Erectile Dysfunction and Metabolic Syndrome. An Entity Little Addressed

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SUMMARY

Metabolic syndrome is considered a risk factor for erectile dysfunction since it generates chronic low-grade inflammation and in turn causing endothelial damage decreasing the ability of nitric oxide synthesis to allow adequate vasodilation allowing erection. Erectile dysfunction is defined as the constant or recurrent inability to achieve and/or maintain a sufficient penile erection for sexual satisfaction. It is important to consider it as an early clinical manifestation of generalized vascular disease and as a risk factor for cardiovascular outcomes.

Keywords: Erectil Dysfunction; Metabolic Syndrome; IIEF; Linear Shock Wave Therapy

Introduction

Metabolic syndrome (MetS) is characterized by: insulin resistance, excess weight, glucose intolerance, elevated triglycerides, decreased HDL and alterations in blood pressure. This also generates low-grade inflammation and prothrombotic state [1]. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) for MetS are:

1) Waist circumference ≥ 90 cm in men or ≥ 80 cm in women;

2) TG ≥ 150 mg/dl;

3) HDL-C < 40 mg/dl in men and < 50 mg/dl in women;

4) Systolic blood pressure ≥ 130 mmHg and diastolic ≥ 85 mmHg, or antihypertensive drug treatment; and

5) Fasting plasma glucose ≥ 126 mg/dl, or prior diagnosis or treatment of Diabetes Mellitus [2].

All of these are considered risk factors for the development of erectile dysfunction. Either as part of the complications due to endothelial damage, neuropathy or secondary to the consumption of drugs to control these pathologies. Erectile dysfunction (ED) is defined as the constant or recurrent inability to achieve and/or maintain a sufficient penile erection for sexual satisfaction [3]. It is important to consider it as an early clinical manifestation of generalized vascular disease and as a risk factor for cardiovascular outcomes [4].

Etiology

ED can have various etiologies and it is essential to identify the underlying diseases, such as: pathologies of the endocrine, central nervous and cardiovascular system. The prevalence of ED increases with age, however, those patients who present with diabetes mellitus have an increase in the prevalence of this compared to those who do not diabetic: 23% vs 11% respectively worldwide [5]. In Mexico, 45% of diabetic patients will have ED. This depends on the severity and evolution of diabetes however diabetes mellitus increases up to twice as much the risk of developing erectile dysfunction [6]. There are other etiologies associated with ED, such as: low levels of vitamin D and COVID-19 [7]. The latter becomes

