. ED may also be iatrogenic and related to some drugs, pelvic surgery, or radiotherapy. The main etiology is vascular in nature, with risk factors that are common to other cardiovascular diseases. Several drugs, mechanical and prosthetic devices, and surgical procedures are used to alleviate ED. Lifestyle modulation is increasingly being added as first-line treatments for ED. These include lack of physical activity and cigarette smoking. Obesity and an unhealthy quality of diet are also lifestyles that affect ED. This manuscript narratively reviews the impact of excessive caloric intake, various dietary ingredients, and special diets on ED.

Keywords: Erectile dysfunction; diet; cardiovascular disease; plant-based diet; alcohol; dietary macronutrients; dietary micronutrients.

1. INTRODUCTION

Erectile dysfunction (ED) is defined as man's constant or recurrent disability to obtain and/or maintain penile erection sufficient to achieve and complete satisfactory sexual intercourse (Fourth International Consultation on Sexual Medicine) [1]. It is a common disease [2]. It is expected to affect over 322 million men globally by 2025 [3]. Its incidence and prevalence increases with age -

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ED affects >50% of the elderly men [4]. ED is often accompanied by comorbid conditions such as diabetes mellitus (T2DM), hypertension (HTN), hypercholesterolemia, and obesity [5]. ED is twice as common in men with metabolic syndrome [6]. Anywhere from 20–85% of diabetic patients also have ED [7]. In addition, Wang et al. reported that hypertension was associated with an increased risk of ED (summary OR = 1.58) [8]. Its risk factors (hypertension, obesity, and smoking) are common with other cardiovascular disease (CVD) [9], especially coronary artery disease (CAD). and ED is an independent predictor of CVD events [10]. The reverse is also true – patients with CAD often have ED [11].

The severity of erectile dysfunction is often described as mild, moderate, or severe according to the five-item International Index of Erectile Function (IIEF) questionnaire, with a score of 1–7 indicating severe, 8–11 moderate, 12–16 mild–moderate, 17–21 mild and 22–25 no erectile dysfunction [12]. ED may be caused by psychological factor (absence of sexual education, phobias, and presence of situational factors), organic factors (vascular such as atherosclerosis, venous insufficiency), neurological factors (such as stroke, spinal cord injuries, herniated disc), and metabolic factors (such as diabetes mellitus, hypogonadism, hyperprolactinemia). ED may also be iatrogenic and may be caused by some drugs (antidepressants, tranquilizers, non-selective b-blockers, antiandrogens), pelvic organ surgery or radiotherapy [13]. Almost 85% of men suffer from ED after invasive urological procedures, such as radical prostatectomy [14]. A plethora of evidence now clearly indicates that the predominant cause of ED seen in clinical practice is vascular [15,16].

ED is usually treated with oral, (including phosphodiesterase type 5 inhibitors such as sildenafil, vardenafil, and tadalafil; apomorphine; and synthetic prostaglandin E1 (alprostadil), phentolamine, and papaverine intraurethral. It may also be treated with intra-cavernosal medications, vacuum devices, or penile prosthesis [17,18]. Injection of stem cells or platelet-rich plasma is also being used, mainly experimentally [19]. Herbal treatment (Panax ginseng, Pygnogenol, Prelox and Tribulus terrestris) has also been tried but adequate human experiments documenting efficacy and safety are lacking [20]. Lifestyle changes can prevent progression or improve regression of ED and is increasingly being added as first-line treatment for ED [21]. Deleterious lifestyles include lack of physical activity, obesity, unhealthy diets, and cigarette smoking. Erectile dysfunction results in a reduced self-esteem, psychological frustration, poor quality of life, and stress [22,23]. Although not a killer disease, ED is a marker of increased risk of CVD, and all-cause mortality [24].

2. DISCUSSION

Lifestyle modification help improve ED [21,25-27]. A systematic review of 6 randomized controlled trials demonstrated beneficial effects of lifestyle interventions on erectile function after follow-up of 2–24 months [28]. Lifestyles such as physical activity help prevent and improve ED [29]. Cigarette smoking increases the risk of erectile dysfunction (Odds Ratio=1.4) [30] and smoking cessation helps reduce the risk [31]. Similarly, in a large study of 31,724 men who were free of ED at baseline, a 40% increased risk of ED was noted with the development of obesity [32]. Both weight loss and a healthy diet have been associated with improvements in erectile function [33]. The European Association of Urology states that “lifestyle changes and risk factor modification must precede or accompany any erectile dysfunction treatment” [34].

