Endothelial Dysfunction: A Concatenation Of Facts In, Erectile Dysfunction, Benign Prostatic Hyperplasia And Cardiovascular Risk

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Abstract

It is evident that Erectile Dysfunction (ED) and Lower Urinary Tract Symptoms secondary to Benign Prostatic Hyperplasia (BPH) overlap on many occasions and in turn Erectile Dysfunction is considered as a predictor of endovascular organic damage. Recent results indicate that the aforementioned pathologies may have a common underlying cause, such as a decreased blood supply in their tissues. This pathophysiological evidence could be indicating us a subclinical arteriosclerosis and if we go beyond, a way of expression of target organ injury. All of this leads us to study these entities also, from a cardiometabolic point of view, for the vascular mechanisms they share (endothelial dysfunction) and to ask more about them to our patients, since the penis has become a “barometer” of endothelial health.

Keywords: Erectile dysfunction, BPH, Cardiometabolic risk, Endothelial dysfunction.

Introduction

The act of concatenating situations in medicine, has to go beyond uniting or linking, symptoms, syndromes or therapeutic attitudes, since the above being valid, it falls short, because the “Leitmotiv” has to go ahead, it is say advance to what may happen, through predictors or alarm symptoms, that make us think about the role of prevention of target organ injuries (LOD) (primary prevention), in the three entities to develop, as they are Erectile Dysfunction (ED), Benign Prostatic Hyperplasia (BPH) and Cardiovascular Risk (CVR) [1-8]. The ED and lower urinary tract symptoms (LUTS) secondary to BPH are prevalent and often coexisting diseases in middle-aged and elderly men (Figure 1), and decrease their quality of life. On the other hand, ED of arterial vascular cause is the most common in subjects older than 50 years.

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Both the American Heart Association and the International Diabetes Federation emphasize that a high percentage (52%) of patients with ED have classic cardiovascular risk factors (CVRF), which in turn and in a silent manner carry the LOD. Within these, the carotid intima-media thickness (IMCI) is a marker of subclinical arteriosclerosis. Numerous studies have shown that IMCI is associated with the traditional CVRF, and independently, to cardiovascular and cerebrovascular events such as myocardial infarction and ischemic encephalic vascular accident, even after adjusting for traditional CVRF [2,3]. ED and BPH share a series of risk factors that predispose to these pathologies, such as age, atherosclerosis, ischemia or neuropathies. Recent results indicate that ED and LUTS associated with BPH may have a common underlying cause: a reduced blood supply, which would indicate a subclinical atherosclerosis and, at the same time, its predictive symptoms, organic endovascular damage. All this has to make us think that patients with ED with LUTS due to BPH symptoms, organic endovascular damage. All this has to make us think that patients with ED with LUTS due to BPH may have a higher cardiovascular risk, determined by the presence of LOD at the level of different organs or vascular structures IMCI (Figure 2). Therefore, we should ask more about this aspect and when this is presented, study it in a broader way, both at the urological level and at the cardiovascular level, because of the agreement between these three entities. Given that ED is, in general, earlier than ischemic heart disease, it is currently considered a risk factor for future cardiovascular events or, as it has been cataloged, a “sentinel” of cardiovascular disease (CVD), with a value predictive similar to that of classic risk factors, and the penis has come to be considered a “barometer” of endothelial health [4-10].

Development Of The Topic

Erectile Dysfunction And Cardiovascular Disease

ED is defined as the consistent (durable, stable) inability to achieve or maintain a penile erection sufficient to allow a satisfactory sexual relationship [5]. Currently, it is considered that organic causes predominate, being the main responsible for endothelial dysfunction (DL). The ED has a high prevalence, estimated to affect about 100 million adult men in the world and that will affect 322 million in the year 2025. Effectively, ED and CVD share risk factors and production mechanisms. It is increasingly accepted that ED responds in most cases to DL, and it is known that this is an early alteration in atherosclerotic disease [6,7], hence the vascular study of the penis, a test to keep in mind (Figure 3).

ED usually precedes classical CVD in its presentation. With a perhaps too simplistic concept this advance has been attributed to the smaller size of the penile arteries (in the order of 1-2 mm in diameter) compared to that of the coronary arteries (3-4 mm), the carotids (5-7 mm) and the iliofemoral muscles (6-8 mm). Whether this hypothesis is true or not, what is important is the verification that ED usually manifests itself two to three years earlier than the manifestations of ischemic heart disease and, therefore, its detection could allow the adoption of therapeutic measures that could prevent the most serious CV complications [8]. Conversely, more than two-thirds of men with coronary heart disease have, when questioned, a history of ED.

