Sohag University Sohag Medical Journal Faculty of Medicine

Review Article

Pathogenesis of erectile dysfunction: an update

Haisam Abdelrhman Ahmed[1],
Osama Eltaher Mahmoud Ahmed[2],
Mahmoud Hamdy Ahmed[3]

1-Department of Dermatology, Venereology, and Andrology, Sohag Faculty of Medicine. Sohag University.
2- Department of Neuropsychiatry, Sohag Faculty of Medicine. Sohag University.
3-Department of Internal Medicine, Sohag Faculty of Medicine. Sohag University.

Abstract:

Erectile dysfunction (ED) is a global sexual disease of males characterized by a poor impact on many aspects of the lives of both husbands and wives. Although the incidence of ED rises significantly with age, the authors reported that fifty to seventy percent of males in the age range of fifty to seventy years were normal as regard erection. Despite the high magnitude of the problem, not all patients search for medical advice; only 50 % of them interested in solving the problem. The authors classified erectile dysfunction into two categories, one occurs in males with decreased sexual desire and the other occur with normal desire. As regards the aetiology of erectile dysfunction, the authors classified the causes as arteriogenic, venogenic, and neurogenic. Also, there are other causes such as anatomical, hormonal, and drug-induced. Some patients with ED may complain of psychogenic factors. The role of microRNAs in erectile dysfunction is a recent theory. MicroRNAs **(miRNAs)** are ribonucleic acids with 22 nucleotides in length that are characterized by being single-stranded non-coding molecules. Nowadays, these single- stranded RNA molecules play a role in the development of different disorders. These disorders are related to miRNAs molecules: cardiovascular disease, diabetes, neurological dysfunction, and metabolic syndrome. MiRNAs have an essential role in male infertility and ED. MiRNAs may be as biomarkers and novel therapeutic targets for ED. The mechanisms that may explain the role of miRNA in ED include apoptosis, fibrosis, angiogenesis, and other mechanisms.

Keywords: Erectile dysfunction, MicroRNAs, pathogenesis

DOI: 10.21608/SMJ.2024.262078.1443
Correspondence : ahaitham122@yahoo.com

Received: 10 January 2024
Revised: 02 February 2024
Accepted: 28 February 2024
Published: 01 May 2024

Definition:

Erectile dysfunction (ED) is a global sexual disease of males characterized by a poor impact on many aspects of the lives of both husbands and wives. ED has many definitions reported in the literature. From these definitions, what was approved in 1992 by the National Institutes of Health Consensus Development Conference. Also, another definition was approved by the American Psychiatric Association‘s Diagnostic and Statistical Manual of Mental Disorders. Also, the World Health Organization's International Classification of Diseases approved another definition for ED.(1)

One of the accepted ED definitions was approved by the National Institutes of Health. It is characterized by failure of initiation and/or maintenance of erection for satisfactory sexual intercourse. (1) Also, ED is defined as the persistent or

recurrent failure in the initiation and/or maintenance of erection of the penis. [2]

Epidemiology:

In multicentre clinical trial was conducted in many countries such as England, USA and Australia, ED prevalence was reported. The higher occurrence was detected at the age of eighty years, which was about thirty to forty percent. In the age of seventy, ED was about fifteen percent in the age of seventy. At the age of sixty, ED prevalence was about ten percent. In ages less than sixty years, ED prevalence was about five percent. In many clinical trials, it was reported that ED is related to aging, psychiatric disorders, being overweight, and a sedentary lifestyle. Also, increased blood glucose levels, increased blood pressure, and an abnormal lipid profile are associated with ED. Also, cardiovascular disorders and urinary tract disorders, such as benign prostatic hyperplasia are related to ED. [3,4]

In a clinical trial conducted in Egypt, it was reported on the erectile dysfunction prevalence and correlations by Seyam et al. The study reported that, with aging, the occurrence of erectile dysfunction increased. A complete ED represented about thirteen percent of the sample. At the age of fifty, 26% showed ED. At the age of sixty, 49% showed ED. At the age of more than seventy, 52% showed ED. Also in the trial, it was reported that there was a moderate correlation between sexual desire, sexual satisfaction, and state of erection. Also, in that trial it was reported that ED was lower between males in urban zones and those with higher social and economic status. Also, prevalence was higher among smokers. Also, ED was higher in those with an increased blood glucose level and increased blood pressure. Cardiovascular disorders, hepatic disorders, gastric ulcers and kidney disorders are also related to ED. [5]