relevant since we continue to be on alert for this pandemic. Recently, the presence of viral particles in seroconverted COVID-19 patients in the endothelial cells of the penis has been studied, even after recovery [8]. What generates an association between ED and Covid-19 without forgetting the inflammatory state and endothelial damage that characterize this virus and its pathophysiology through the union with ACE-2 receptors, the affectation to mental health, the metabolic lack of control and the shortage of medicines generated as collateral damage of the COVID-19 pandemic are also factors that favor the appearance of ED [9-11] Figure 1.
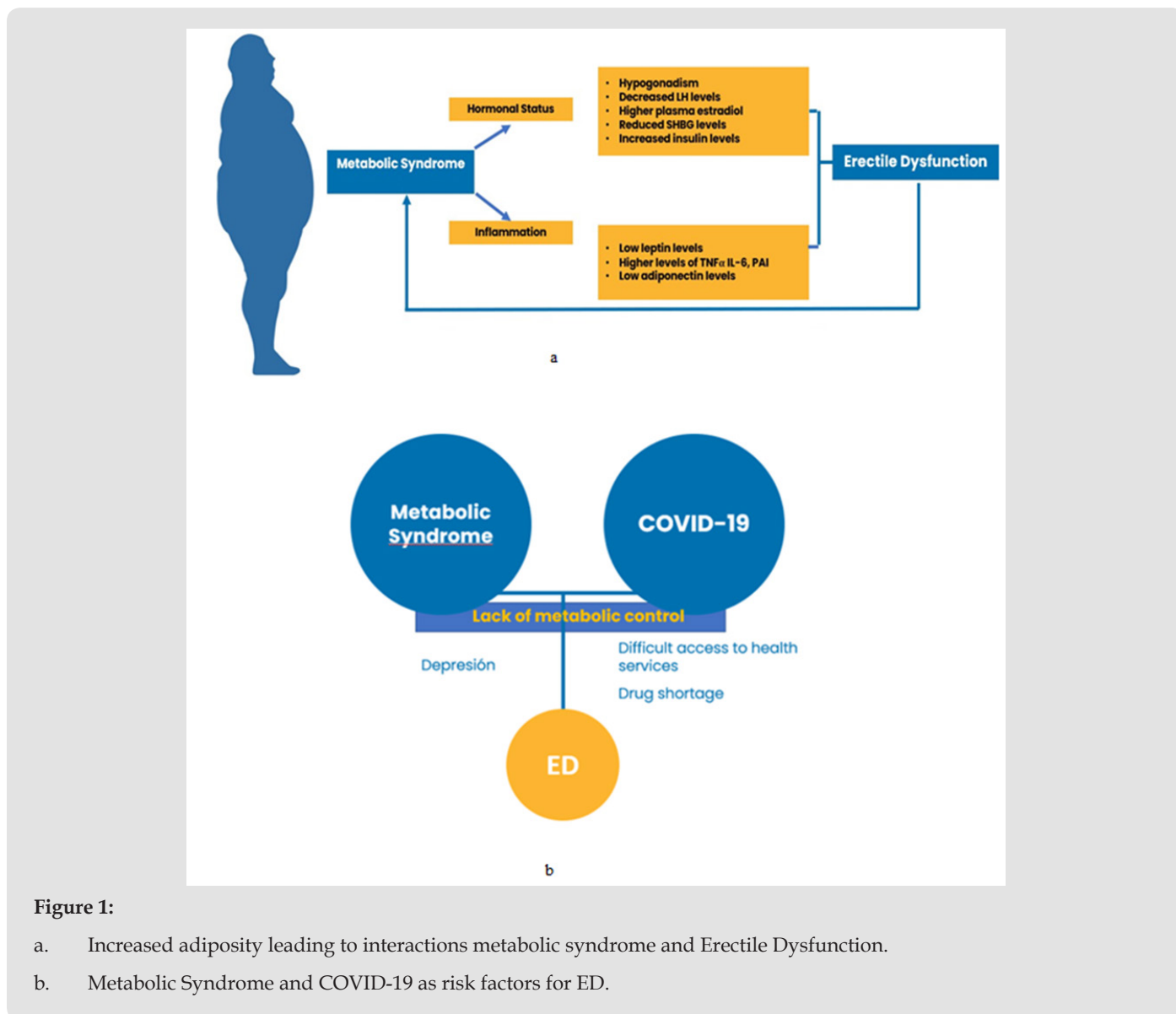

Figure 1:

 a. Increased adiposity leading to interactions metabolic syndrome and Erectile Dysfunction.

 b. Metabolic Syndrome and COVID-19 as risk factors for ED.

Overweight and obesity, as well as the number of factors associated with MetS is directly proportional to the frequency of occurrence of ED, that is, the greater the components of the SMet, the greater the risk of developing it by up to 53.3% [5].

Likewise, there are drugs associated with ED used mostly for the control of SMet and for major depressive disorder mainly, such as: Alpha blockers, benzodiazepines, beta blockers, clonidine, digoxin, histamine H2 receptor blockers, ketoconazole, alpha-methyldopa, monoamine oxidase inhibitors, phenobarbital, phenytoin, selective serotonin reuptake inhibitors, spironolactone, thiazide diuretics and tricyclic antidepressants [3]. In addition to these, the use of statins to improve endothelial function for their pleiotropic effects is controversial since it has been reported in various clinical trials and preclinical trials to offer no benefit at the level of erectile function. Mostly reported with the use of simvastatin, compared to the rest of the statins. There are several theories that support the involvement of O_2 and nitric oxide (NO) in statin-induced changes

in endothelial function and suggest lower availability of NO for signaling, possibly through reaction with O_2 to form peroxynitrite. On the other hand, erectile function has also been evaluated before and after the start of statin therapy, where the IIEF decreased in score and improves after one week of stopping treatment with these, as well as the increase in the percentage of the prevalence of patients with ED after the start of therapy [12,13].

