Erectile dysfunction therapy in countries where implant is economically not feasible

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Abstract: Erectile dysfunction (ED), a frequent complaint in the primary care setting, is strongly associated with obesity, cigarette smoking and other common cardiovascular risk factors like hypertension, diabetes mellitus (DM), lipid disorders and the metabolic syndrome. The prevalence of these cardiovascular disorders is rising at staggering rates in most Latin American countries. ED is a symptom that mainly affects economically productive men (40–70 years of age) potentially causing major psychosocial repercussions and reduced quality of life. The management of ED in these developing countries is increasingly challenging due to poor patient education and non-adherence to the medical treatment of theses concomitant comorbidities. The financial implications of commonly prescribed medications and surgical procedures limit their use to a minority of patients. For this reason, the clinician must adopt a holistic approach in the management of this disease focusing on preventive measures based on patient education and non-surgical interventions. This review summarizes common associated risk factors of ED and outlines non-pharmacological interventions for the management of this disease.

Keywords: Erectile dysfunction (ED); non-pharmacologic treatment; lifestyle modification

Introduction

Erectile dysfunction (ED), a common complaint of male sexual medicine, is defined as the inability to attain and/or maintain an adequate penile erection for successful sexual intercourse (1). It is estimated, that by 2025 the worldwide prevalence of ED will be of approximately 322 million patients, with the largest projected increase being in the developing world (2). ED is classified as psychogenic and/or organic, the latter being responsible for over 80% of cases and it is divided into endocrine and non-endocrine etiologies (3). Age is the most important risk factor for ED. Data from two key epidemiological studies report a prevalence of mild to moderate ED in 30–52% of men aged 40–79 years (4,5). There is a clear association between vasculogenic ED, the leading cause of this disease, and other cardiovascular risk factors. Recent data has linked ED with endothelial dysfunction and cardiovascular disease (CVD); additionally, an Asian study even proposed that it should be considered a surrogate marker for coronary artery disease (CAD) in young patients (6).

The most important risk factors reported in a European cross-sectional study of 2,869 consecutive men were age (>50 years, OR 1.7–3.32), physical activity (OR 1.35), psychological stress (OR 1.68), hypertension (OR 2.05), diabetes mellitus (DM) (OR 3.0), hyperlipidemia (OR 2.29) and lower urinary tract symptoms (OR 2.2) (7). Social (partner availability) and psychogenic factors appear to play an important role in ED in younger patients (<40 years of age) (8).

The aim of this review is to discuss the non-surgical

management of ED with a focus on risk factor assessment and lifestyle modification.

Obesity

Obesity is a major global public health concern with colossal economic implications. It is estimated that at least 1 billion people worldwide are overweight or obese and current epidemiological trends indicate that the prevalence of this disease is increasing at an alarming rate in Latin American countries (9,10). In 2010, 68% of the Mexican male population was estimated to be overweight or obese and this rate is expected to increase to 88% by 2050 (11). Obesity is associated with arteriosclerosis and endothelial dysfunction as well as elevated cholesterol and a pro-inflammatory state which results in a decrease in the availability and activity of nitric oxide (NO) (12,13). Furthermore, obesity is also associated with reduced circulating testosterone levels and the metabolic syndrome (insulin resistance and endothelial dysfunction) leading to an increased prevalence of ED in this population (13). Data from prospective observational studies report that overweight to obese individuals have an increased risk of ED (OR 1.4–2.46) (13). A cross-sectional study of 256 consecutive patients with ED in Brazil demonstrated that central obesity was associated with the presence of ED in men older than 60 years. The presence of any of the following commonly used anthropometric indicators was independently associated with the presence of ED: waist-hip index >0.91 (OR 8.56, 95% CI: 1.44–50.73) and waist circumference >102 cm (OR 19.37, 95% CI: 1.15–326.55) (14).

