

## Erectile Dysfunction and Cardiovascular Diseases

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### Abstract

Erectile dysfunction (ED) is the most common male sexual dysfunction and its prevalence is higher in men with cardiovascular diseases (CVD). Inflammation, endothelial dysfunction and oxidative stress are important in the pathogenesis in both of ED and CVD. Also aging, diabetes, smoking, sedantary life style and obesity are risk factors of these disorders. CVD such as coronary artery disease, heart failure (HF), and ED share several common risk factors, including diabetes mellitus, hypertension, smoking, and dyslipidemia. It is important to examine men with ED because ED is a symptom which is observed before CVD appears.

**Key words:** erectile dysfunction, cardiovascular diseases, risk factors

### Introduction

Erectile dysfunction (ED) is the most common male sexual dysfunction, is defined as the consistent or recurrent inability to acquire or sustain an erection of sufficient rigidity and duration for sexual intercourse persisting in 6 months and more (1). The prevalence of ED is very high in the general population. A study of 2126 men in United States stated that ED was seen in 24% of men aged 20 years and older. The incidence of ED, which was seen in 5% between the ages of 20-39, increased with age and it was seen in 70% of men aged 70 years and older (2).

A multinational study (MALES) which is performed in 27,839 men aged 20-75 years in eight countries (Brazil, France, Germany, Mexico, Italy, Spain, United Kingdom and United States) suggests that the ED prevalence is 16% and it increases with age. ED prevalence is higher in men with co-morbid situations like ischemic heart diseases (IHD), hypertension, and psychosocial conditions like depression (3).

### Pathophysiology of Erectile Dysfunction

Vascular and neural systems need to be healthy, correlated and work properly for erectile function. Penis blood flow is supplied by internal pudendal artery through the cavernose branches and its venous outflow is performed with venules plexus which could be compressed easily.

When the stimulation occurs for erection, spinal cord's sacral segment activates parasympathetic system and nitric oxide (NO) release cascade. Increased NO raises intracellular cyclic guanosine monophosphate (c(GMP)) which causes decreased intracellular calcium levels. This results in relax of vascular smooth muscle and increase in blood flow into the corpus cavernosum (4). The rapid flow of blood causes compression to the venous plexus and decrease in venous

outflow, and consequently the increase of intracavernous pressure causes erection. Accordingly, the impairs of vascular and neural systems may cause ED. The ED etiology is classified as psychological, physiological (neural, vascular, hormonal, medications, etc) or mixed.

### Psychological Factors of ED

Non-organic or sympathetic-mediated ED is defined as psychologic ED. Performance anxiety (fear of failure during intercourse) is one of the important factors related to ED. The other psychological factors are depression and psychosocial stress. Although adequate studies have not been conducted about psychogenic factor, psychologic ED is seen in a significant proportion in the society (4).

### Neurological Factors of ED

The deficit of nerve signalling to the corpora cavernosa causes neurogenic ED. This can be caused by spinal cord injury, multiple sclerosis, Parkinson disease, lumbar disc disease, traumatic brain injury, radical pelvic surgery (radical prostatectomy, radical cystectomy, etc.) and diabetic neuropathy. Spinal cord injury above T10 do not affect the local penile functions but can cause ED by inhibiting the central nervous system control. Spinal cord injury in sacral segment can cause functional and structural changes in penis because of the inhibition of innervation. S2-S4 injury causes reflexogenic erections (5).

### Hormonal Factors of ED

The major hormones for penile development and functions are androgens and they have an important role in ED (6, 7). Hypogonadism in men which is the deficiency of testosterone and dihydrotestosterone

hormones called androgens affects approximately 5% of the adult male population (8, 9). But the replacement of androgens in ED patients has controversial results. Both of low levels of testosterone and ED seen in older ages may cause discrepancies in these results. The increasing association of ED and the progressive decline of testosterone levels with ageing do not necessarily imply a causal link (10, 11).

Androgens have some other beneficial effects on both cardiovascular and penile tissues. Endothelial cells and smooth-muscle cells are the main cellular targets for direct androgen effects in both tissues. Androgens promote vascular endothelial cell survival, reduce endothelial expression of proinflammatory markers, and inhibit proliferation and intimal migration of vascular smooth-muscle cells. In turn, low androgen levels are associated with apoptosis of endothelial cells and smooth-muscle cells in penis (12).

Additionally, the other hormones such as thyroid hormones, prolactin, growth hormone, insulin-like growth factor 1, dehydroepiandrosterone and oxytocin have roles in erectile function (13, 14). Although these hormones play roles in erectile physiology, their impact on incidence of ED is thought to be low and awaiting more detailed studies. Prolactin is the second cause of hormonal ED. Hyperprolactinaemia inhibits gonadotropin secretion and induces hypogonadism. Thus, prolactin should be evaluated together with testosterone in men with ED.