Pathophysiology

Vasodilation is the main physiological point of erection that is mediated by NO in the penis. Phosphodiesterase-5 (PDE-5) has a key role in erectile physiology, as it contributes to the conversion of cGMP to GMP which contributes to the relaxation of smooth muscle with calcium- dependent channels to generate vasodilation [14]. The synthesis of NO from arginine, through nitric oxide synthase (NOS), which requires a series of cofactors and cosubstrates, as they are not sufficient or are oxidized, the NOS produces superoxide anion, which interacts with the NO to produce peroxynitrites, generating vasoconstriction and this accelerates endothelial damage and culminates in atherosclerosis, creating a proplatelet state and finally ED [15]. MetS is a risk factor for the development of ED due to impaired endothelial function due to chronic low-grade inflammation managed by these patients through various biochemical and immunological pathway. The accumulation of adipose tissue is a triggering factor for MetS which generates changes in the body at the hormonal and inflammatory levels. Generating hypogonadism due to decreased LH levels, increased plasma estradiol, and hyperinsulinemia. At the same time, there is a decrease in the levels of leptin and adiponectin with an increase in proinflammatory markers, increasing the risk for ED by contributing to the decrease in testosterone [16] Figure 1a.

There are also other risk factors that decrease testosterone levels, mentioned below [3].

Risk Factors

- Smoking
- Obesity
- Sedentary lifestyle
- Metabolic syndrome
- Chronic alcohol use
- Hypothyroidism/hyperthyroidism

Diagnostic Approach

Perform clinical history to evaluate concomitant diseases, chronic use of medications and finally evaluate the presence or not along with the severity of ED using the IIEF test. The consultation of the patient suffering from erectile dysfunction should be carried out in a comfortable environment respecting and safeguarding the patient's privacy. In order to diagnose and know the degree of ED, Rosen et al. formulated the International Index of Erectile Function (IIFE). Which is a validated tool and very practical and easy to use in everyday medical consultation. Its elaboration included the selection of 5 questions that evaluate different parameters of the ED in the last six months. The IIFE consists of 5 questions covering: erectile function, orgasmic function, sexual desire, satisfaction with sexual intercourse and overall satisfaction. Each with 5 possible answers with a score of 5-25. In addition, it demonstrates high sensitivity and specificity to detect changes in erectile function in response to treatment. The degree of ED is rated from 0 to 25 points with lower score greater severity of SD [17] (Charts 1a & 1b).

Chart 1a: IIEF test.

1.- How would you rate your confidence in being able to maintain an erection?				
Very low	Short	Moderate	High	Very high
1	2	3	4	5
2.- When you have erections through sexual stimulation, how often are your erections hard enough for penetration?				
Not often	Often	Sometimes	Many Times	Usually
1	2	3	4	5
3.- During sexual intercourse, how often can you maintain your erection after you have penetrated your partner?				
Not often	Often	Sometimes	Many times	Usually
1	2	3	4	5
4.- During sexual intercourse, how difficult is it to maintain your erection until the end of the sexual act?				
Extremely difficult	Very difficult	Hard	Slightly difficult	Not difficult
1	2	3	4	5
5.- When you try to have sex, how often are they satisfying for you?				
Extremely difficult	Very difficult	Hard	Slightly difficult	Not difficult
1	2	3	4	5

Chart 1b: ED score and severity.

22-25	Without ED
17-21	Mild ED
12-16	Mild-moderate ED
8-11	Moderate ED
5-7	Severe ED

IIEF Test

Another of the US scales that exist to evaluate the degree of ED is the SEAR (Self-Esteem And Relationship Questionnaire), which was designed to specifically evaluate psychosocial aspects associated with ED. It consists of 14 items, with 5 possible response options, through which the following 2 dimensions are evaluated with respect to the last 4 weeks: Sexual relations (items 1-8) and Self-confidence (9-14), which in turn is divided into 2 subdimensions: Self-esteem (items 9-12) and Relationships in General (items 13 and 14). Finally, the questionnaire evaluates the degree of patient satisfaction with erectile function in general with respect to the last 4 weeks (final item) [18] (Charts 2 & 3).