Risk factors of erectile dysfunction:

Erectile dysfunction is characterized by being predisposed by irreversible and reversible common risk factors or both. Those risk factors include cardiovascular diseases (CVDs), being overweight, increased blood glucose levels, hyperlipidaemia, metabolic syndrome, a sedentary lifestyle, and smoking. [6]

So, patients with mild ED and those with severe ED have similar risk factors for ED. And also, ED is considered a predisposing factor for cardiovascular diseases. [7]

Some clinical trials approved that changes in a bad lifestyle [8] and medical treatment [9] for predisposing factors of cardiac disorders may solve the problem of erectile dysfunction. However, other controlled prospective clinical trials are important to detect the impact of increased physical activities or changes in the sedentary lifestyle on the correction of ED. [10]

Relation between disorders of the urinary tract system such as benign prostatic hyperplasia (BPH) and erectile dysfunction was reported in many clinical trials, in spite of different predisposing factors. [4]

A multi-centre clinical trial was conducted in Europe and USA by the Multinational Survey on the Aging Male (MSAM-7). In that study, investingators examined about 12,000 patients for erectile dysfunction and disorders of the urinary tract system. A relationship between erectile dysfunction and disorders of the urinary tract system was approved, where ninety percent showed lower urinary tract symptoms and forty-nine percent showed erectile dysfunction. [11]

Physiology of erection:

The state of flaccidity of the penis under normal conditions is maintained by corpus cavernosum smooth muscle contractions. Erections develop after exposure of the male to sexual stimului resulting in relaxations of smooth muscles that enlarge the corpora cavernosa, causing local venous compression and preventing venous return temporarily. And so, contractions and relaxations of the corpora cavernosa smooth muscles have an important role in the erection of the penis. [12]

Multiple signaling pathways play a role in the development of the erection of the penis. The NO/cGMP pathway represents the main pathway that mediates penile erection. The RhoA/ROCK pathway represents another pathway that also mediates penile erection throw relaxation of smooth muscles. [13]

Cyclic guanylate phosphate (cGMP) is formed under the effect of guanylate cyclase (GC) from guanosine triphosphate (GTP) in the presence of nitric oxide. Then, in the smooth muscle cells of both corpora cavernosa of the penis, cGMP kinase is activated, leading to a decrease in intracytoplasmic levels of calcium during relaxation. Finally, the myosin light chain (MLC) is dephosph-

orylated, leading to the erection of the penis throw relaxation of corpora cavernosa smooth muscle cells [14] as shown in figure 1 below.

Vice versa, substances like norepinephrine and endothelin reverse the erection state, developing detumescence. That occurs through increase in the level of ionized calcium inside the smooth muscle cell cytoplasm. This in turn leads to smooth muscle cell of corpora cavernosa contraction due to myosin light chain (MLC) phosphorylation. [15]

And so, Rho-related protein kinase (ROCK) is activated. This is followed by an increase in the intracytoplasmic level of Ca2+ which in turn stimulates MLC phosphorylation, which is followed by contractions of the smooth muscles of the penile corpora cavernosa, causing penile weakness.[15]