## Medications

The 25% of ED may be caused by medications like antihypertensives, antidepressants, and antipsychotics but the exact mechanism has not been clearly identified. Specific medications which causes ED are  $\alpha$ -blockers, benzodiazepines,  $\beta$ -blockers, clonidine, digoxin, histamine,  $H_2$ -receptor blockers, ketoconazole, methyldopa, monoamine oxidase inhibitors, phenobarbital, phenytoin, selective serotonin reuptake inhibitors, spironolactone, thiazide diuretics, and tricyclic antidepressants (4). The use of antihypertensives such as thiazide diuretics and  $\beta$ -blockers are most commonly associated with ED (15).

## Vasculogenic Factors of ED

Vascular diseases are the most common causes of ED. Thus ED can be considered as a manifestation of an underlying vascular disorder. In these circumstances, blood inflow reduces, arterial insufficiency occurs and sometimes stenosis onsets and then all of them lead to ED. Of the vascular diseases hypertension can be a risk factor for ED. In hypertension cases, main cause of ED is alterations in the arterial walls. Also chronic hyperglycemia promote endothelial damage and vascular complications such as ED. In addition, atherosclerosis related to various disorders can lead to arterial stenosis and the vascular injury and decrease in oxygenation of affected tissue. Corpora cavernosal oxygenation decreasing factors cause an increase in profibrotic cytokines leading to increased collagen synthesis. When collagen synthesis increases and replaces smooth muscle, this situation results in impairment of vascular elasticity in penis (16). In turn, due to these vascular alterations, ED can occur.

All factors mentioned above are also effective ones in the development of cardiovascular diseases (CVD) such as IHD, hypertension and atrial fibrillation. Indeed, if vasculogenic ED is present in one patient, it can be an important risk factor for the presence of CVD. In other words, ED and CVD can be regarded as sharing a common underlying vascular pathology.

But ED becomes apparent 2-5 years before the onset of CVD. This state can be best explained by arterial size hypothesis suggested by Montorsi et al. (17). When common risk factors such as oxidative stress and inflammation cause deterioration of vascular structures of the body, endothelial dysfunction, intima-media thickening, vascular obstruction and flow-limiting stenoses happen respectively. According to this, because penile arteries are smaller than coronary arteries, disturbances

in penile arteries' blood flow result in earlier unwanted manifestations than in any other larger vessels such as coronary arteries. Thus ED can be considered as an early manifestation of systemic vascular disorders. In general, plaque can be tolerated by wider vascular structures but even if stenosis does not even appear, as penile arteries are smaller, oxygenation reduces.

## Impact of Inflammation and Endothelial Dysfunction on ED and CVD

ED is a complex and multifactorial condition, but it is known that endothelial dysfunction is an early event in the atherosclerotic process and has a pivotal role in the pathophysiology of ED (18). Major cardiometabolic risk factors such as diabetes, hypertension, hypercholesterolemia, obesity, sedentary life style, smoking, and aging are all associated with endothelial damage due to endothelial dysfunction; a condition in which the endothelial layer of the small arteries fails to function normally. Additionally low grade inflammation results in endothelial dysfunction. In one study aimed to show association among endothelial dysfunction, inflammation and ED in patients with or without IHD, it was found that serum levels of inflammatory and endothelial dysfunction markers increased in ED patients with or without IHD. Authors concluded that inflammation and endothelial dysfunction can be important conditions in ED (19).

## Oxidative Stress

In ED pathogenesis, oxidative stress has an important role. In normal conditions, reactive oxygen species (ROS) are continuously formed at low concentrations as a result of various reactions and these are eliminated by enzymatic and nonenzymatic antioxidant molecules (e.g. superoxide dismutase and ascorbic acid respectively). When either cells are exposed to excessive levels of ROS or there is an imbalance between pro-oxidants and antioxidants in favour of pro-oxidant, oxidative stress exists. Superoxide ( $O_2^{\cdot-}$ ) is the most important ROS. Excessive  $O_2^{\cdot-}$  and NO react on each other to yield peroxynitrite. Peroxynitrite not only has an important role in atherosclerosis (20) but also inactivates superoxide dismutase. This situation results in more and more increased peroxynitrite and decreased NO (21). Also, increased ROS especially  $O_2^{\cdot-}$  and peroxynitrite can cause endothelial cell apoptosis. Thus NO releasing decreases as well. (20). In addition to these effects,  $O_2^{\cdot-}$  has a vasoconstrictory effect (22). All these events caused by oxidative stress lead to not only ED but also CVD.

## The Potential Risk Factors in ED and CVD

### Aging

Today the studies showed that the aging is inevitable risk factor for ED (23-25). Because aging causes endothelial dysfunction with changing sex hormones like testosterone. It is known that men aged 30 start facing decrease of serum testosterone levels by 1% every year (26) and it is described as late-onset hypogonadism. Age-dependent decrease in testosterone production by luteal cells of testicle is partly cause of this situation.