3. OBESITY

Obesity is significantly related to the development of ED [32,35-37]. Obesity was found to increase the likelihood of acquiring ED by 40% in the Health Professionals Follow-up Study in the United States, which included 31,724 men who were free of ED at the start [32]. Overweight or obese men had a higher risk of having ED (70 percent–96 percent higher) than normal weight men, according to prospective studies with follow-up ranging from 5 to 25 years [35-37]. Moreover, the severity of ED has been shown to be correlated with comorbid obesity, and the presence of the latter results in a reduced responsiveness to phosphodiesterase 5 (PDE5) inhibitors [38]. In another study, 79 percent of males with ED had a BMI of 25 kg/m^2 or higher, and obese men with a BMI of over 30 kg/m2 were three times more likely than the general population to have sexual dysfunction [39]. Furthermore, obese individuals' ED is more severe than non-obese patients', leading in a higher rate of PDE5 inhibitor refractoriness in severely obese patients [40]. According to a meta-analysis, the overall refractory rate for

sildenafil, tadalafil, and vardenafil is 30% to 35%, which drops to less than 20% when comorbid problems are improved [41]. Weight reduction with bariatric surgery significantly improves ED in obese men [42]. An animal study demonstrated that bariatric surgery improves glucose tolerance and elevates intra-cavernosal pressure and endothelial nitric oxide synthase and nervous nitric oxide synthase expressions in Otsuka Long-Evans Tokushima fatty rats [43]. Moreover, Kun et al. observed that gastric bypass surgery decreases serum cholesterol and triglycerides levels and carvernosal intima-media thickness and increases endothelial function score in a human study [44].

Diet influences obesity [45]. Obesity is defined by body mass index (BMI). A normal BMI is between 18.5 kg/m² to 24.9 kg/m². A BMI of 25 kg/m² to 29,9 kg/m² is considered overweight, while at or >30 kg/m² is diagnosed as obese [46]. The 10-y odds of ED was 2.0 comparing men with a BMI ≥28 with men with a BMI <28 at baseline [47]. A 2016 data showed that the RR of ED for obese men (BMI ≥30) was almost twice that of men with an ideal BMI (<25) (RR = 1.9) [48]. Obesity results in higher levels of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-6 [49]. Obese individuals have more reactive oxygen species, increased insulin resistance, and this reduces vascular nitric oxice (NO), resulting in endothelial dysfunction [50,51]. Obesity is also associated with low-testosterone levels has been established in healthy men [52].

Measures indicating abdominal adiposity have been suggested as being superior to BMI when evaluating ED risk [53]. Fillo et al observed that men with abdominal obesity had a higher incidence rate of ED and the incidence rate was elevated in proportion to the degree of obesity [54]. Abdominal obesity is ascertained by several anthropometric measurements [55-57]. Waist circumference (WC) should ideally be <102 cm in males and <88 cm in females when measured to the nearest 0.1 cm at the umbilical level in a standing position [55].The waist-hip ratio is normally 0.85 or less for women and 0.9 or less for men [56]. Less commonly used is the waist-height ratio – this is calculated by dividing the WC by height. A ratio > 0.5 is consistent with central obesity [57]. In a study from Slovakia, 73% of men older than 40-years-old with abdominal obesity had some degree of ED [58]. Visceral adipose tissue is more metabolically active than peripheral subcutaneous fat. It is often associated with decreased glucose tolerance, reduced insulin sensitivity and adverse lipid profiles. It is associated with more inflammation, reduced testosterone levels and worse endothelial function [59]. Weight loss helps60. Patients can avoid or alleviate ED include, by reducing weight (5%–10%) or achieving a BMI ≤ 30 kg m2 [60]. In 110 obese men without diabetes, hypertension or dyslipidemia, ED was strongly correlated with waist/hip ratio and was significantly improved with weight loss and increased activity, which lowered glucose, insulin, waist/hip ratio, blood pressure and triglycerides, and increased endothelial NO production [61]. Another study in obese men, also showed that weight loss induced by diet and vigorous activity resulted in increased insulin sensitivity and reduced circulating insulin, and this was strongly associated with increased NO production [62].