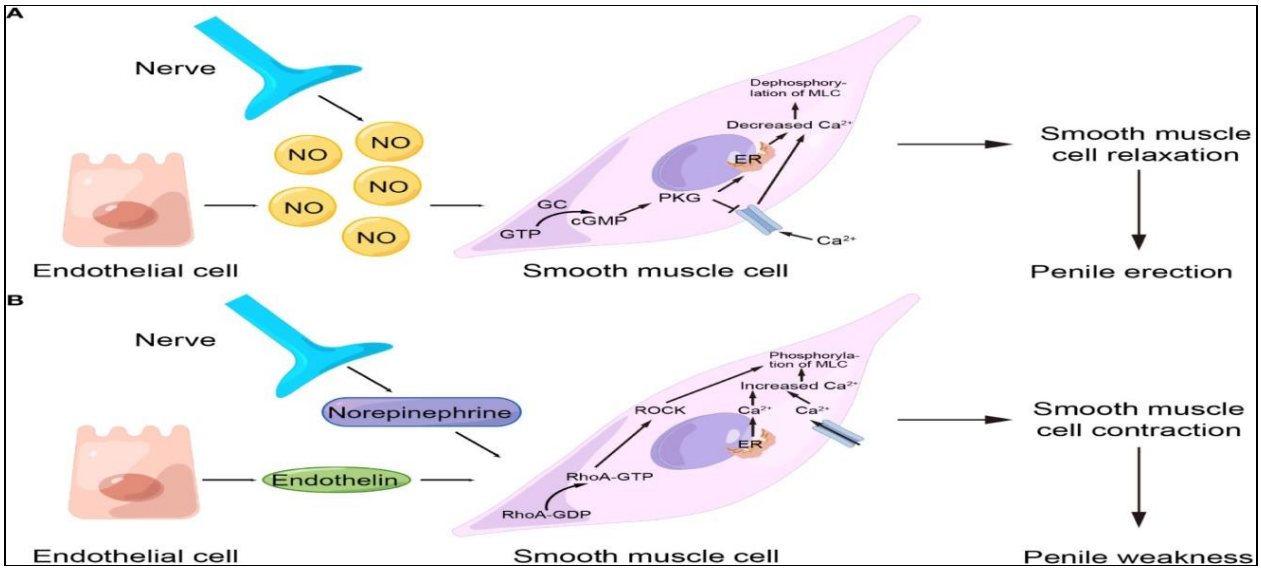

Figure 1: Physiology of erection (15).

Erectile dysfunction pathophysiology:

The authors classified erectile dysfunction into two categories: one of them occurs in males with decreased sexual desire, and the other occurs with normal desire. Those with decreased sexual desire are characterized by diminished attraction towards one's wife. That may be due to diseases, or it may also be due to long-time husband and wife relationships. Also, that condition may be due to psychogenic disorders or organic problems. The second condition (normal desire) is usually associated with organic causes, as will be described below in the coming words. **(16)** As regards the aetiology of erectile dysfunction, the authors classified the causes as arteriogenic, venogenic, and neurogenic. Also, there are other causes such as anatomical, hormonal, and drug-induced. **(17)**

1-Vasculogenic as:

- Cardiovascular diseases as increased blood pressure, ischaemic heart disease, and peripheral vascular diseases.
- Diabetes mellitus.
- Hyperlipidaemia.
- Smoking.
- Major pelvic surgery as radical prostatectomy or radiotherapy (pelvis or retro peritoneum).

2-Neurogenic as

- Central causes as degenerative disorders like multiple sclerosis, Parkinson's disease and multiple atrophy. Also trauma or disease of the spinal cord, stroke and tumours of the central nervous system.
- Peripheral causes as polyneuropathy, insulin dependent or non-insulin dependent diabetes mellitus and chronic renal failure. Also surgery in the pelvis or retro peritoneum, radical prostatectomy and colorectal surgery.

3-Anatomical or structural as micropenis, peyronie's disease, hypospadias and epispedias.

4-Hormonal as hypogonadism, hyperprolactinemia and hyper- and hypothyroidism. Also hyper- and hypocortisolism, panhypopituitarism and multiple endocrine disorders.

5-Drug-induced: antipsychotics as neuroleptics, antiandrogens as GnRH agonists and antagonists, H2-antagonists, ACE-inhibitors, recreational drugs (alcohol, heroin, cocaine, marijuana, methadone, synthetic drugs, anabolic steroids and antihypertensives as thiazide diuretics and antidepressants as selective serotonin reuptake inhibitors & tricyclics antidepressants.

6-Psychogenic as lack of arousability, disorders of sexual intimacy, partner-related troubles, performance-related issues, or distress)

7-Trauma.

