Review article

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Erectile dysfunction and its correlation with arterial hypertension and cardiovascular diseases

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ABSTRACT

Nowadays many patients suffering from arterial hypertension appear to experience beforehand also erectile dysfunction (ED) which can be regarded as a risk factor for cardiovascular disease (CVD). Over the last years, various clinical trials have demonstrated a resilient correlation between CVD and ED, sharing common pathophysiology. Consequently, ED is highly perceived as an early marker for a patient to experience symptomatic CVD. Endothelial dysfunction, atherosclerosis, low plasma testosterone levels represent common pathophysiological phenomena that are encountered by hypertensive patients who are suffering from ED and CVD events. In every case that ED gets identified at an early stage, it usually precedes by two to five years to a CVD event. Furthermore, its identification represents a low cost-effective prognostic tool for primary and secondary prevention for both CVD and all-cause mortality. Diuretics and β-blockers and diuretics are some of the cardiovascular drugs that affect negatively in ED that physicians need to take seriously into account. Meanwhile nebivolol and renin–angiotensin–aldosterone system inhibitors are proved to affect positively when administered to a patient. PD5 inhibitors represent a breakthrough therapy when dealing with ED and are considered to be safe for the cardiovascular system. Additionally, PD5 inhibitors are beneficial to treat sexual dysfunction and they represent a safe solution for hypertensive patients who take or not antihypertensive drugs. Up to date conducted testosterone replacement therapy (TRT) studies lead to contradictory results related with CVD risks and when such a therapy is used, physicians should closely monitor for possible adverse effects.

KEY WORDS: *Arterial hypertension, atherosclerosis, erectile dysfunction, sexual dysfunction, cardiovascular disease, cardiovascular drugs and treatment, risk factors, pathophysiology, inflammation, testosterone levels, phosphodiesterase type 5 inhibitors*

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ABBREVIATIONS: *ACE: Angiotensin Converting Enzyme, ADMA: Asymmetric Dimethylarginine, ARB: Angiotensin Receptor Blocker, cGMP: cyclic Guanosine MonoPhosphate, CAD: Coronary Artery Disease, CCB: Calcium-Channel Blocker, CVD: Cardiovascular Disease, CNP: C-type Natriuretic Peptide, CRP: C-Reactive Protein, ED: Erectile Dysfunction, eNOS: Endothelium Nitric Oxide Synthase, nNOS: Neuronal Nitric Oxide*

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Synthase, ET-1: Endothelin-1, ICAM-1: Intercellular Adhesion Molecule, IIEF: International Index of Erectile Function, MCP: Monocyte Chemotactic Protein, NO: Nitric Oxide, PD5-i: Phosphodiesterase type – 5 inhibitors, PGI: Prostaglaandin, RF: Risk Factor, TRT: Testosterone Replacement Therapy, VCAM: Vascular Cell Adhesion Molecule

INTRODUCTION

Arterial hypertension is considered an important worldwide health problem with over a billion of adults being currently affected. High blood pressure levels provoke serious vascular malfunction; therefore, increased cardiac, cerebrovascular, and renal disease rates are connected with hypertension. One crucial factor to anticipate a cardiovascular disease in a hypertension patient is erectile dysfunction which is not systematically associated by physicians in order to proceed to a substantiated diagnosis[1].

Many individuals with hypertension are affected by erectile dysfunction which is regarded nowadays as a common clinically meaningful problem. Therefore, identifying the problem of ED at an early stage, it could help physicians to gain a sufficient time frame quite in advance in order to anticipate additional future CVD-related risks and consequently diminish the risk for opposite cardiovascular results[2]. A considerable number of studies have revealed how prevalent factor is erectile dysfunction in individuals suffering from a CVD or patients risking to experience hypertension, dyslipidemia, diabetes, obesity and peripheral artery disease[3]. Although ED is explained due to the existence of same pathophysiological function with cardiovascular diseases, hypertension patients receive several medications in order to deal with CVD that may impact their sexual life[4].

This article aims to highlight and bring to the physician's attention the importance of ED as a prognostic factor when dealing with patients with hypertension and CVD. Erectile dysfunction, a well-known medical condition that is often coexists with hypertension, is the reason that contributes unevenly to the hypertensive patients and their sexual partners health well-being as well[5]. Consequently, it is extremely important to highlight that erectile dysfunction can truly be considered as a valuable indicator for asymptomatic or similar associated CVD events[3]. Outstandingly, it was shown that ED precedes the coronary artery disease (CAD) by two to five years. The successful management of ED has been particularly advanced by introducing phosphodiesterase-5 (PDE-5-i) inhibitors which effectively provided individuals with a simple and well-tolerated oral therapy[6].

PREVALENCE OF ARTERIAL HYPERTENSION & ERECTILE DYSFUNCTION

According to recent assessments, arterial hypertension has affected an estimated 26.4% of the population worldwide in 2000. It is alarmingly important to highlight that by 2025, arterial hypertension is estimated to concern the 60% of the planet's adults rising the number of affected cases up to 1.5 billion patients worldwide[6,7]. The prevalence of hypertension is growing substantially depending primary on age, estimated to touch up to 60% in older patients over 60 years. It goes without saying that arterial hypertension is prevalent to any population regardless of nationality, race or tribe or whether the concerned affected population comes from low, medium or high-income countries[8,9].