ED in men with late-onset hypogonadism is associated with systemic endothelial dysfunction. Several studies has shown that hypogonadism is one of the causes of the increased oxidative stress and decreased NO bioavailability (27, 28). Also low-grade inflammation is another mechanism by which hypogonadism alters endothelial function.

Recently it has been shown that lower testosterone levels are correlated with higher risk of CVD (29). Also in one metaanalysis of 70 studies related to hypogonadism, it was demonstrated that hypogonadism is associated with increased risk of CVD and cardiovascular mortality (30).

### Obesity

Obesity, especially central obesity and physical inactivity are risk

factors for not only ED but also for CVD. Obesity generally includes risk factors of CVD such as hyperglycemia, hypertension, elevated triglyceride and low density lipoprotein-cholesterol (LDL-C), and decreased high density lipoprotein-cholesterol (HDL-C). The prevalence of obesity in men reporting symptoms of ED may be as high as 79% (31), but vascular risk factors seen in obesity mentioned above can be regarded to have important role in ED.

In one experimental obesity model, authors showed that obesity alone significantly impairs erectile function by inducing penile smooth muscle atrophy, endothelial dysfunction, and lipid accumulation. Furthermore, obesity treatment ameliorated the erectile function in patients with obesity and ED (32). Also in an insulin-resistant obese rat model investigating penile artery changes, reduction in the internal diameter of the penile artery was observed (31).

## Diabetes Mellitus

ED is a major complication of diabetes. In one metaanalysis including 145 studies and 88 577 male participants with diabetes, the overall prevalence of ED in diabetes was 59.1%. Type 2 diabetes patients had higher prevalence for ED than those with type 1 diabetes (33). Diabetic men also tend to have ED 10 to 15 years earlier compared to non-diabetics (34). It was also reported that there was a positive association between ED and glycaemic control (35).

As in CVD, it was shown that ED is the first symptom of diabetes (36). Namely, in men with ED, the prevalence of diabetes undiagnosed is higher than in the general population. So, erectile dysfunction can be regarded as a determinant symptom of diabetes and men with erectile dysfunction, should be scanned for diabetes (37).

Penile erection occurs as a result of smooth muscle relaxation in the cavernous body and associated blood vessels. Decreased NO (has a major role in the erection) and endothelial dysfunction have been described in experimental diabetes models as well as in human (38). Severe hyperglycemia causes increase in collagen content which shows fibrosis formation and apoptosis, and also decrease in smooth muscle in corporal tissue sections as well as other vascular structures (39) leading to insufficient smooth muscle relaxation. Accordingly, corpora cavernosa smooth muscle relaxation reduces. Additionally, micro- and macrovascular arterial disease due to oxidative stress, dyslipidaemia, arterial hypertension, hypogonadism, and drug side effects are contributing factors for ED. In one study it was found that diabetes negatively affects erectile parameters in patients with coronary artery disease (37). In the same study it was indicated that vascular occlusion due to above factors plays a great role in ED in patients with diabetes.

Regarding sexual activity and the psychological impact of ED in men with diabetes mellitus, significant and positive associations have been found between depressive symptoms and ED. In addition, ED contributes strongly to poorer quality of life in men with diabetes mellitus. Therefore, early detection of ED is essential to improve the psychological health and men's quality of life.

## Smoking

Smoking is the most widespread addiction worldwide. Smoking hasn't only been associated with several types of cancer, cardiovascular and respiratory diseases, but it has also been associated with ever increasing risk of ED. One of the effects of smoking on reproductive system is ED in men (40). It was demonstrated that smoking causes lower levels of testosterone (41). Also smoking is proven to cause lower levels of testosterone, arterial stenosis and intensify vascular injury and thereby result in ED (40, 42).

In one study analysing the relationship between smoking and ED, authors showed that while smoking is a risk factor for ED, risk of developing ED is considered not to be markedly affected with changes in smoking habits (43).

Smoking is a risk factor not only for coronary artery disease and atherosclerosis but also ED and it doubles the likelihood of ED (44).

According to some clinical studies, it is evident that smoking has some negative effects on erectile function by causing impairment of endothelium-dependent smooth muscle relaxation (44, 45). It is apparent that the association of ED with CVD rises in smokers. Therefore, a young man should be recommended to stop smoking even if he is not a patient with ED.