4. FRUITS AND VEGETABLES

Growing evidence suggests that higher dietary flavonoid consumption improves endothelial function and blood pressure [63-65], suggesting that flavonoids are more likely than other dietary variables to improve erectile performance. Flavonoids are anti-inflammatory compounds found in a variety of plant-based foods and drinks, including fruit, vegetables, tea, herbs, and wine [66,67]. They inhibit LDL oxidation and endothelial NADPH oxidase, modify endothelial nitric oxide synthase activity, and increase NO status [68]. The beneficial effects on ED were confirmed by Wang et al. who found that there was a 10% risk reduction with each additional daily serving of fruit/vegetable consumed [69]. Fruits and vegetables are rich in antioxidants [70]. Antioxidants play an important role in modulating intra-cavernosal blood flow, and smooth muscle relaxation [71]. Zhang et al. that antioxidants improve ED by protection of NO bioavailability [72].

5. WHOLE GRAINS/FIBER/NUTS

The benefits of intake of whole grains and nuts is derived from the benefits of Mediterranean diet on ED. In one study, intake of 100 g pistachio nuts for 3 weeks resulted in an improvement in the IIEF-15 score (International Index of Erectile Function (IIEF) Questionnaire) [73]. The IIEF-15 evaluates erectile dysfunction and treatment outcomes in clinical trials. Mean IIEF-15 score was 36 ± 7.5 before the diet and 54.2 ± 4.9 after the diet Mean peak systolic velocity values

before and after the pistachio diet were 35.5 ± 15.2 and 43.3 ± 12.4 cm, respectively [74]. This study further supports the beneficial role of nuts in ED.

6. FISH

Research has revealed that omega-3fatty acids exert beneficial effects in the development and progression of atherosclerosis [75]. Fish is a good source of omega 3 polyunsaturated fats (PUFA), namely eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [76]. In a review, Zher et al. found that n-3 PUFA supplementation successfully improved endothelial dysfunction in individuals with traditional risk factors for atherosclerotic CV disease [77]. Endothelial dysfunction plays an important role in the pathogenesis of ED [78]. In an erectile dysfunction rat model, omega 3 fatty acids improved intra-cavernosal pressure [79]. Omega 3 fatty acids in a dose of 500–1000 mg taken daily by men under age 60 years has been suggested to help improve ED [80,81]. The direct association between fish intake and ED is still not specifically been studied.

7. COFFEE/TEA/CHOCOLATE

Coffee is high in caffeine, antioxidants, and anti-inflammatory substances, and it has been linked to a reduction in the risk of chronic diseases [82,83]. Benefits have also been noted in patients with ED [84]. In a cross-sectional analysis using the National Health and Nutrition and Examination Survey from 2001–2004, a nationally representative sample of the US noninstitutionalized male population (3724 men (≥20 years old), the equivalent of 2–3 cups of coffee per day was associated with a lower likelihood of ED [85]. Coffee is rich is polyphenols and may also increase testosterone levels [86-88]. The result may be relaxation of the cavernous smooth muscle and improved blood flow through penile arteries [89]. However, in the Health Professionals Follow-Up Study, (a prospective analysis of 21,403 men aged 40–75 years old) followed for 10 years with a 34% rate of patients with incident ED (n = 7,298), did not support an association between coffee and ED [90]. Tea is known to increase NO and has beneficial effects in coronary artery disease [91,92]. In animal studies, there is reduction in atherosclerotic progression in cavernous tissue in aged rats following chronic ingestion of catechin-rich beverages like green tea [93]. ED is associated with reduced NO production in the systemic vasculature. NO is a powerful indicator of flow mediated dilation (FMD). A decreased FMD is associated with erectile dysfunction [94]. Chocolate consumption improves FMD. Ingestion of chocolate with 55% cocoa, improves FMD [95]. Dark chocolate intake (with low sugar content) should therefore be beneficial in ED patients.