Chart 2: SEAR quiz.

Sexual relations and self-confidence.
1.- I have felt calm when thinking about starting each sexual relationship with my partner. 2.- I have felt sure that my erection would last long enough during sexual intercourse.
3.- I have felt satisfied with how I have functioned sexually.
4.- I have felt that I could have sexual relations when they arose spontaneously. 5.- I have felt predisposed to start sexual relations myself.
6.- I have felt safe to function sexually.
7.- I have satisfied felt with my sexual life.
8.- My partner has felt dissatisfied with the quality of sexual relations.
Self-esteem subscale 9-12.
Subscale of Relations in general.
13.- My partner has felt satisfied with our relationship in general.

Chart 3: SEAR quiz answers.

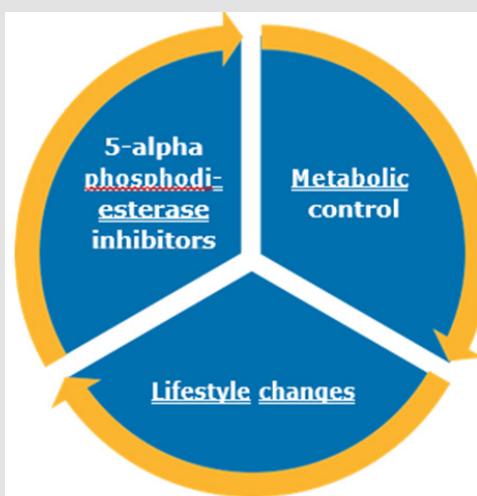| Never	Rarely sometimes	More often	Most of the time	Always
1	2	3	4	5

Treatment

Figure 2: Multidisciplinary management of ED.

The treatment of a patient who presents ED and also SMet factors will require a multidisciplinary management that involves the metabolic control of concomitant diseases, offer changes in lifestyle with hygienic-dietary measures and finally pharmacological and non-pharmacological treatment as an alternative to these measures. Figure 2. In the case of those patients who present use of drugs that affect erectile function, it will be important to offer some replacement therapy.

Lifestyle Modifications

These interventions are necessary to reduce the risk of the appearance of ED and also improve this condition, such as: hygienic-dietary measures and exercise. Hygienic-dietary measures include changes in diet and include those foods that have shown usefulness in ED, such as: the use of the Mediterranean diet and the consumption of red fruits, such as: blueberries, cherries, raspberries, blackberries, eggplant. etc. The use of the Mediterranean diet regains importance because the favorable response in endothelial function is proven, reducing the risk for major cardiovascular events, as well as the incidence of them [19]. The consumption of flavonoids in the diet, such as red fruits stimulate the synthesis of nitric oxide since they inhibit RhoA/Rho kinase pathway and stimulate [20]. Also 60 to 90 g of walnut improve markers of inflammation and endothelial damage. It is also recommended to include almonds, chestnuts, walnuts, hazelnuts and pine nuts [21]. It is also part of it as a preventive treatment to reduce the risk of cardiovascular diseases and therefore complications such as ED.

Pharmacological Treatment

Drug	Action start time	Half-time	Posology
Sildenafil	30–60 min	12 p.m.	20/25/50/100 mg (24 h)
Tadalafil	60–120 min	36 h	5/10/20 mg (24 h)
Vardenafil	30–60 min	10 a.m.	10/20 mg (24 h)

Figure 3: Characteristics of 5 phosphodiesterase inhibitors.