## Dyslipidemia

The association between atherosclerotic arterial disease and ED is well-established. Early observations that cholesterol is a key component of arterial plaques gave rise to the cholesterol hypothesis for the pathogenesis of atherosclerosis. Elevated levels of LDL-C and apolipoprotein B (apoB) 100, the main structural protein of LDL, are directly associated with risk for atherosclerotic cardiovascular events. Indeed, infiltration and retention of apoB containing lipoproteins in the artery wall is a critical initiating event that sparks an inflammatory response and promotes the development of atherosclerosis. The association between hyperlipidemia and ED is originally attributed to atherosclerosis in the hypogastric-cavernosal arterial bed, with a subsequent insufficiency in penile arterial inflow (46). Thus LDL-C therapeutic possibilities now exist to lower LDL-C to very low levels. On the other hand lower LDL-C levels were significantly associated with lower free testosterone and lower free androgen index in general men (47). And consequently serious discussions in clinical practice continue about decreasing the levels of LDL and the question of whether low LDL-C levels *per se* may provoke adverse effects in humans arises. In one recent study aimed to explore the association of LDL-C with androgen and ED in a general population of men, authors found that free testosterone levels increased with increasing LDL-C (48). But increased total cholesterol and LDL levels have impact on ED due to above mentioned effects.

With regard to other lipid parameters, Pinnock et al. found that high total cholesterol and triglyceride levels were independent predictors of ED (49). Roumeguere et al. reported that patients with ED have low levels of HDL-C (50). Because HDL transports cholesterol from extrahepatic tissues to the liver, where removed from the body, higher levels of HDL is considered as beneficial.

## Erectile Dysfunction and Ischemic Heart Disease

IHD is known as coronary artery disease and main type of CVD. It is the main cause of death, accounting for >9 million deaths in 2016 according to the World Health Organization (WHO) estimates. The major cause of myocardial ischemia is atherosclerosis and endothelial dysfunction plays an important role in the atherosclerosis progression (51). Many previous studies have documented that IHD and ED are linked. IHD can be used to predict the risk of ED because both conditions have the same risk factors. Conversely, ED may trigger events that further lead to IHD.

Also it was reported that there is a correlation between erectile function and number of coronary vessel disease in patients with IHD (52). In other words, severity of the ED correlates with the severity of the coronary artery disease.

In another study authors aimed to evaluate the erectile function in men with coronary artery disease and whether or not there is an association between the degree of ED and the age of their first acute myocardial infarction (53). In this study, male survivors of AMI in whom AMI occurred before the age of 45 and after the age of 65 were investigated. Patients of AMI survivors were divided to two groups and ED incidence analyzed. While in post-AMI male patients younger (<45 years) ED occurred in 33%, 90% of the older AMI patients (>65 years) complained of ED. The overall increase in ED presence suggests that the background of their coronary event is may reflect a generalized atherosclerotic process (53). Furthermore, treatment for ED after a first AMI (with phosphodiesterase-5 inhibitors) reduced mortality and HF hospitalisation ratios (54). This finding supports the information of the ED and CVD should be considered as different manifestations of a common underlying vascular pathology.

## Erectile Dysfunction and Atrial Fibrillation

Atrial fibrillation (AF) is the most common type of arrhythmia which is presented in 33 million people worldwide and it can affect quality of life (55). AF causes 2-fold cardiovascular mortality. Although the mechanism of AF is not yet fully established, oxidative stress, chronic inflammation, endothelial dysfunction are thought to play an important role in the development of AF (56-58).

Recent studies showed that AF may be a risk factor for ED development (59, 60). ED prevalence in AF male patients is 57% (61). A cohort study in 19,258 people suggested that AF is an independent risk factor for the development of ED (59). ED and AF have similar etiologies like endothelial dysfunction, inflammation, oxidative stress, vascular and hemodynamic deterioration especially due to atherosclerosis (62, 63). AF predisposes hypercoagulation via changing the blood flow in the the heart and increasing the level of coagulation markers as fibrinogen and P-selectin and it generates vascular risk correspondingly (64).

In a study which presented in 129 male patients, the association of prothrombotic situations and peripheral thromboembolism like microthrombi in penile arteries in AF patients and its impact on ED were investigated. The association between ED and peripheral thromboembolism was evaluated with CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>VASc scores. Both of these scores were significantly higher in with ED groups than without ED groups which mean ED in patient with AF is associated with elevated cardioembolic risk. This results showed that ED diagnosis should be a marker for prothrombotic situations especially for men over 65 (65). But a cohort study with 6273 people in Taiwan suggested that there was no relation between AF and ED (66). These controversial results may be caused by presence of IHD, diabetes mellitus, chronic obstructive pulmonary disease, chronic renal failure, stroke and medications like beta-bloker which are more common in AF group than the control group. This situation increases the probability of bias.

## Erectile Dysfunction and Hypertension

Arterial Hypertension is a CVD that leads to important systemic alterations and impairs normal organ function over time. It affects 1 in 3 adults in the United States (67). Also it was well defined that association between hypertension and ED was obvious. In hypertensive population, ED is more frequent than in normotensive ones (68, 69).

In case of prolonged high systemic blood pressure, endothelial damage occurs and this results in endothelial dysfunction. Additionally high levels of circulation of vasoactive molecules such as angiotensin II can lead to endothelial alterations. As mentioned earlier penile arteries are smaller and have a greater endothelial surface. Thus, high degree of

vasodilation is required for erection. As a result, the same degree of endothelial dysfunction which cannot be clinically manifested in coronary artery may be give clinical findings (i.e. failure of erection) (70).