DM

DM, mainly type 2 DM, is a systemic disease associated with a wide array of chronic micro and macrovascular complications that generate a major economic burden. The global prevalence of diabetes is increasing and the total number of people with diabetes worldwide is projected to rise from 171 million in the year 2000 to 366 million in 2030 (15). The estimated prevalence in Latin American countries is expected to increase by 56% (over 32 million individuals) (15). Genitourinary complaints, primarily ED, are common, have an earlier onset and are more severe in this population (16). These are mainly related to chronic vasculopathy or neuropathy. However, hypogonadism is more common in diabetics and it may also contribute to ED by several mechanisms, such as decreased libido, fatigue,

mood swings, decreased body and bone mass (17). Men with DM are 3 times more likely to report ED than non-diabetics with a reported prevalence that ranges from 25–75% (18,19). In addition, men with type 1 DM (RR =3, 95% CI: 1.5–5.9) have a significantly higher risk than men with type 2 DM (RR =1.3, 95% CI: 1.1–1.5) and non-diabetic men (18). Moreover, disease onset also occurs up to 15 years earlier compared with non-diabetic subjects (20).

Risk factors for ED in men with diabetes include: age (>50 years), smoking, younger age at diagnosis, poor glycemic control, drug use (antihypertensives and/or hormones), and the presence of late complications (neuropathy and vasculopathy) (19). There is also increased risk of ED with regard to the pharmacological treatment of diabetes: oral hypoglycemic agents (OR 2.14, 95% CI: 1.87–2.46), insulin use (OR 3.07, 95% CI: 3.13–4.40) and both oral hypoglycemic agents and insulin (OR 4.14, 95% CI: 3.42–5.02) (19).

CVD, hypertension and smoking

A strong association between ED and CVD has been well established in epidemiological studies. It has similar predictive value than traditional CVD risk factors, including family history and is now considered an independent marker for overall coronary heart disease (RR 1.46, 95% CI: 1.31–1.63, P<0.001), stroke (RR 1.35, 95% CI: 1.19–1.54, P<0.001) and all-cause mortality (RR 1.19, 95% CI: 1.05–1.34, P=0.005) (21). This association naturally occurs because these two conditions share common cardiovascular risk factors and essentially the same pathophysiology. The lifetime risk of atherosclerotic CVD in men over 50 years of age is greater than 50% (22). ED has been identified as a sentinel symptom of men with subclinical or occult vascular disease and this can be explained by the "artery size" hypothesis; the smaller penile atherosclerotic arteries (1–2 mm diameter) are obstructed earlier than the larger coronary arteries (3–4 mm diameter) (23). For this reason, ED is now considered a harbinger of CAD; the time interval between the onset of ED and the occurrence of symptomatic CAD or a CVD event is 2–3 years and 3–5 years, respectively (24). An estimated 1.5 billion people are expected to suffer from hypertension worldwide and ED is twice as common in hypertensive patients compared to normal subjects (25). The prevalence of this disorder has increased to 30% in Mexico and it is responsible for

14% ($1.8 billion) of the countries total annual healthcare expenditure (26). Antihypertensive therapy (mainly thiazide diuretics, aldosterone antagonists and β-blockers) is also associated with this disorder and a detailed medical history should rule them out. Angiotensin receptor blockers (ARBs) potentially enhance erectile function and are considered first line treatment in men with hypertension and concomitant ED (25). PDE-5 inhibitors are safe and effective in these patients even with simultaneous multidrug antihypertensive therapy. However they are contraindicated in patients treated with short or long acting nitrates and caution is advised with simultaneous alpha-blocking agents (orthostatic hypertension) (27).

Smoking

Cigarette smoking is the leading preventable cause of mortality in the world causing an estimated 6 million deaths per year. The global number of smokers is expected to increase by 10% to 872 million by 2030 and data from the WHO suggest that nearly 80% of active smokers live in low and middle-income countries (28). It is considered an independent risk factor for atherosclerosis and CVD and it has been linked with ED in large epidemiological studies (4,5,29). Pooled data from a meta-analysis of 3819 impotent men revealed that impotent men were more likely to be smokers than men in the general population (40% *vs.* 28%, P<0.05) (30). An Italian cross sectional study of 2010 men observed that current smokers (OR 1.7, 95% CI: 1.2–2.4) and ex-smokers (OR 1.6, 95% CI: 1.1–2.3) were more likely to have ED than non smokers and that this association was present even without a history of other CVDs (31). Condra *et al.* observed that mean penile blood pressure was abnormally low among smokers (20.9%) when compared with non-smokers (8.8%) and suggested that cigarette smoking was a significant risk factor for ED (32). Furthermore, this habit appears to amplify the risk in patients with other cardiovascular disorders. This risk has also been found to be dose-dependent and that among ex-smokers the risk decreases with increasing number of years of tobacco cessation (33). Smoking affects sexual function by multiple mechanisms: centrally (by neuroregulatory effects in the CNS) (34), peripherally (chronic sympathetic activation and heart rate variability) (35) and biochemically (by impairment of NO synthesis and endothelium dependent smooth muscle relaxation) (36).