Additionally, due to the fact that life expectancy has been continuously prolonged over the last years through medical advances along with the fact that hypertension and sexual dysfunction are both related to the age of a patient, it is expected that both arterial hypertension and ED are going to be prevalent within the world's population in the future decades. Nonetheless, arterial hypertension is deeply connected with erectile dysfunction[6]. Recent studies have revealed that pathophysiology of ED implicates essential hypertension per se and their correlation and coexistence is unarguably a medical given fact[7].

Based on the findings collected through various observation studies, erectile dysfunction prevalence is high both to men and women[7,9]. In particular, it has been specified that erectile dysfunction may concern a percentage of a maximum 74% in a specific population between 55- and 75-years old hypertension patients[6]. However, ED is mainly prevalent in the male population of the above age category, reflecting a percentage of 15-20%[7]. It should be noted though that sexual dysfunction affects more the female than the male individuals[7,9].

Prevalence of ED is present especially in individuals with essential arterial hypertension. Several studies have underlined the correlation and interaction between these two diseases[10]. The first expanded trial, well known as the Treatment of Mild Hypertension Study (TOMHS) which revealed the extent to which ED is prevalent to patients with hypertension has been conducted in 1997[7]. The study has revealed that sexual dysfunction has been claimed by 14.4% of men and 4.8% of women included in the assessment. However, it should be noted that TOMHS study has excluded patients suffering from diabetes or severe hypertension, and especially male or female population with age over 70 years old[8]. Furthermore, the means for assessing the population's sexual function or erectile dysfunction were limited by asking only one related

question and not with the later advanced and elaborated validated tools (specific number of item questionnaires, i.e. IIEF-5 or IIEF-15)[6].

The study draws the attention to some additional qualitative characteristics that deserve to get high lightened. Patients with hypertension experience a more severe ED than those without hypertension. Secondly, the coexistence of other cardiovascular risk elements increases substantially the chances for a hypertension patient to experience a more prevalent ED. As more as the patient accumulates a number of comorbidities, the higher are the chances that ED appears to be more prevalent to that type of patient[11].

Individuals who suffer from an overt cardiovascular disease are prone to get diagnosed with ED whose prevalence is increasingly high in this category of individuals[6]. Recent studies such as the ONgoing Telmisartan Alone together with Ramipril Global Endpoint Trial (ONTARGET) and Telmisartan Randomized Assessment Study in ACE intolerant subjects with cardiovascular disease (TRANSCEND) trials along with SPRINT, demonstrate that ED affects half of individuals suffering from acute and/or chronic coronary artery disease while the great majority of men who suffer from heart failure is detected with ED[8,9]. All in all, hypertensive individuals compared with normal blood pressure individuals appear double chances to experience a prevalent ED whose prevalence is expected to get established permanently[12].

ED AND CVD SHARE A COMMON PATHOPHYSIOLOGY

Male erectile function involves a complex vascular process[11]. As far as their pathophysiology is concerned, endothelium of penis along with its smooth muscle tissue have great adherence with any change, functional and structural[12]. The damage of endothelium and its inflammation whether it is dependent or independent from the relaxation of the smooth muscle (this is what we call at an initial stage as functional vascular ED) or the obstruction of the cavernosal arteries due to atherosclerosis (this is what we call at a late stage as structural vascular ED) or both of the above combined result in vasculogenic erectile dysfunction[13].

Based on current data, endothelial dysfunction interacts in a complex way with subclinical inflammation and androgen deficiency. This common pathophysiological base explains the correlation of ED with CAD at clinical level[14]. The "artery size" hypothesis reveals the reason that an individual suffering from CAD may experience often ED prior to their detection with CAD[15]. Consequently, that proves that the larger coronary arteries are getting obstructed at a later stage than the smaller penile arteries whose proper function seem to happen beforehand and at a considerably earlier stage[16].

Non-obstructing atherosclerosis can also be explained with the same hypothesis: in comparison with other organs arteries, penile artery is smaller and its endothelial surface is greater, thus a large degree of vasodilation is necessary to occur for erection to happen[17]. These smaller vessels will experience the same endothelial dysfunction which will be simply symptomatic but subclinical in the larger vessels (i.e. coronaries). Similarly, arterial aging may also be the reason to have a similar outcome since, as measured by arterial stiffening large arteries of patients identified with erection dysfunction can be also affected.[6,18].

Incremental inflammatory and endothelial pro-thrombotic activation is strongly associated with erectile dysfunction[19]. It is very interesting that CAD patients without erectile dysfunction may experience an equal prothrombotic activation, while when these two conditions are combined, then the patient has to deal with an additional trouble[6,20]. Last but not least, another element like the androgen deficiency may be also regarded the reason of implication within the shared ED and CVD pathogenetic pathways, nonetheless, such an assumption cannot be sustained without a further substantiate research[13].