In one metaanalysis aimed to evaluate the relation between hypertension and ED, eighteen cross-section studies involving a total of 41,943 participants and 10,151 cases of ED were used in this analysis. Authors found that there was an increased risk of ED in hypertensive patients with OR 1.84 (71).

Additionally, it was suggested that tighter blood pressure control is associated with lower incidence of ED. In a long time of follow-up, Hsiao et al. found that overall incidence for ED was 13.9. In their study, higher average systolic blood pressure was associated with a higher risk of ED and large variation in blood pressure was associated with a higher incidence of ED and a shorter time for the development of ED (72). According to this data, it may be concluded that hypertension treatment should be under strict control in order that ED doesn't develop.

## Erectile Dysfunction and Heart Failure

Sexual activity is one of the important indicators of quality of life and is significantly impaired in patients with HF. Studies have shown that there is a significant decrease in sexual interest in 60% to 90% of these patients and that sexual activity has stopped in approximately 25% (73, 74). Depression and anxiety are common manifestations in HF. Depression due to HF is another cause of ED, but it is still not fully understood whether HF and/or ED causes depression or whether these conditions develop independently (75).

Performance anxiety and fear of death may also play a role in sexual dysfunction in patients with HF. Even more complex is that selective serotonin reuptake inhibitors used in the treatment of depression and anxiety may also cause ED. Significantly reduced left ventricular function may further limit the physical effort required for satisfactory sexual intercourse by reducing cardiac capacity. In one study investigating the role of right ventricular function in sexual dysfunction, it was found that right ventricle dysfunction in patients with HF were associated with ED (76).

Schwarz et al. investigated the prevalence of ED in patients with HF and found to be 84% in a population of men with an average age of 59 years and chronic compensated HF (75). Recently it was found that cardiac resynchronization therapy (CRT) improved erectile function in HF status in Kuyumcu et al.'s study. Also a positive CRT response was found to be an independent predictor of increase in the erectile functions (77).

In conclusion, ED is complex and multifactorial condition and the underlying causes are similar to those of CVD. Since ED is seen before CVD symptoms, in order to prevent a possible cardiac events, such cases should be consulted with cardiologists regarding the CVD aspect.

## References

- Puppo V, Puppo G. Re: K. Hatzimouratidis, I. Eardley, F. Giuliano, et al. (2015) Guidelines on Male Sexual Dysfunction: Erectile Dysfunction and Premature Ejaculation. The Netherlands: European Association of Urology; 2015. <http://uroweb.org/guideline/male-sexual-dysfunction>. Eur Urol. 68(6):e136-7.
- Selvin E, Burnett AL, Platz EA.( 2007) Prevalence and risk factors for erectile dysfunction in the US. Am J Med.;120(2):151-157.
- Rosen RC, Fisher WA, Eardley I, Niederberger C, Nadel A, et al ( 2004) The multinational Men's Attitudes to Life Events and Sexuality (MALES) study: I. Prevalence of erectile dysfunction and related health concerns in the general population. Curr Med Res Opin;20(5):607-617.
- Irwin GM. Erectile Dysfunction.( 2019) Prim Care.;46(2):249-255
- Brackett NL, Lynne CM, Ibrahim E, Ohl DA, Sonksen J. (2010) Treatment of infertility in men with spinal cord injury. Nat Rev Urol.;7(3):162-172.
- Corona G, Maggi M.( T2010) The role of testosterone in erectile dysfunction. Nature Reviews Urology.;7(1):46.
- Corona G, Isidori AM, Aversa A, Burnett AL, Maggi M.( 2016) Endocrinologic control of men's sexual desire and arousal/erection. The journal of sexual medicine.13(3):317-337.
- Araujo AB, Esche GR, Kupelian V, O'Donnell AB, Travison TG, et al. (2007).Prevalence of symptomatic androgen deficiency in