ED would then be considered a matter that simply affects the quality of life of a sentinel who warns of the possibility of developing clinical manifestations of CVD, becoming a matter of great interest for physicians in general and for cardiologists in particular [8, 10].

Mechanisms Of The Penezian Erection

The erection of the penis is a neurovascular phenomenon mediated by nitric oxide, a potent vasodilator released in the nerve terminals and the endothelium of the vessels of the penis. Therefore, for an erection to occur, an adequate endothelial function is required [9,10].

The penis is a hydraulic organ, consisting of spongy tissue that houses small capsules called corpora cavernosa. When the blood reaches them, they expand. Histologically, we have sinusoids that, when filled with venous blood from the venous plexuses and thanks to the trabecular tissue, produce at that level the appropriate changes to produce an increase in penile tumescence [4,6]. This tumescence depends on the collapse
of the venous drainage plexus, located inside a membrane that is not extensible, the albuginea. This collapse occurs when the sinuousoids of the corpora cavernosa (covered by endothelium) expand by relaxing the smooth muscular fibers that surround them and that maintain, outside the erection, a tonic contraction. The relaxation of these smooth muscle fibers is, therefore, the trigger of the erection. Detumescence is produced by the release of noradrenaline, which re-triggers the contraction of smooth muscle cells. Curiously, the erection, paradigm of virility is, in essence, a passive phenomenon, a consequence of the relaxation of a smooth muscle, and the energy it requires does not depend on the virile member, but on the heart. The relaxation of smooth muscle that promotes these hydrodynamical changes is a response to the release of nitric oxide by endothelial cells [11,12]. The increased content of nitric oxide produces a decrease in the concentration of calcium in the smooth muscle cell and, therefore, less contraction. One of the pathways involved in this phenomenon is that of cGMP (cyclic guanosine monophosphate); 5-phosphodiesterase is involved in the degradation of cGMP (PDE5) [5]. The inhibitors of PDE5 (sildenafil, vardenafil, tadalaflil and avanafil) increase the availability of cGMP and are currently the most effective drugs for the treatment of ED. Nitrites increase the production of cGMP, which is why their simultaneous use with PDE5 inhibitors (which produce a decrease in degradation) can lead to marked and unpredictable hypotensions and constitutes the basis for the contraindication of the association. All this process depends, for its final success, without forgetting the psychological factors, of an adequate balance of the activity of the autonomic nervous system (the parasympathetic activity is compromised in patients with diabetes, depression and central and peripheral neurological diseases, the sympathetic activity that prevents the relaxation of smooth muscle is increased in smoking and in the processes that affect the urinary tract, such as BPH), the integrity of the anatomical structures involved and the presence of neuronal nitric oxide synthetase (nNOS) and endothelial (eNOS); the deficits of the first tend to be iatrogenic, as results of surgery or prostate or pelvic irradiation; those of the second, more frequent, constitute DL and are associated with the same risk factors as atherosclerotic disease [13,14,15].

**Prostatic Blood Flux And Bottom Urinary Tract**

There is a complex network of arteries that supply oxygenated blood to the lower urinary tract (UTI) and the prostate. The blood supply to the pelvic area comes from the internal iliac artery. Two branches of the internal iliac artery are the superior and inferior vesical arteries, which supply blood to the bladder.

The inferior vesical artery provides oxygenated blood to the prostate. The urethra obtains its blood supply from the internal pudendal artery and the dorsal artery of the penis. If the supply decreases in these arteries, it can affect the health of the prostate and the TUI. In addition, blood vessels have a structure that can influence blood flow [16]. A decrease in the release of nitric oxide, through the internal zone that covers the blood vessels, which reaches the organs of the penis, prostate and bladder, would produce an insufficient blood supply to these areas with the consequent involvement of the due to lack of vascular oxygen [17]. The latest medical guides of different specialties are recommending that, in the initial assessment of the male with BPH, one should also ask about the sexual function of the patient and other comorbidities of elevated CVR [9].

**Nitric Oxide And Endothelial Dysfunction**

Nitric oxide (NO) produced by the endothelium regulates vascular tone, inhibits platelet activation, adhesion and aggregation, inhibits vascular smooth muscle cell proliferation and models the endothelial cell-leukocyte interaction. DL has been associated primarily with a decreased bioavailability of nitric oxide. DL is currently considered one of the first manifestations of CVD and arteriosclerosis. The endothelium, a monolayer of cells that covers the luminal wall of blood vessels, regulates the interaction of cells and circulating proteins with the cells residing in the vascular wall, playing a central role as sensor and transmitter of signals.