COEXISTENCE OF ED AND CVD

Clinical trials and physicians have concluded that ED serves as an independent factor and prognostic marker that may lead eventually to cardiovascular diseases and mortality[6,21]. Several researches and studies have demonstrated the tight interaction of these two comorbidities, specifying the association of ED of a hypertensive patient to experience certain risks for coronary artery disease, cardiovascular disease, cerebrovascular disease, and mortality of all cause[3,6,22]. Both ED and CVD appear to align with the same principal cardiovascular risk factors along with identical pathophysiological pathways[13]. Moreover, with regards to ED, various non-ordinary risk factors of psychological nature, like psychological depression, decreased mood for sexual activity, and feelings of love uncertainty from a partner, have led to the conclusion that a worse CVD prognosis is closely associated with that state of mind[6,21] In relation with the above and what is interesting to highlight is that ED is accentuated in men where ED prevalence is dependent on the CVD severity and duration[6,20,21]. Below there is a schematic depiction of the ED and CVD shared pathways.

Studies have shown that ED usually precedes coronary artery disease with an average of 3 years[22]. Physicians may take advantage of this ''time window"and take ac-

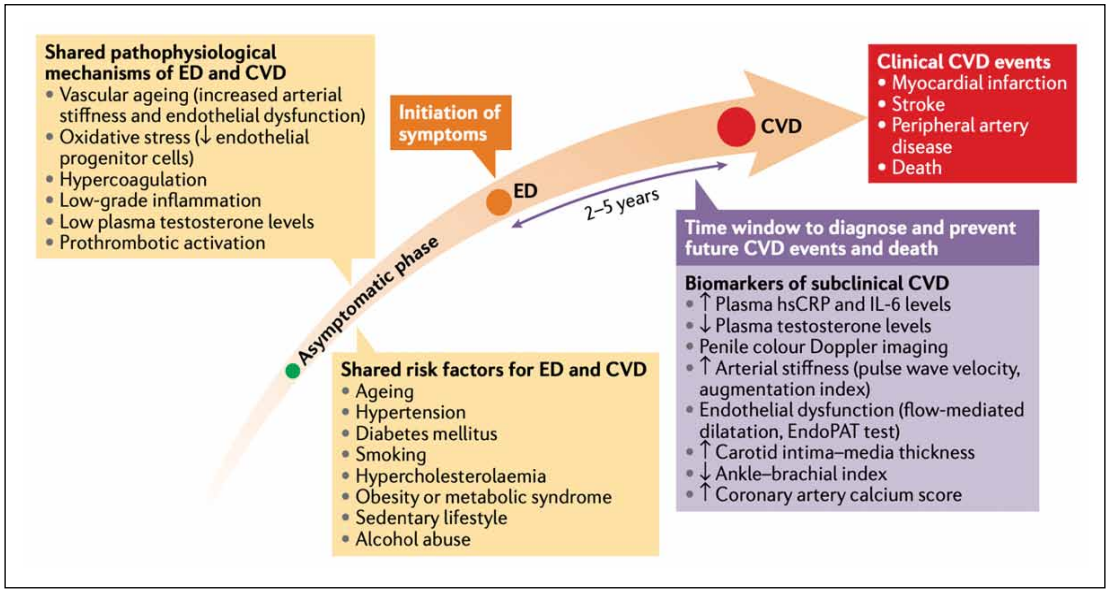

FIGURE 1. ED and CVD sharing the same pathways. The image depicts that erectile dysfunction (ED) and cardiovascular disease (CVD) share similar risk factors and pathophysiological mechanisms. ED manifestation may precede from 2-5 years before the CVD events appearance, a "window" timeframe during which physicians may take measures for prevention like hsCRP, high-sensitivity C-reactive protein.

tion as well in intervening and preventing CVD events in the future in favor of hypertensive patient. Regarding the male population suffering from chronic CAD, it has been proved that ED precedes CAD by 1–3 years[6,23]. The specific period can be specified based on how many diseased vessels have been affected (single-vessel disease is assessed with one year, two-vessel disease is assessed with two years, and three-vessel disease is assessed with three years)[24]. In order to substantiate further this correlation is the fact that the severity of symptoms can specify in which category of ED belong each patient and consequently these symptoms can further improve or predict a CVD and death in the future[6,25]. In case a patient does not present any cardiac symptoms, the ED can become a clear indicator or marker of CAD[26].

The importance of ED as a prognostic role is remarkable even in the men who are categorized as patients with high risk for CVD events like diabetes, CAD or heart failure, so consequently ED is perceived as a credible biomarker in order to prevent secondarily any CVD[27]. Diabetes represents, among the above comorbidities, the best case that has been studied in men with ED. ED and CVD events correlation was assessed in four studies, especially referring to male individuals with both type of diabetes[6,8]. These studies have unanimously concluded that ED has been proven to be the ultimate element that predicts potential CVD events in these types of patients. Moreover, the ONTARGET/TRANSCEND trials have proved and underlined that ED plays a prognostic role while diagnosing men with high risk of CVD[18,26]. Last but not least, data stipulate also that there is a high tendency for men with HF and ED to be exposed to mortal outcomes in comparison with men who suffer from HF but not from ED[26].

Nonetheless, it has been observed through various studies and time-length clinical trials that male population who are exposed to a low risk for CVD appear to belong at a younger age and hold no factors for an overt cardiovascular risk[6,26]. This category of men is most probable to experience psychogenic ED and not vasculogenic ED, thus it is not implied that these men suffer from vascular aging[6,19]. In such cases, the concerned population needs to be treated properly when psychogenic ED is identified[19,26].