The inhibitors of alpha 5-phosphodiesterase. Phosphodiesterases are a superfamily of enzymes whose main action is to inactivate cyclic adenosine monophosphate (cAMP) and cyclic guanosine monophosphate (cGMP) which are second messengers of prostacyclin and NO respectively, which promote vasodilation. In the case of the enzyme 5 phosphodiesterase, its main function is to accelerate the degradation process of cGMP and limit the vasodilator effects of NO [22]. Because of this it is the pharmacological target of sildenafil, tadalafil and vardanafil. These three with pharmacokinetic parameters distinct from each other, however, have all demonstrated adequate efficacy and tolerability for the treatment of ED. It is administered every 24h and each offers a different half-life of 10 to 36 h on which the duration of the pharmacological effect depends. Figure 3. The most common adverse reactions are: headache, flushing, myalgia, rhinitis, among others [1]. Several studies have reported the consumption preferences of these three, where both men and women have preferred Tadalafil by up to 70% [3,23,24]. This can be due to multiple reasons and one of them is the ease in the dosage that it presents and the duration of its half-life of up to 36 h that is greater than the rest of the drugs which can generate a mostly prolonged effect on erectile function [22]. Likewise, it was observed that with the use of Tadalafil significantly improved the severity of ED evaluated with the IIEF with a change of 10 to 18 points in this score p<0,013 3,24. Mentioning in an important way that these investigations have been based on consumption preference on the part of patients and not on pharmacological superiority.

Non-Pharmacological Treatment

For the purpose of this article, we refer to the non-pharmacological treatment of shock wave therapy as one of the alternatives that exists for this pathology. It is considered an innovative and painless treatment and its main mechanism of action is to generate neovascularization and thus favors the synthesis of NO. Generating various shots through a transducer that generates waves of different intensities directed towards the corpora cavernosa, with an approximate duration of 20 min. These sessions can be practiced 1-2 times a week [25]. An 80% success rate in erectile function has been reported in patients using this therapy with a response at 6 months with respect to baseline evaluating them with IIEF in Mexico [26]. However, it is important to mention that no treatment today is curative, it helps to improve erectile function while employing them.

Other Treatments for ED

Sex therapy, local treatments with intracavernous injections of prostaglandin analogues, hormonal therapy in the presence of clinical signs suggestive of an androgenic deficit confirmed by biological tests by the determination of a testosteronemia lower than normal and finally the surgical implant consisting of the surgical placement of two implants, one in each cavernous body, which produces a mechanical erection. They are indicated when the other treatments fail [4].

Conclusion

ED is an age-dependent pathology whose prevalence increases derived from the factors associated with SMet, so it is imperative the adequate control of the underlying diseases to reduce the risk of the appearance of cardiovascular diseases and therefore of ED. The approach of the patient with ED should always be multidisciplinary, starting by generating an adequate metabolic control and individualizing the pharmacological therapy to inquire about adverse reactions of each patient and assess concomitant therapy existing in SMet to reduce the risk of ED associated with medications. Today there are multiple therapeutic approaches aimed at improving erectile function, however, it is important to consider the preference of the patient diagnosed with ED. Mentioning that nothing is healing to date and only transiently improves erectile function. The use of statins for their already known pleiotropic effects on endothelial function remains uncertain within the improvement in erectile function of these patients. The prevention of this pathology lies primarily in reducing the risk of the appearance of fators associated with SMet. the Mediterranean diet, red fruits and seeds will always be part of the first step to cardiovascular prevention. Not forgetting that the metabolic syndrome and the current COVID-19 pandemic contribute to the increase in the prevalence of ED.

References

1. Guillermo C, Cardoso-Saldaña, Yamamoto-Kimura L, Alarcón GV (2020) Metabolic syndrome, lipoprotein(a) and subclinical atherosclerosis in Mexican population. Arch Cardiology of Mexico 91(3): 307-314.

2. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) (2002) Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report Circulation 106: 3143-31421.

3. Irwin GM (2019) Erectile Dysfunction. Primary Care: Clinics in Office Practice 46(2): 249-255.

4. Vlachopoulos C, Loakeimidis N, Terentes-Printzios D, Christodoulos S (2008) The triad: erectile dysfunction-endothelial dysfunction-cardiovascular disease. Current pharmaceutical design 14(35): 3700-3714.

5. Molina-Vega M, Asenjo-Plaza M, Banderas-Donaire M, Ollero MDH, Moreno SR, et al. (2020) Prevalence of and risk factors for erectil dysfunction in young nondiabetic obese men: results from a regional study. Asian J Androl 22(4): 372-378.

6. Maalmi H, Herder C, Bönhof GJ, Strassburger K, Zaharia OP, et al. (2022) Differences in the prevalence of erectile dysfunction between novel subgroups of recent-onset diabetes. Diabetologia 65(3): 552-562.