The endothelium protects the arterial wall against the development of lesions and contributes to vascular homeostasis through this continuous control of the stimuli it receives and the adaptation of its functional state [15,16]. Endothelial cells, through a program of gene expression and a highly regulatable protein synthesis and processing, are able to detect changes both physical (mechanical hemodynamic stress) and chemical (release of molecules in their environment) and transform them into adaptive functional responses. This ability to adapt confers a key role in the regulation of vascular homeostasis. The endothelium has antithrombotic functions (inhibits platelet adhesion and coagulation, and regulates the fibrinolytic system), controls the activity of smooth muscle cells of the middle layer (vascular tone / proliferation) and modulates the transit of macromolecules, such as lipoproteins, and the adhesion of leukocytes (monocytes / T lymphocytes) to the arterial wall.

DL can be defined as an imbalance in the bioavailability of active substances of endothelial origin that predispose to inflammation, vasoconstriction and increased vascular permeability, and that may facilitate the development of arteriosclerosis, platelet aggregation and thrombosis. In recent decades it has been shown that well-known vascular risk factors (LDL-C low-density lipoprotein cholesterol, smoking diabetes, hypertension, etc.) and other emerging factors (oxygen free radicals, homocysteine, infections, estrogen deficiency, etc.) produce DL [17].

**Cardiometabolic Risk**

Classically, it can be stated that Cardiometabolic Risk (RCM) predisposes us to arteriosclerosis and type 2 diabetes mellitus, which originates from the association of conventional CVRF with the alterations of the Metabolic Syndrome (MS) [9]. Among the latter, abdominal obesity and insulin resistance are those that have a greater role. It is not a disease in itself, but a group of cardiovascular and metabolic disorders. The genetics of MS being complex, plays an important role [9, 10]. In a recent review, 44 loci associated with obesity were collected in genomic and linkage studies. The 3p, 15p and 18q regions are related to obesity and diabetes. Also the 7q region, where the leptin gene is located, seems to be associated with hyperinsulinemia, hypertension and obesity. In the RCM, there are, therefore, disorders of hydrocarbon metabolism and lipids, and a proinflammatory and prothrombotic state, which are part of the MS, together with various atherogenic factors, including hypertension, smoking and hypercholesterolemia [1,4,8]. The identification of the RCM is of great clinical importance, since a vigorous action directed to the global control of the factors that compose it prevents the cardiovascular disease, in all its manifestations and as we had indicated previously, we can value
certain alarm symptoms or predictors in the three concatenated pathologies, that help us to avoid greater evils [11]. Thus in (Figure 4), it is revealed how the biochemical processes that lead to DL in CVD are shown from the endothelium towards the lumen of the vessel.

**Symptoms Of Lower Urinary Tract Vs Benign Prostatic Hyperplasia And Erectile Dysfunction**

A series of hypotheses have been formulated to explain the existence of a common pathophysiology between LUTS and ED. Currently, the relationship between LUTS and sexual dysfunction is supported by four theories, not mutually exclusive, that include (Figure 5).

a) autonomic hyperactivity and the MS hypothesis [9].

b) changes in nitric oxide / nitric oxide synthase (NOS / NO) of the guanine monophosphatase pathway in the prostate and penis.

c) Rho-kinase activation and the endothelin pathway, and

d) The pathophysiological consequences of pelvic atherosclerosis.

It is possible that LUTS and ED share a common etiology related to CVD and MS, explaining in this way that both pathologies present the same risk factors, highlighting diabetes mellitus, hyperlipidemia and obesity, which are directly responsible for the progressive damage of the endothelium of the cavernous tissue, altering the generation of nitric oxide, preventing the relaxation of the cavernous smooth muscle and modifying the cascade of actions that cause vasodilatation and erection [7]. On the other hand, endothelin plays an important role as long-term regulators of the smooth muscle tone of the corpora cavernosa and an undoubted role in the physiology and physiopathology of the penis [8,17].

We must not forget to mention the role of inflammation markers in the diagnosis and prognosis of DL, especially atherosclerotic. Both acute phase and chronic phase reactants are being considered as potential diagnostic markers that open the way to preventive options [17].

**Clarifications In Sexual Health, Benign Prostate Hyperplasia (Stui) And Cardiometabolic Risk Help Us Understand What We Do**

We must break many myths regarding sexual health and the treatments we use both in the ED and in the BPH from the cardiovascular point of view. Thus and thanks to the “Second Princeton Consensus”, patients are divided into 3 risk strata (low, medium and high), depending on their comorbidities [14]. The low risk group can maintain relations freely (beyond 6 weeks after an uncomplicated infarction), while the high risk group would need prior stabilization of their pathologies (obstructive hypertrophic cardiomyopathy, severe aortic stenosis, NYHA III or IV heart failure, angina unstable ...) and those of intermediate risk a cardiovascular evaluation (as for example DE without cardiovascular symptoms, but 3 or more risk factors excluding gender) [11,12,14]. With respect to pharmacological treatment, say that in patients with ED and coronary disease, phosphodiesterase 5 inhibitors (such as Tadalafil) are effective and do not increase the risk of myocardial infarction or cardiovascular mortality. If, on the other hand, they are contraindicated in those who take nitrates, and it is recommended in smaller doses in which they also take alpha-blockers or drugs that act on the CIT P450 3A4 (ketoconazole, erythromycin, inhibitors of the HIV protease).