DIAGNOSIS OF ERECTILE DYSFUNCTION

ED is regarded to be the hard binder during the diagnosis of a patient through his medical and sexual history. Physicians need to take into account thoroughly the medical record of a patient when they proceed to the diagnosis of ED[6,21]. The alarming aspects of a patient's medical history may contain probable cardiovascular symptoms, various risk factors and comorbidities like obesity, hypertension, diabetes, dyslipidemia. Additional factors like family record of premature atherothrombotic cardiovascular disease, lifestyle and medications that have been previously administered need also to be included during the ED assessment[22]. Further useful information might be also revealed by individual's sexual record. Especially when the diagnosis is to be determined between

psychogenic ED and organic/vasculogenic ED, physicians possess simple but tangible indicators to concretize successfully their diagnosis[6,23].

Specifically, psychogenic ED is determined by various reasons like the presence of acute onset, intermittent course, normal erections in the morning, and a history of psychosexual problems[6]. On the other hand, constant symptoms, the gradual onset and non regular morning erections lead to the conclusion that the patient is suffering from organic/vasculogenic ED[19]. Additional elements that may lead a physician to diagnose a predominant vasculogenic ED is when the patient experiences a cardiovascular disease or is exposed to high risk factors like advanced age and metabolic abnormalities[6,27].

Two specialized questionnaires have been used to assess the sexual history of a patient and identify potential ED[6]. The most common one is the International Index of Erectile Function (IIEF-15) questionnaire which is comprised of fifteen validated questions for self-evaluation. IIEF-15 is widely used and focuses its questions in order to assess penile function, desire, satisfaction, orgasmic function, and the general sexual fulfilment[28]. Likewise, IIEF-5, including only 5 questions, is also widely used to rapidly assess the sexual activity of concerned individuals.

In order to identify ED, six questions out of 15 of IIEF-15 questionnaire aim to reveal whether scoring less than 25 is an indication for ED diagnosis. Likewise, scoring 21 or below than score in the IIEF-5 questionnaire indicates an ED[28,29]. Both questionnaires are widely used by all general practitioners and clinical doctors like internists, cardiologists, diabetologists and nephrologists, and not only by andrologists and urologists exclusively. Furthermore, physicians need to perform thorough clinical tests of the individual's heart and peripheral circulation[6,26]. Urinary protein, fasting plasma glucose and an estimation of glomerular filtration rates represent some of the performed laboratory exams that may lead a physician to precisely assess whether a patient is exposed to any cardiovascular risk[6]. Additionally, calculating the cardiovascular risk score (SCORE or Framingham) to all concerned patients would stratify what is their level for cardiovascular risk[24,30]. Last but not least, it is also recommended to quantify the levels of testosterone in all relevant individuals suffering from organic ED, particularly when sexual function of patients has not been improved with the PDE-5 inhibitor therapy[6].

For patients who do not suffer from any cardiovascular disease and having no symptoms as well, it is important to determine various cardiovascular biomarkers who may provide with useful information in order to assess if the patient is exposed to any cardiovascular risk. Coronary artery calcium, central intima-media thickness, albuminuria, ankle–brachial index and aortic stiffness are associated with ED diagnosis and cardiovascular events[6,21]. It has been proven that especially albuminuria and aortic stiffness[19] are certainly leading a patient who suffers form ED to experience a cardiovascular event[13,22]. Lastly, organic/vasculogenic ED is also identified by using a penile Doppler[31,32].

MANAGEMENT OF ERECTILE DYSFUNCTION

Since ED is an indicator for potential CVD risk, all physicians should question their patients with vasculogenic ED about their sexual and medical history which will the baseline of assessment in order to anticipate whether these patients were initially exposed to any cardiovascular disease risk[33]. These patients need to be investigated by their physician in order to define the initial risk stratification which will defined according to the Framingham Risk Score[24,30]. This method helps physicians to identify within their concerned patients any potential risk for cardiovascular event or death, occurring within a 10-year timeframe[34]. Specifically, the Framingham Risk Score method takes into account various risk factors like the total and high-density lipoprotein cholesterol, sex, age, smoking, systolic blood pressure and the use of antihypertensive medications as well[35].

Male population who appears ED symptoms are expected to experience a cardiovascular disease and they can be considered themselves as being patients at high risk for any CVD event[6,27]. According to the Framingham Risk Score assessment, some of the tests that can be used by physicians in order to define which male population is exposed to a cardiovascular risk are the following ones: a complete and extensive medical history, the physical examination of the patient that includes measuring of visceral adiposity, evaluation of the ED duration and severity, resting electrocardiogram, assessing the fasting plasma glucose and serum creatinine (glomerular filtration rate) and albumin: ratio of creatinine and the metabolic syndrome attitude (presence or absence)[24]. Last but not least, sleep apnea should be also considered for examination of patients by their physician[6]. The physician should also determine whether the patient may respond to stress testing and the ability to exercise so as to assess the CVD risks and stratification[30].

According to the SCORE or Framingham Risk Score assessment, patients who are not exposed to overt CVD or any type of diabetes (type 1 or type 2) need to undergo an evaluation by their physician in order to identify if they run any risk for future cardiovascular events[24,30]. Patients who have been detected with a cardiovascular disease or any type of diabetes are classified as being in increased risk category[6,34]. Patients who demonstrate sufficient exercise

ability or perform a negative stress test, they can initiate sexual activity and get access to ED treatment[36]. On the other hand, patients who perform a positive stress test or are considered to be in high risk to produce a positive stress test, they need to delay any sexual activity until the moment they treat and stabilize their cardiac condition[6,35]. In any case, it is recommended that patient ought to follow up his physicians' advices for reassessment[6].