Management

ED is now considered an early clinical sign of a systemic CVD in young men. As such, the attending clinician must adopt a holistic approach in the treatment of these patients. Management should include an adequate treatment of non-modifiable risk factors (mainly, hypertension, dyslipidemia and diabetes) and the adoption of a healthy lifestyle (smoking cessation, weight loss, physical activity, and an appropriate diet). A large prospective study of risk factors for ED that included 22,086 subjects in the United States during a 14 year follow-up found that obesity (RR 1.9, 95% CI: 1.6–2.2) and smoking (RR 1.5, 95% CI: 1.3–1.7) were associated with increased risk of ED while physical activity (RR 0.7, 95% CI: 0.7–0.8) had a protective effect (37). Gupta *et al.* demonstrated that lifestyle modification and an adequate treatment of cardiovascular risk factors was associate with improvement in sexual function (measured by IIEF-5 scores): weighted mean difference, 2.66 (95% CI: 1.86–3.47) (38). A European cross sectional study of 1000 men with cardiovascular risk factors found that a high education level (OR 0.52; 95%, CI: 0.33–0.83, P=0.001), high-intensity physical activity (OR 0.50; 95% CI: 0.29–0.86, P=0.045) and a stable relationship (OR 0.43; 95% CI: 0.21–0.88, P=0.046) were associated with decreased risk of ED (39). Evidence may be contradictory in some aspects, for example: data analyzing modifiable risk factors and lifestyle changes from the MMAS longitudinal study after 8 years follow up in middle-aged men observed that: changes in obesity, smoking status or heavy drinking were not associated with ED risk and that men who initiated physical activity (adjusted OR 0.3) had decreased risk of ED (40). An Italian randomized, single-blind clinical trial of 110 obese men revealed that lifestyle changes (reducing caloric intake and increasing level of physical activity) was associated with improvement in sexual function (41). Weight loss appears to be a safe and effective method that mitigates the inflammatory response and improves endothelial function (42).

Asymptomatic men with a recent ED diagnosis require a cardiovascular risk assessment. The ACCF/AHA 2010 guidelines recommend the Framingham Risk Score (see http://www.cvriskcalculator.com) as an adequate tool for global cardiovascular risk assessment because it is highly predictive of cardiovascular events in men ≥40 years of age (43). This instrument considers the "classic" cardiovascular risk factors like: age, sex, race, total

cholesterol, HDL, systolic and diastolic blood pressure, anti-hypertensive medicine use, the presence of diabetes and smoking status, and calculates the 10 year risk for a cardiovascular event (heart disease or stroke). Based on this assessment, early referral for a full cardiologic work-up is warranted in men with significant risk factors (21).

Smoking cessation

Smoking cessation is an imperative public health goal that prevents most excess cardiovascular mortality. Mortality risk is reduced by 50% if patients quit by the age of 50 and is avoided almost as a whole if they quit by the age of 30 (29). Diverse public health strategies (i.e., smoke-free environment, tobacco prices, taxes, policy and legislation) are being adopted worldwide along in order to achieve the WHO goal of a 25% reduction in the risk of deaths due to non-communicable diseases by 2025 (44). Multiple interventions in the primary care setting have also proven to be effective, such as: cognitive behavioral therapy, implementation of intensive smoking cessation centers and pharmacotherapy. First-line drugs recommended for smoking cessation include: nicotine replacement therapy, bupropion and varenicline (45). A randomized clinical trial of 697 patients compared gradual *vs.* abrupt smoking cessation and found that abrupt cessation was more likely to lead to long lasting abstinence (46). The effect of smoking cessation on erectile function has not been prospectively addressed and data from retrospective epidemiological studies is contradictory; however, we may infer from the available evidence that this intervention may reverse or at least halt disease progression (36). A multi-disciplinary approach in the primary care setting should be used to encourage patients to quit smoking.