Special mention to Tadalafil, since the European Urology journal published a study in which said drug improved the symptoms of ED in men who, in addition to the signs and symptoms of BPH, also presented this pathology. This is the first international study evaluating the use of Tadalafil in parallel with Tamsulosin (as active control), controlled with placebo, for the treatment of signs and symptoms of BPH in the same population. Tadalafil shows a significant improvement in the signs and symptoms of BPH after one week and a significant increase in the maximum urinary flow rate (Qmax) at 12 weeks [18].

**Conclusions**

1. The ED is an alteration of a very high and increasing
prevalence and in most cases responds to organic causes, mainly atherosclerotic vascular disease, or the initial functional alteration of atherosclerosis, DL.

2. The ED shows a frank association with classic cardiovascular pathology, with which it shares common risk factors. As with BPH with LUTS, since sometimes hyperplastic prostates can lead us to ED and treating ED with Tadalafil as we have seen, we improve sexual function and LUTS in ED.

3. Therefore, those who consult by ED are patients who should be considered high risk CV until demonstration of the contrary, and submitted to a correct CV evaluation.

4. The questioning of a patient tending to evaluate the possibility of the presence of a CV disease should include the ED investigation. The generalization of the interrogation of the ED would help to overcome the inhibitions that patients have in the consideration of this subject, and on the other hand be able through early symptoms to go from one to another as much in their early diagnosis (which forces us to have them more present and ask more about them to our patients), as in the therapy used, since the scientific evidence shows us that the improvement in one of them can result in the others and more when there are so many myths in their approach with some drugs in concrete.

5. The greatest value of the MS from the point of view of the family doctor and cardiologist is that, since, in general, manifestations of ED precede those of CVDs, the presence of SD constitutes a warning signal about the possibility of subclinical CV abnormalities that can be controlled before the appearance of more serious complications (coronary syndrome).

### Block Of 6 Questions With 5 Answers

1. BPH, together with Erectile Dysfunction and Cardiometabolic Risk share some of these affirmations

   a) The so-called Lower Urinary Tract Symptoms (LUTS).
   
   b) Inhibitors of Phosphodiesterase 5 are contraindicated in patients who do not take nitrates.
   
   c) Erectile Dysfunction is a predictor of endovascular organic damage.
   
   d) They do not share endothelial dysfunction.
   
   e) If they share the vascular theory that relates them.

   The answers c and e are correct.

2. In relation to Nitric Oxide and Endothelial Dysfunction, which statements are correct

   a) Nitric oxide regulates nervous tone.
   
   b) Increases platelet aggregation.
   
   c) Inhibits the proliferation of the smooth muscle cell of the vessels.
d) The endothelium contributes to vascular homeostasis.
e) Smoking does not produce endothelial dysfunction.

The answers c and d are the correct ones.

3. Currently, the relationship between LUTS and sexual dysfunction is supported by four theories, not mutually exclusive, that include any of these statements

a) Autonomic hyperactivity and the metabolic syndrome hypothesis.
b) The pathophysiological consequences of pelvic atherosclerosis.
c) Rho-kinase activation and the purine pathway.
d) The cAMP channel.
e) None is correct.

The answers a and b are correct.

4. In the Second Princeton Consensus, which statements are correct

a) Classify patients by NYHA degree.
b) It stratifies according to the pharmacological treatment.
c) All questions are correct.
d) Patients are divided into three risk strata.
e) Patients at intermediate risk, require a cardiovascular evaluation.

The answers d and e are correct.

5. The Tadalafil is

a) An inhibitor of phosphodiesterase 4.
b) It is contraindicated in patients taking nitrates.
c) It is less effective than Tamsulosin in the symptoms of emptying of BPH.
d) The correct answers are c and a.
e) It can be used in substitution of alpha blockers in patients with Erectile Dysfunction.

The answers b and e are correct.

6. Of all these tests, which are the ones that confirm target organ injuries

a) Carotid intima media thickness.
b) Left ventricle ejection fraction.
c) Peak systolic velocity.
d) IPSS (International Prostate Symptom Score).
e) All of them.

The answers a and c are correct.

References