Furthermore, patients need to be urged by their physicians for lifestyle changes by introducing a healthier diet, motivation for physical exercise and quitting smoking which are widely considered to decrease cardiovascular risks and reestablish erectile function[26]. Male population which is classified as being at high risk for CVD events need to be also consulted by cardiologist[33]. Patients of intermediate risk with vasculogenic ED and no overt CVD need to undertake additional non-invasive assessment of cardiovascular risk though various available methods like exercise stress testing, ankle-brachial index, intima-media thickness or determination of coronary artery calcium scores[6,35]. There is no proof that any order of testing is adequate and it has not been established that any of these tests is more important one over the other in order to proceed to prognosis[24]. Physician who run the patients' tests need to select and customized tests according to patient's clinical profile, physician's judgment along with availability of test and cost involved[30].

Last but not least, the physician may examine the patient for testosterone levels in order to define the ED[6,33,34]. Testosterone constitutes a vital element and contributor in the physiological mechanism of erectile function. Testosterone contributes in stimulating the sexual desire, arousal and behavior[6,26]. Clinical trials have demonstrated that testosterone levels appear to be in lower levels of concentration especially in patients with ED who experience decreasing levels of sexual desire[33]. It should be highlighted that corporeal expression and activity of endothelial and neuronal NOS are regulated by testosterone while it enhances NO production[6]. Given the fact that testosterone is connected with CVD, physicians are encouraged to measure the levels of testosterone in all patients who are identified with vasculogenic ED, particularly in those cases of patients who responded unsuccessfully to phosphodiesterase type 5 (PDE5) inhibitor therapy[6,32].

CVD DRUGS IMPACT ON ERECTILE FUNCTION

While lifestyle changes like body training, healthier diet (particularly the Mediterranean diet), weight loss and quitting smoking are recommended to men with CVD as an additional prevention strategy, drugs related to CVD therapies or prevention may cause a decrease of sexual performance of an individual, thus consequently experiencing ED[6,37]. Although this is a common reality for men with CVD, this holds a close relation with the disease mechanism, various other factors of risk, sentimental state of mind like fear and anxiety, comorbidities, and methods of therapy especially to patients who have stable CAD, chronic heart failure (HF) or hypertension as well as patients who have undergone cardiac intervention like defibrillator implant, bypass graft surgery of coronary artery or heart transplantation[36].

Undoubtfully, individuals who suffer from a CVD and have been undergone a treatment are more probable to experience ED compared to those who have not undergone any treatment. This status implies that the treatment of a CVD event may contribute to an undesired and negative effect on erectile function. Earlier studies conclude that individuals who have undergone a treatment against hypertension are keen on experiencing a prevalent ED compared to those whose hypertension remained untreated[6,37]. The main explanation of such an event is because of the impact after β-blockers and/or diuretics use against patients with hypertension[38]. The above outcome confirms that although several antihypertensive medications like angiotensin-receptor blockers (ARBs), calcium-channel blockers and angiotensin-converting enzyme inhibitors are considered to be "erection-friendly", ED appears to be more prevalent in individuals who have undergone treatment against hypertension in comparison to the patients whose hypertension has not been identified[6,38]. However, the severity of ED remains the same in both cases[39]. Patients may experience a negative effect in penile blood flow because of the antihypertensive medications especially in cases where patients show low levels of blood pressure[33]. It is more alarming that when a patient is administered with a large number of CVD drugs, he is more probable to experience a more important ED deleterious effect[6,34]. A CVD therapy implies considerable effects on patient with ED, thus appropriate management of CVD drugs is recommended for its adherence[38].

Antihypertensive drugs demonstrate a resilient interaction between hemodynamic factors (like heart rate and/or blood pressure) and erectile dysfunction, so these drugs are considered as the best researched CVD drugs with an impact on men who suffer from erectile dysfunction[38]. It can be stated that physicians are getting genuinely challenged by the impact of the antihypertensive drugs on ED where they need to assess what strategy to follow in order to eliminate these side effects by offering to patients

with ED a sustainable and solid therapy against ED while improving the quality of their sex life[6,35]. Given the fact that these antihypertensive drugs may negatively affect men with ED, physicians need to support with insightful clinical assessment and as per patient's needs and profile by urging them to share these undesired side effects on the erectile function[35]. Categorizing antihypertensive drugs in classes, it can be clearly stated that some of them may have a neutral effect, some may have a beneficial one while others affect negatively patients with ED[38]. Consequently, according to each case of a patient with ED, physicians need to revise their decision to alter antihypertensive drugs of one class into the equivalent of another class[6]. Alternatively, by changing agents belonging in the same class of antihypertensive medications might be proved useful and successful to deal with a patient's erectile dysfunction[38].

All in all, antihypertensive medications of older generations (like first and second generation β-blockers, diuretics and methyldopa that is considered to be a central-acting agent) provoke a negative impact on erectile function[38]. Nonetheless, calcium-channel blockers, α-blockers and angiotensin-converting enzyme inhibitors represent a newer generation of antihypertensive medications with neutral impact on erectile function. Lastly, nebivolol and ARBs are the ones who affect in a beneficial way to men with ED[38].