- men. *The Journal of Clinical Endocrinology & Metabolism*;92(11):4241-4247.
9. Tajar A, Huhtaniemi IT, O'Neill TW, Finn JD, Pye SR, et al.(2012) Characteristics of androgen deficiency in late-onset hypogonadism: results from the European Male Aging Study (EMAS). *The Journal of Clinical Endocrinology*.97(5):1508-1516.
  10. Baskin LS, Sutherland RS, DiSandro MJ, Hayward SW, Lipschutz J, et al (1997) The effect of testosterone on androgen receptors and human penile growth. *J Urol.*;158(3 Pt 2):1113-1118.
  11. Boas M, Boisen KA, Virtanen HE, Kaleva M, Suomi AM, et al. (2006) Postnatal penile length and growth rate correlate to serum testosterone levels: a longitudinal study of 1962 normal boys. *Eur J Endocrinol.*;154(1):125-129.
  12. Mirone V, Imbimbo C, Fusco F, Verze P, Creta M, et al (2009) Androgens and morphologic remodeling at penile and cardiovascular levels: a common piece in complicated puzzles? *European Urology*.56(2):309-316.
  13. Sansone A, Romanelli F, Gianfrilli D, Lenzi A. (2014) Endocrine evaluation of erectile dysfunction. *Endocrine*.;46(3):423-430.
  14. Gabrielson AT, Sartor RA, Hellstrom WJG. (2019) The Impact of Thyroid Disease on Sexual Dysfunction in Men and Women. *Sex Med Rev*;7(1):57-70.
  15. Francis ME, Kusek JW, Nyberg LM, Eggers PW. (2007) The contribution of common medical conditions and drug exposures to erectile dysfunction in adult males. *J Urol.*;178(2):596; discussion 6.
  16. Moreland RB. (1998) Is there a role of hypoxemia in penile fibrosis: a viewpoint presented to the Society for the Study of Impotence. *Int J Impot Res.*;10(2):113-120.
  17. Montorsi P, Ravagnani PM, Galli S, Rotatori F, Briganti A, et al. (2005) The artery size hypothesis: a macrovascular link between erectile dysfunction and coronary artery disease. *Am J Cardiol.*;96(12b):19m-23m.
  18. Chang ST, Chu CM, Hsu JT, Hsiao JF, Chung CM, et al.(2010) Independent determinants of coronary artery disease in erectile dysfunction patients. *J Sex Med.*;7(4 Pt 1):1478-1487.
  19. Vlachopoulos C, Aznaouridis K, Ioakeimidis N, Rokkas K, Vasiliadou C, et al. (2006) Unfavourable endothelial and inflammatory state in erectile dysfunction patients with or without coronary artery disease. *European heart journal*.;27(22):2640-2648.
  20. Beckman JS, Koppenol WH.( 1996) Nitric oxide, superoxide, and peroxynitrite: the good, the bad, and ugly. *American Journal of Physiology-Cell Physiology*.;271(5):C1424-C37.
  21. Durackova Z. (2010) Some current insights into oxidative stress. *Physiol Res.*;59(4):459-469.
  22. Katusic ZS, Vanhoutte PM. (1989) Superoxide anion is an endothelium-derived contracting factor. *American Journal of Physiology-Heart and Circulatory Physiology*.;257(1):H33-H7.
  23. Sasayama S, Ishii N, Ishikura F, Kamijima G, Ogawa S, et al. (2003) Men's Health Study: epidemiology of erectile dysfunction and cardiovascular disease. *Circ J.*;67(8):656-659.
  24. Grover SA, Lowensteyn I, Kaouache M, Marchand S, Coupal L, et al. (2006) The prevalence of erectile dysfunction in the primary care setting: importance of risk factors for diabetes and vascular disease. *Arch Intern Med.*;166(2):213-219.
  25. Kloner RA. (2003) Erectile dysfunction in the cardiac patient. *Curr Urol Rep*. 2003;4(6):466-471.