7. Dumbraveanu I, Banov P, Arian I, Ceban E (2020) The Correlations of Clinical and Biochemical Indices of Vitamin D with Erectile Dysfunction. Journal of medicine and life 13(2): 144-150.

8. Kresch E, Achua J, Saltzman R, Khodamoradi K, Arora H, et al. (2021) COVID-19 Endothelial Dysfunction Can Cause Erectile Dysfunction: Histopathological, Immunohistochemical, and Ultrastructural Study of the Human Penis. World J Mens Health39(3): 466-469.

9. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, et al. (2021) Post-acute COVID-19 syndrome. Nat Med27(4): 601-615.

10. Frydman TD, Atkinson-Ginsburgb NM, Alpízar Salazar M (2020) When two pandemics meet Endocrinol Diabetes. Metab J 4(2): 1-3.

11. Reyes M, Alpízar M (2021) Type 2 Diabetes Mellitus and Covid-19 in Mexico A Comprehensive assessment. Biomed J Sci & Tech Res 39(1).

12. Cui Y, Zong H, Yan H, Zhang Y (2014) The effect of statins on erectile dysfunction: a systematic review and meta- analysis. J Sex Med 11(6): 1367-1375.

13. Zhang Z, Zhang HY, Zhang Y, Li H (2019) Inactivation of the Ras/MAPK/PPARγ signaling axis alleviates diabetic mellitus-induced erectile dysfunction through suppression of corpus cavernosal endothelial cell apoptosis by inhibiting HMGCS2 expression. Endocrine 63(3): 615-631.

14. Basu A, Ryder R (2004) New Treatment Option for Erectile Dysfunction in Patients with DM. Drug 69: 2667-2688.

15. Alonso Renedo FJ, A Casas Herrero A, Iraizoz Apezteguı I Sexual dysfunction in the elderly Pathophysiological and medical issues. Treatment of erectile dysfunction.

16. S Raúl Valdevenito, L Dorón Vantman (2014) Late-onset hypogonadism in Men. Rev Med Clin Condes 25(1): 61-68.

17. Ceballos M Álvarez, Villarraga J, Silva Herrera JM, Uribe JF, Mantilla D (2015) Guide to erectile dysfunction. Colombian Society of Urology 24(3): 185e2-185e22.

18. Zegarra L, Loza C, Perez V (2011) Psychometric validation of the international index of erectile function in patients with erectile dysfunction in Peru. Rev Peru 28 (3): 477-483.

19. Ramón Estruch R, Ros E, Salvadó S, Covas MI, Corella D, et al. (2013) Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med 368: 1279-1290.

20. Cassidy A, Franz M, Rimm EB (2016) Dietary flavonoid intake and incidence of erectile dysfunction. Am J Clin Nutr 103: 534-541.

21. Huetos AS, Muralidharan J, Galiè S, Salvadó JS, Bulló M (2019)Effect of nut consumption on erectile and sexual function in healthy males: A Secondary outcome analysis of the fertinuts randomized controlled trial. Nutrients 11: 1372.

22. Beltrán-Gámez ME, Sandoval-Zarate J, Pulido T (2015) Phosphodiesterase-5 inhibitors for the treatment of pulmonary arterial hypertension. Arch Cardiol Mex 85(3): 215-224.

23. Mirone V, Fusco F, Rossi A, Sicuteri R, Montorsi F 2009) Tadalafil and Vardenafil vs Sildenafil: a review of patient-preference studies. BJU Int103(9): 1212-1217.

24. Gong B, Ma M, Xie W, Yang X, Huang Y, et al. (2017)Direct comparison of tadalafil with sildenafil for the treatment of erectile dysfunction: a systematic review and meta-analysis. Int Urol Nephrol 49(10): 1731-1740.

25. Kertzman P, Lenza M, Pedrinelli A, Ejnismand B (2015) Shockwave treatment for musculoskeletal diseases and bone consolidation: qualitative analysis of the literature. Braslian Orthopedics 50(1): 3-8.

26. Pelayo-Nieto M, Linden-Castro, Alias-Melgar A, Grovas DEP, Rosa FC, et al. (2015) Linear shock wave therapy in the treatment of erectile dysfunction. English Urological Acts 39(7): 456-459.

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