It is quite complicated to explain precisely diuretics negative impact that may lead to erectile dysfunction. Sympathetic nervous system is mainly believed to get inhibited with the mediation of β-blockers since nervous system is also responsible for provoking erection and stimulate the release of testosterone[38]. Anxiety is the main outcome that β-blockers may produce as an adverse effect and consequently that may lead a patient to experience erectile dysfunction[39]. However, the use of selective β-blocker nebivolol, which blocks β1-adrenergic receptors, seems to contribute in a beneficial manner and against erectile dysfunction in comparison with non-selective β-blockers[6,38]. Especially with regards to non-selective β-blockers, it is important to underline that they reduce the sympathetic tone in the body causing an unproper vasodilatation[38]. This means that the levels of testosterone in plasma are getting reduced since these non-selective β-blockers affect the luteinizing hormone which ultimately would lead to sleepiness or depression, thus a libido is getting weaker[38].

As far as the renin-angiotensin-aldosterone system is concerned, angiotensin II plays also a major role, thus endothelial function is improved by ARBs who are also responsible for the promotion of adequate vasorelaxation, thus erectile function is improved considerably[6]. Concerning α-blockers, early studies that have been conducted with controlled administration of a placebo in random samples of patients suffering from benign prostatic hyperplasia, they demonstrate that therapy with a-blockers has at least a neutral effect on erectile function[7,37]. Nevertheless, the Treatment of Mild Hypertension Study (TOMHS) has shown that using the α-blocker doxazosin as an antihypertensive agent, erectile dysfunction still occurs almost at the same level, if not below, with the sample of patients who received a placebo[24,30].

Statins are presented to possible affect in a beneficial way and in favor of erectile function obstructing premature vascular aging (endothelial function is getting improved like arterial stiffness as well) which is very common in male population with erectile dysfunction[40]. Consequently, physicians may administer either statins alone or together with phosphodiesterase type 5 (PDE5) inhibitors as a therapy against ED[32].

As far as medications against arrhythmia are concerned, it seems that they have no effect to erectile function, however, β-blockers as well as digoxin do have an effect[23,41]. As an alternative solution to β-blockers, Ivabradine may act in favor of erectile function especially in male population who suffer from heart failure[23,41]. Last but not least, antiplatelet, anticoagulant agents and nitrates act mostly in a neutral way on erectile function[7,42].

Limited data exist for the new antidiabetic medications in favor of erectile function (dipeptidyl peptidase 4 inhibitors, glucagon-like peptide 1 receptor agonists, and sodium–glucose cotransporter 2 inhibitors). However, few findings show that erectile function can be improved with glucagon-like peptide 1 receptor agonists action. Given the limited results of these agents limited results for erectile function, physician need to customize cardiovascular medications therapy according to each patient's profile that may have ED symptoms[43].

ED TREATMENT AND ITS EFFECT ON CVD EVENTS

Changes in lifestyle (i.e., constant body exercise, losing weight, avoiding salt, adopting a healthier diet like the Mediterranean one, quitting smoking, restricting alcohol), avoiding medication associated with erectile dysfunction and counseling on sex activity represent important pillars for managing ED[6]. Similar strategies are implemented in order to deal with CVD events; however, the outcomes may vary and changes need to be applied to the concerned patients. Although different systemic and local treatments have been put forward by physicians in order to manage erectile dysfunction, these treatments are also linked with the risk of CVD events[42,43]. The most common systemic

treatments against ED are the administration of PDE5 inhibitors and appliance of testosterone-replacement therapy (TRT)[6].

PDE5 INHIBITORS

Introducing PDE5 inhibitors (PDE5-i) in order to manage ED in men, it was a historic breakthrough in modern drug development. However, the fact that it has not been introduced a similar treatment for women over the last years, it creates an unequal perception in the treatment of sexual and erectile dysfunction between the two genders[32].

The cGMP escapes from getting degraded with the blocking help of PDE5 inhibitors, who subsequently promote the blood flow into the penile body and reestablish the erectile function. PDE5 inhibitors have a mild hypotensive effect, since PDE5-i appears present in smooth muscle cells of blood vessels[44]. The process of the cGMP–nitric oxide also regulates the blood pressure[38]. In the rare scenario that the administration of PDE5 inhibitors has failed, this is due to the fact that endothelial has been extensively damaged which consequently decreases the nitric oxide bioavailability. In that case, an alternate therapy option has to be envisaged by physicians[6,45].

For the time being, sildenafil, avanafil, vardenafil and tadalafil represent the four worldwide approved drugs for extensive use PDE5 inhibitors while mirodenafil, udenafil and lodenafil are three additional drugs that are approved and administered in a small number of countries[45]. Sildenafil was the first drug that has obtained the approval as a therapy tool against ED with an approximate 20 min onset of action, also a 4-h half-life and a 12-h duration of long action[46]. Vardenafil appears to have the same profile like sildenafil. Tadalafil holds an impressive half-life of 17.5-h and a 36-h long duration of action[47]. On the contrary, Avanafil holds the shortest onset of action but it stays active for more than 6-h, which is considered at least a preferable safe alternative drug to be administered by physicians[48].