  26. Harman SM, Metter EJ, Tobin JD, Pearson J, Blackman MR. (2001) Longitudinal effects of aging on serum total and free testosterone levels in healthy men. *Baltimore Longitudinal Study of Aging. J Clin Endocrinol Metab*;86(2):724-731.
  27. Yang J, Wang T, Yang J, Rao K, Zhan Y, et al. (2013) S-allyl cysteine restores erectile function through inhibition of reactive oxygen species generation in diabetic rats. *Andrology*.;1(3):487-494.
  28. Novo S, Iacona R, Bonomo V, Evola V, Corrado E, et al. (2015) Erectile dysfunction is associated with low total serum testosterone levels and impaired flow-mediated vasodilation in intermediate risk men according to the Framingham risk score. *Atherosclerosis*.;238(2):415-419.
  29. Kloner RA, Carson C, Dobs A, Kopecky S, Mohler ER, (2016) Testosterone and Cardiovascular Disease. *J Am Coll Cardiol.*;67(5):545-557.
  30. Corona G, Rastrelli G, Monami M, Guay A, Buvat J, et al. (2011) Hypogonadism as a risk factor for cardiovascular mortality in men: a meta-analytic study. *Eur J Endocrinol.*;165(5):687-701.
  31. Villalba N, Martinez P, Briones AM, Sanchez A, Salaces M, et al. (2009) Differential structural and functional changes in penile and coronary arteries from obese Zucker rats. *Am J Physiol Heart Circ Physiol.*;297(2):H696-707.
  32. Esposito K, Giugliano F, Di Palo C, Giugliano G, Marfella R, et al.(2004) Effect of lifestyle changes on erectile dysfunction in obese men: a randomized controlled trial. *Jama.*;291(24):2978-2984.
  33. Kouidrat Y, Pizzol D, Cosco T, Thompson T, Carnaghi M, et al. (2017) High prevalence of erectile dysfunction in diabetes: a systematic review and meta-analysis of 145 studies. *Diabetic Medicine*.;34(9):1185-1192.
  34. Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB.( 1994) Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. *The Journal of urology*.;151(1):54-61.
  35. Binmoammar TA, Hassounah S, Alsaad S, Rawaf S, Majeed A. The impact of poor glycaemic control on the prevalence of erectile dysfunction in men with type 2 diabetes mellitus: a systematic review. *JRSM open*. 2016;7(3):2054270415622602.
  36. Lewis RW.(2001) Epidemiology of erectile dysfunction. *Urologic clinics of north America*.;28(2):209-216.
  37. Sairam K, Kulinskaya E, Boustead G, Hanbury D, McNicholas T. (2001) Prevalence of undiagnosed diabetes mellitus in male erectile dysfunction. *BJU international*.;88(1):68-71.
  38. De Berardis G, Pellegrini F, Franciosi M, Belfiglio M, Di Nardo B, et al. (2007) Clinical and psychological predictors of incidence of self-reported erectile dysfunction in patients with type 2 diabetes. *The Journal of urology*.;177(1):252-257.
  39. Ferrini MG, Rivera S, Moon J, Vernet D, Rajfer J, Gonzalez-Cadavid NF. The genetic inactivation of inducible nitric oxide synthase (iNOS) intensifies fibrosis and oxidative stress
  40. Jandikova H, Duskova M, Starka L. (2017) The influence of smoking and cessation on the human reproductive hormonal balance. *Physiol Res.*;66(Supplementum 3):S323-s331.
  41. Hruskovicova H, Duskova M, Simunkova K, Hill M, Pospisilova H, et al. Effects of smoking cessation on hormonal levels in men. *Physiol Res*. 2013;62(1):67-73.
  42. Kovac JR, Labbate C, Ramasamy R, Tang D, Lipshultz LI. (2015) Effects of cigarette smoking on erectile dysfunction. *Andrologia*.;47(10):1087-1092.
  43. Austoni E, Mirone V, Parazzini F, Fasolo CB, Turchi P, et al. (2005) Smoking as a risk factor for erectile dysfunction: data