Dietary patterns and the Mediterranean diet

A strong association between dietary patterns, endothelial and erectile has been established in observational studies. A high flavonoid diet intake has been linked to a reduced ED incidence in a recent prospective study of 25,096 men with 10 years follow up (47). The "Mediterranean diet" is among the healthiest of diets and it consists in a high intake of foods of vegetable origin (cereals, fruits, vegetables, legumes, nuts), olive oil as the main source of fat, a moderate consumption of alcohol (1–2 glasses of red wine per day) and a low consumption of meat (except fish) and dairy products. It is now considered more than a dietary

pattern because it promotes the adoption physical activity and a healthy lifestyle (48). This diet appears to have a protective effect against type 2 DM and obesity because it prevents weight gain, insulin resistance and pancreatic beta cell dysfunction (49). Moreover, a randomized clinical study of 180 subjects demonstrated that a Mediterranean style diet was associated with improved endothelial function and a significantly reduced serum concentrations of high-sensitivity C-reactive protein (P=0.01), interleukin 6 (P=0.04) and decreased insulin resistance (P<0.001) in patients with the metabolic syndrome after two years follow up (50). It appears that close adherence to a Mediterranean diet improves endothelial function even in the short term (2 months) in patients with abdominal obesity (51). Based on this data, it is reasonable to assume that this dietary pattern has beneficial effects in erectile function. Evidence suggests that this diet ameliorates or even restores erectile function in men with obesity or the metabolic syndrome (52). This link was further demonstrated in an Italian study where the Mediterranean diet was found effective in reducing the prevalence of ED in men with the metabolic syndrome after two years follow up (53). This dietary pattern also appears to reduce systemic inflammation and improve sexual function in women with the metabolic syndrome (54).

Conclusions

The management of patients with ED in low and middle-income countries is increasingly challenging. There is a high incidence of non-compliance to lifestyle modification habits and pharmacological treatment adherence of concomitant diseases. Moreover, widespread use of available phosphodiesterase type 5 inhibitors is limited in some areas due to high costs (see *Table 1*). Lack of efficacy from non-pharmacological and pharmacological interventions is also common and this is in part due to inadequate treatment of shared cardiovascular risk factors such as, obesity and advanced type 2 DM. This was illustrated in a prospective study of 511 PDE5 inhibitor naive Latin American men observed that two thirds of the patients were persistent and adherent to pharmacologic therapy after 6 months of follow up and that the main reasons for non persistence included medication cost and lack of efficacy (55). Surgical management of this disorder is not widely available in Latin America because it is not economically feasible in most countries. For this reason, patient management of ED in these countries must include non-pharmacological

Table 1 Common available phosphodiesterase type 5 inhibitors in Latin America

Variables	Sildenafil (Viagra)	Tadalafil (Cialis)	Vardenafil (Levitra)
Dosage	25–100 mg; no dosage adjustment in renal or hepatic impairment	5–20 mg; caution in renal & hepatic impairment	2.5–20 mg; caution in hepatic impairment
Onset of action	30–60 min	Within 1 hour	30–60 min
Duration	2–4 hrs	Up to 36 hours	4–6 hrs
Significant adverse reactions	Flushing (10–19%), headache (16–46%), dyspepsia (3–17%), visual disturbance, epistaxis	Flushing (1–13%), headache (3–42%), dyspepsia (1–13%), nausea (10%), nasopharyngitis (2–13%)	Flushing (8–11%), headache (14%)
Food interactions	Yes (take on empty stomach)	No	Yes (take on empty stomach)
	Avoid grapefruit juice (may increase serum levels/toxicity)		
Pricing	100 mg [30]: $1,738.10	20 mg [30]: $1,862.64	20 mg [30]: $1,620.08

Source: Lexicomp Online.

preventive measures, such as lifestyle modification including smoking cessation and an adequate treatment of concomitant CVDs.

Footnote

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