Based on individual's needs, a customized and individual therapy approach is possible to be implemented by physicians because of its pharmacokinetic and pharmacodynamic properties. Many clinical researches have examined the safety of PDE5 inhibitors in favor of cardiovascular events[6,46-47]. It has been confirmed that particularly sildenafil in comparison with placebo gives no sign of a potential risk for myocardial infraction or death[48]. Most of the mild side effects are like headache, dizziness, facial flushing, rhinitis, palpitation, nausea and dyspepsia while individuals with hypertension tolerate generally the above medications against ED[49].

The PDE5-i act in blood pressure without any synergy with the rest antihypertensive agents like calcium-channel blockers, β-blockers, angiotensin-converting enzyme inhibitors, diuretics or ARBs[6,37]. It is strongly recommended not to administer jointly PDE5-i and nitrates since there is an increased risk for the concerned individuals to experience symptomatic hypotension[47]. PDE5 inhibitors can be jointly administered with α-blockers that physicians may prescribe to manage benign prostatic hyperplasia, however, they need to be precautious in order to eliminate the chance for their patients to experience orthostatic hypotension[47]. For that reason, it is suggested that the two drugs need to be administered with a 6-h interval[48]. Physicians may also administer uroselective α-blockers but physician need to urge patients to report any side effect concerning ejaculation[49]. When administering a treatment whether with a PDE5 inhibitor or with an α-blocker, physicians should make sure that patients have followed their previous therapy on a stable pace for more than a month while the initial dose must be half of the typical dose and careful with gradual titration upscale[6,32,50].

There is growing evidence that PDE5 inhibitors act benignly on the cardiovascular system[32]. Some of them is that PD5-i foster the endothelial function, reverse the vascular aging based on the condition of patient's arterial stiffness and decrease active inflammation and oxidative stress[51]. Additionally, PDE5-i improve pulmonary and exercise hemodynamics while offer protection to penile from adverse side effects of any injury due to ischemia-reperfusion[49-51]. The administration of PDE5 inhibitors offers numerous advantages in a number of comorbidities like protection against probable CVD events while they offer benefits for survival of patients suffering from HF, peripheral artery disease and CAD[6,32,52]. Furthermore PDE5-i reduce considerably mortality risks in male population suffering from diabetes[53]. Nonetheless, depending on age and comorbidities of an individual, PDE5-i beneficial effects might not be similar to all patients and additional researches need to be conducted to substantiate this type of argumentation[32].

Testosterone Replacement Therapy (TRT)

The close relation and interaction between low testosterone levels and CVD events has been revealed in many recent research[6,26]. ED was proved to be the outcome of low testosterone levels which are prevalent in male population suffering from hypertension, or any type of diabetes, and metabolic syndrome[33]. Men experiencing erectile dysfunction need to undergo testosterone tests since exogenous testosterone replacement therapy (TRT) can improve dysfunction which is related to hypotestosteronemia[54].

According to the recent updated guidelines, there is no indication that it is important to check hypogonadal men suffering from hypertension for testosterone screen or to provide testosterone supplement. Only if it is recommended by the physicians, men with erectile dysfunction may get beneficial results through a combined therapy of TRT with PDE5 inhibitors[55]. Yet, such a therapy can take place exclusively to men with ED showing decreased total testosterone level (<8nmol/L) or to men with intermediate total testosterone levels (8-12nmol/L) and whose prior treatment only with PDE5 inhibitors did not give successful results or sufficient progress[6,55].

TRT has been proved to have beneficial effects in boosting muscle mass, fosters corporal strength and enhances erythropoiesis[55]. There are various methods for administrating testosterone such as through injection, transdermal and subdermal preparations or simply by oral and buccal routes[56]. However, adverse cardiovascular events, prostate cancer or exacerbation, sleep apnea or erythrocytosis are some of the potential side effects that a patient may experience afterwards and in the long-run.

A number of reports in the recent years claimed that TRT has caused raise in cardiovascular events in hypertensive men, thus remaining skeptical about TRT efficiency and raising concerns about TRT as a therapy approach which might against cardiovascular health[57]. However, it should be mentioned that these reports lack credibility, since the methodology used, was not in line with scientific standards like the volume of participants, sample, and period conducted[6]. On the other hand, different reports underline that TRT as a treatment approach offers substantial cardiovascular benefits to patient with hypertension, thus considering TRT as a safe method in favor of cardiovascular well-being[56-57]. In any case, further studies have to be conducted so as to reach more concrete assessments, with the examination of TRT effects on cardiovascular health or mortality in relation to a pre or post-treatment of testosterone levels in an hypertension patient suffering from erectile dysfunction[6,55].

CONCLUSION

Cardiovascular disease events and erectile dysfunction share common pathophysiological characteristics, while and they are subject to common risk factors like inflammation and dysfunction of the endothelium[6]. Furthermore, erectile dysfunction represents itself an independent risk factor leading to potential cardiovascular events in the future for a hypertensive individual[17]. It is certain and clinically approved that erectile dysfunction can be considered as an important tool of prognosis that can be used in order to predict any potential CVD risk especially for men over 40 years old[19].