- from the andrology prevention weeks 2001–2002: a study of the Italian Society of Andrology (SIA). *European urology*.;48(5):817-818.
44. McVary KT, Carrier S, Wessells H. (2001) Smoking and erectile dysfunction: evidence based analysis. *J Urol.*;166(5):1624-1632.
  45. Tostes RC, Carneiro FS, Lee AJ, Giachini FR, Leite R, et al. (2008) Cigarette smoking and erectile dysfunction: focus on NO bioavailability and ROS generation. *J Sex Med.* 5(6):1284-1295.
  46. Sullivan ME, Keoghane SR, Miller MA. (2001) Vascular risk factors and erectile dysfunction. *BJU Int.*;87(9):838-845.
  47. Dobs AS, Schrott H, Davidson MH, Bays H, Stein A et al. (2000) Effects of high-dose simvastatin on adrenal and gonadal steroidogenesis in men with hypercholesterolemia. *Metabolism.*;49(9):1234-1238.
  48. Chen C, Zhai H, Huang G, Cheng J, Xia F, et al. (2018) Is lower low-density lipoprotein cholesterol associated with lower androgen and erectile dysfunction in men? *Nutr Metab Cardiovasc Dis.*;28(12):1304-1310.
  49. Pinnock CB, Stapleton AM, Marshall VR.?( 1999) Erectile dysfunction in the community: a prevalence study. *Med J Aust.*;171(7):353-357.
  50. Roumequere T, Wespes E, Carpentier Y, Hoffmann P, Schulman CC. (2003) Erectile dysfunction is associated with a high prevalence of hyperlipidemia and coronary heart disease risk. *Eur Urol.*;44(3):355-359.
  51. Matsuzawa Y, Lerman A. (2014) Endothelial dysfunction and coronary artery disease: assessment, prognosis, and treatment. *Coron Artery Dis.*;25(8):713-724.
  52. Greenstein A, Chen J, Miller H, Matzkin H, Villa Y, Braf Z. (1997) Does severity of ischemic coronary disease correlate with erectile function? *Int J Impot Res.*;9(3):123-1236.
  53. Dostalova G, Hlubocka Z, Bayerova K, Belohlavek J, Linhart A, et al (2017) Erectile Dysfunction in Young Myocardial Infarction Survivors: Evaluation, Follow Up. *Am J Mens Health.*;11(6):1739-1744.
  54. Andersson DP, Trolle Lagerros Y, Grotta A, Bellocco R, Lehtihet M, et al (2017) Association between treatment for erectile dysfunction and death or cardiovascular outcomes after myocardial infarction. *Heart.*;103(16):1264-1270.
  55. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, et al. (2001) Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *Jama.*;285(18):2370-23755.
  56. Li J, Solus J, Chen Q, Rho YH, Milne G, et al.(2010) Role of inflammation and oxidative stress in atrial fibrillation. *Heart Rhythm.*;7(4):438-444.
  57. Korantzopoulos P, Kolettis TM, Galaris D, Goudevenos JA. (2007) The role of oxidative stress in the pathogenesis and perpetuation of atrial fibrillation. *Int J Cardiol.*;115(2):135-143.
  58. Guazzi M, Arena R. (2009) Endothelial dysfunction and pathophysiological correlates in atrial fibrillation. *Heart.*;95(2):102-106.
  59. Lin WY, Lin CS, Lin CL, Cheng SM, Lin WS, et al (2015) Atrial fibrillation is associated with increased risk of erectile dysfunction: A nationwide population-based cohort study. *Int J Cardiol.*;190:106-10.
  60. Yilmaz S, Kuyumcu MS, Akboga MK, Sen F, Balci KG, et al. (2016) The relationship between erectile dysfunction and paroxysmal lone atrial fibrillation. *J Interv Card Electrophysiol.*;46(3):245-251.
  61. Platek AE, HRYNKIEWICZ-SZYMANSKA A, Kotkowski M, Szymanski FM, , et al. (2016) Prevalence of Erectile Dysfunction in Atrial Fibrillation Patients: A Cross-Sectional, Epidemiological Study. *Pacing and Clinical Electrophysiology.*;39(1):28-35.
  62. Harada M, Van Wagoner DR, Nattel S. (2015) Role of inflammation in atrial fibrillation pathophysiology and management. *Circ J.*;79(3):495-502.
  63. Griffiths HR, Lip GY. (2014.)New biomarkers and risk stratification in atrial fibrillation: simplicity and practicality matter.
  64. Fu R, Wu S, Wu P, Qiu J.(2010) A study of blood soluble P-selectin, fibrinogen, and von Willebrand factor levels in idiopathic and lone atrial fibrillation. *Europace.*;13(1):31-36.
  65. Szymański FM, Filipiak KJ, Platek AE, Kotkowski M, Opolski G. (2015) Can thromboembolic risk be associated with erectile dysfunction in atrial fibrillation patients? *Cardiology journal.*;22(4):446-552.
  66. Liu KL, Ye LL, Chou SH, Tung YC, et al. (2016) Erectile Dysfunction Is Not a Predictor of Atrial Fibrillation: A Population-Based Propensity-Score Matched Cohort Study. *J Sex Med.*;13(1):55-62.
  67. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, et al. (2013) Executive summary: heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation.*;127(1):143-152.
  68. Nunes KP, Labazi H, Webb RC. (2012) New insights into hypertension-associated erectile dysfunction. *Current opinion in nephrology and hypertension.*;21(2):163.
  69. Barrett-Connor E.(2005) Heart disease risk factors predict erectile dysfunction 25 years later (the Rancho Bernardo Study). *The American journal of cardiology.*;96(12):3-7.
  70. Nunes KP, Labazi H, Webb RC. (2012) New insights into hypertension-associated erectile dysfunction. *Curr Opin Nephrol Hypertens.*;21(2):163-170.
  71. Vlachopoulos C, Jackson G, Stefanadis C, Montorsi P. (2013) Erectile dysfunction in the cardiovascular patient. *European Heart Journal.*;34(27):2034-2046.
  72. Hsiao W, Bertsch RA, Hung YY, Aaronson DS. (2019)Tighter Blood Pressure Control Is Associated with Lower Incidence of Erectile Dysfunction in Hypertensive Men. *J Sex Med.*;16(3):410-417.
  73. Westlake C, Dracup K, Walden JA, Fonarow G. (1999) Sexuality of patients with advanced heart failure and their spouses or partners. *J Heart Lung Transplant.*;18(11):1133-1138.
  74. Jaarsma T.(2002)Sexual problems in heart failure patients. *Eur J Cardiovasc Nurs.*;1(1):61-67.
  75. Schwarz ER, Kapur V, Bionat S, Rastogi S, Gupta R, et al.(2008) The prevalence and clinical relevance of sexual dysfunction in women and men with chronic heart failure. *Int J Impot Res.*;20(1):85-91.
  76. Koutsampasopoulos K, Vogiatzis I, Ziakas A, Papadopoulos C, Imprialos KP, et al.(2019) Right Ventricular Function and Sexual Function: Exploring Shadows in Male and Female Patients With Heart Failure. *J Sex Med.*;16(8):1199-2111.
  77. Kuyumcu MS, Alagoz M, Yayla C, Unal S, Ozbay MB, Acar B, et al.(2018)The association between cardiac resynchronization therapy response and sexual activity in patients with heart failure. *Hellenic J Cardiol.*