8. ALCOHOL

Alcohol and its relationship with cardiovascular diseases is well known [96-98]. A similar relationship exists between alcohol intake and ED. Cheng et al reported in a meta-analysis that one or two alcoholic drinks daily appears to reduce ED (Odds Ratio or OR=0.79) [99]. In a subsequent meta-analysis of 24 studies (154,295 patients), Wang et al. also found that light to moderate alcohol consumption (<21 drinks/week) was associated with a decreased risk of erectile dysfunction (OR = 0.71) [100]. However, regular (ever vs. never) and high alcohol consumption (>21 drinks/week) had no significant influence on the prevalence of ED (regular: OR = 0.87; high: OR = 0.99) [100]. In laboratory animals [101], moderate alcohol enhances vascular NO, but severe alcohol lowers vascular NO and produces structural changes in the mouse penile endothelium [102,103]. Overall, the little evidence suggests that alcohol use should be limited to mild to moderate levels (one to two drinks per day), which have been proven to prevent ED in a recent meta-analysis.

9. RED MEAT/SATURATED AND UNSATURATED FAT

There are no direct studies associating red meat or saturated fat intake with ED. However, given that a high fat meal increases inflammation, decreases vascular NO, increases oxidative stress, and decreases FMD, it may tend to promote atherosclerosis and ED [104-106].

10. VITAMINS/MICRONUTRIENTS

The role of several vitamins and minerals have been studied in the pathogenesis of ED. The relationship between vitamin D levels and ED has been frequently questioned [107,108]. A recent meta-analysis found no evidence of a strong link between vitamin D and the likelihood of developing ED [109].

Folic acid deficiency and/or supplementation may influence ED. In a meta-analysis (6 studies with

982 ED patients and 860 healthy subjects) Zhang et al. demonstrated that folic acid deficiency was an independent risk factor for ED [110]. Their work also suggested that folic acid supplement may have potentially positive effects in the treatment of ED patients. In another study, ED in diabetic patients treated with the combination of tadalafil and folic acid 5 mg improved significantly as compared with the placebo group [111]. The degree of folic acid deficiency may reflect the severity of ED [112]. It appears to be more commonly seen in younger individuals [112]. This association may be mediated by homocysteine and higher than usual doses of folic acid may be necessary to normalize serum homocysteine levels [113]. Some other minerals and vitamins deserve mention. Calcium supplementation causes a small but significant decrease of blood pressure, the effect being greater in individuals with insufficient dietary intake [114]. Vitamin E is an antioxidant and increases the circulating levels of vitamin C [115] and both may be beneficial in ED patients. L-Arginine in a large dose (5 g per day) has been reported to have some benefit on ED [116].

11. SPECIAL DIETS

Dietary patterns that emphasise whole grains, legumes, vegetables, and fruits while limiting red meat, full-fat dairy products, and sugar-sweetened meals and beverages are linked to a lower risk of ED [117]. The prime example, and probably the most studies, is the Mediterranean diet (MedD). This diet refers to a traditional dietary pattern of people residing around the Mediterranean Sea (Greece, Crete, and Southern Italy) and is regarded as one of the healthiest diets [118]. The MedD is characterized by a high intake of fruits, vegetables, legumes, monounsaturated fatty acids (essentially extra virgin olive oil), a moderate intake of fish and wine, and a low intake of red meat [119]. It is associated with higher levels of omega-3's, folic acid, antioxidants, and anti-inflammatory ingredients [120]. MedD has a beneficial role on erectile function, both diabetic and non-diabetic men [121,122]. Men on a Mediterranean diet consumed more fruits, vegetables, nuts, whole grain, and olive oil after two years than men on a control diet [123], according to Esposito et al. IIEF score increased up to 22 in 13 men in the intervention group and only in 2 men in the control group [123]. Several other studies have replicated the benefits in ED by adhering to a MedD [124-126]. These advantages on atherosclerosis in general and ED in particular can be mediated through a variety of biological processes, including a reduction in oxidative stress, inflammation, endothelial dysfunction, and insulin sensitivity, all of which contribute to increased NO release in the penis arteries [127].

12. CONCLUSION

Most patients with ED share similar risk factors that exist for coronary artery disease [128-131]. They often have asymptomatic coronary artery stenosis [132]. The reverse is also true - the prevalence of ED is relatively high in patients with CAD [133]. The number of studies involved in clarifying the relationship of several dietary ingredients are sparce. However, it is increasingly clear that plant-based diets, such as the Mediterranean diet, are vascular friendly [122,123]. They help reduce the risk of ED and help mitigate its progression. The mechanisms include amelioration of insulin resistance, low grade inflammation and endothelial dysfunction [134].

COMPETING INTERESTS

Author has declared that no competing interests exist.

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