However, identifying and treating ED is not always a priority for physicians and the issue remains partially unaddressed to patients with hypertension and CVD. Patients who appear to have arterial hypertension may also develop ED due to the administration of antihypertensive medications[7]. All in all, antihypertensive medications of older generations (like first and second generation β-blockers, diuretics and methyldopa that is considered to be a central-acting agent) provoke a negative impact on erectile function[23,41]. Nonetheless, calcium-channel blockers, α-blockers and angiotensin-converting enzyme inhibitors represent a newer generation of antihypertensive medications with neutral impact on erectile function[7-37]. Lastly, nebivolol and ARBs are the ones who affect in a beneficial way to men with ED. Statins, antiplatelet and anticoagulant agents have mostly neutral effect to the erectile function of hypertensive patients[40].

Additionally, introducing important changes in lifestyle habits coupled with ED drugs therapy can contribute to foster cardiovascular drug therapy and help men suffering from CVD to achieve a better quality of life. It is of paramount importance that physicians keep raising awareness especially within male hypertensive population to identify and report erectile dysfunction; that would enable physicians to better monitor the evolution or erectile dysfunction within a hypertensive individual. Administering PDE5 inhibitors constitutes an effective and safe solution for hypertensive patients with ED[32]. Additionally, TRT, alone or in combination with PD5 inhibitors forms an alternative therapy management for patients with ED but further substantiated and appropriate randomized studies would unveil the real relation between TRT and cardiovascular results and safety[55].

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Conflict of interest

There is no conflict of interest.

ΠΕΡΙΛΗΨΗ

Η στυτική δυσλειτουργία και η συσχέτισή της με την αρτηριακή υπέρταση και τα καρδιαγγειακά νοσήματα

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Σήμερα, πολλοί ασθενείς που πάσχουν από αρτηριακή υπέρταση φαίνεται να εμφανίζουν εκ των προτέρων και στυτική δυσλειτουργία (ΣΔ) που μπορεί να θεωρηθεί ως παράγοντας κινδύνου για καρδιαγγειακή νόσο. Τα τελευταία χρόνια, διάφορες κλινικές δοκιμές έχουν δείξει μια ανθεκτική συσχέτιση μεταξύ καρδιαγγειακής νόσου και στυτικής νόσου, που παρουσιάζουν κοινή παθοφυσιολογία. Κατά συνέπεια, η ΣΔ λαμβάνεται υπόψη σε μεγάλο βαθμό ως ένας πρώιμος δείκτης για την εμφάνιση συμπτωματικής καρδιαγγειακής νόσου. Η ενδοθηλιακή δυσλειτουργία, η αθηροσκλήρωση, τα χαμηλά επίπεδα τεστοστερόνης στο πλάσμα εμπλέκονται με κοινό παθοφυσιολογικό μηχανισμό στους υπερτασικούς ασθενείς που πάσχουν από ΣΔ και καρδιαγγειακά συμβάματα. Σε κάθε περίπτωση που η ΣΔ εξακριβώνεται σε πρώιμο στάδιο, συνήθως προηγείται κατά δύο έως πέντε χρόνια από ένα σύμβαμα καρδιαγγειακής νόσου. Επιπλέον, η διάγνωση της ΣΔ αντιπροσωπεύει ένα χαμηλού κόστους προγνωστικό εργαλείο για την πρωτογενή και δευτερογενή πρόληψη σε έναν ασθενή τόσο για καρδιαγγειακή νόσο όσο και για τη θνησιμότητα από κάθε άλλη αιτία. Τα διουρητικά και οι β-αναστολείς είναι μερικά από τα καρδιαγγειακά φάρμακα που επηρεάζουν αρνητικά τη ΣΔ και που οι γιατροί πρέπει να λάβουν σοβαρά υπόψη τους. Εν τω μεταξύ, η νεβιμπολόλη και οι αναστολείς του συστήματος ρενίνης – αγγειοτενσίνης - αλδοστερόνης (ΡΑΣ) έχει αποδειχθεί ότι επηρεάζουν θετικά όταν χορηγούνται σε έναν ασθενή. Οι αναστολείς PD5 αντιπροσωπεύουν μια πρωτοποριακή θεραπεία για την αντιμετώπιση της ΣΔ και θεωρούνται ασφαλείς για το καρδιαγγειακό σύστημα. Επιπλέον, οι αναστολείς PD5 είναι ωφέλιμοι για τη θεραπεία της σεξουαλικής δυσλειτουργίας και αντιπροσωπεύουν μια ασφαλή λύση για υπερτασικούς ασθενείς που λαμβάνουν ή όχι αντί-υπερτασικά φάρμακα. Οι μέχρι σήμερα διεξαχθείσες μελέτες με θεραπεία υποκατάστασης τεστοστερόνης (TRT) οδηγούν σε αντιφατικά αποτελέσματα που σχετίζονται με τους κινδύνους καρδιαγγειακής νόσου και όταν χρησιμοποιείται μια τέτοια θεραπεία, οι γιατροί θα πρέπει να παρακολουθούν στενά τον ασθενή για πιθανές ανεπιθύμητες ενέργειες.

ΛΕΞΕΙΣ ΚΛΕΙΔΙΑ: *Αρτηριακή υπέρταση, αθηροσκλήρωση, στυτική δυσλειτουργία, σεξουαλική δυσλειτουργία, καρδιαγγειακή νόσο, καρδιαγγειακά φάρμακα και θεραπεία, παράγοντες κινδύνου, παθοφυσιολογία, φλεγμονή, επίπεδα τεστοστερόνης, αναστολείς φωσφοδιεστεράσης τύπου 5*

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