Classification of erectile dysfunction:

ED is stratified into three types, depending on the cause. These types include psychogenic ED, organic ED, and mixed ED. As the majority of cases are already of mixed type, this classification should be used carefully. So now we use other terms, like primary organic or primary psychogenic. [18]

The role of microRNAs in erectile dysfunction is a recent theory:

MicroRNAs (miRNAs) are ribonucleic acids with 22 nucleotides in length that are characterized by being single-stranded non-coding molecules. Since authors first reported about miRNA in 1993, many clinical trials on humans and animals with regard miRNA have been conducted. So, a more obvious understanding of the genetic nature of those molecules was reached. [19]

RNA polymerase II (Pol II) acts on miRNA genes inside the nucleus, causing transcription of those genes forming primary miRNAs (pri-miRNAs). Endonuclease in tern cleaves primary miRNAs to produce a precursor molecule called pre-miRNA. Then transportation of that precursor molecule to the cytoplasm from the nucleus occurs with the aid of double-stranded RNA-binding proteins. Then the transported pre-miRNAs were changed to small double-stranded RNAs by endonuclease, that then fused with the former binding protein.[20]

At last, the RNA-induced silencing complex (RISC) is formed through the binding of a single strand of the double-stranded RNA molecule with the Argonaute protein. At that level, miRNA can prevent the translation of messenger RNA (mRNA). This occurs through binding with the complementary zone which can affect the expression of genes. [21]

Many clinical trials reported that miRNAs have a role in the initiation and development of different disorders. Cardiac diseases, diabetes mellitus, neurological disorders and metabolic syndrome are examples of those diseases. MiRNAs have an essential role in male infertility and ED. MiRNAs may be considered as biomarkers and novel therapeutic targets for ED. [19]

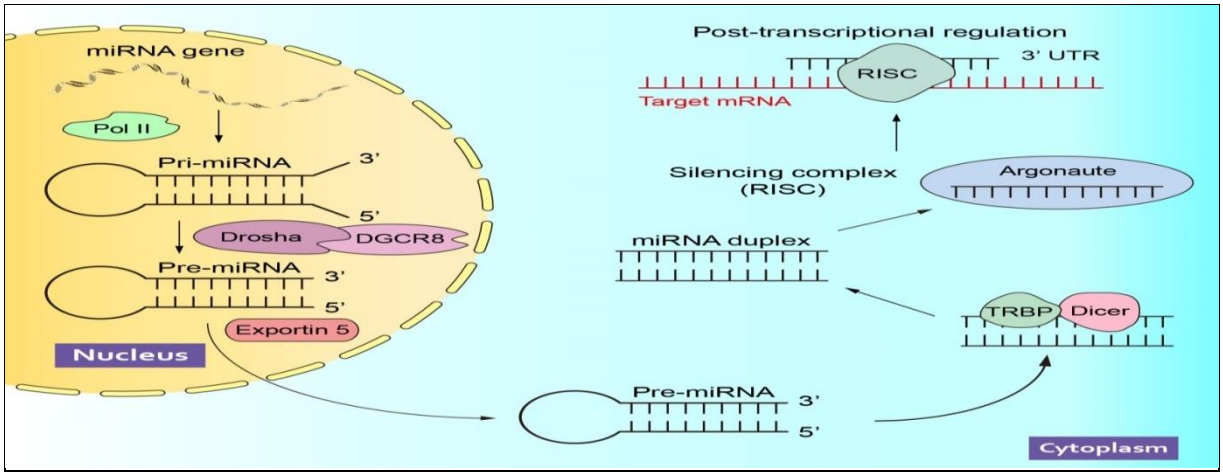

Figure 2 The Biogenesis and Function of miRNAs. (15)

The authors reported that microRNAs (miRNAs) have an important role in the progression of erectile dysfunction. Those molecules are characterized by being single-stranded RNA molecules that cannot be coded for as DNA. Also, those molecules have a role in the pathophysiology of the initiation and progression of ED. [19]

MiRNA expression in ED: Authors reported that, unlike normal conditions, in many disorders,

miRNAs levels may be higher or lower. Not only that miRNAs have a role in the initiation of different diseases, but they can affect the progression of the disease. [22]

With the advancement of molecular technologies, many miRNAs are detected in different types of ED. Up- and down-regulation of different miR-NAs were detected in different ED types. Clinical studies have approved that many miRNAs have a role in the development of ED. Also, many of those miRNAs may be used as diagnostic markers for ED. [22]

Molecular mechanisms of miRNA in ED:

1-Apoptosis**:**

It is considered as one of the main biological mechanisms in the development of ED. Cellular components of the corpora cavernosa, which include endothelial cells and smooth are affected by apoptosis through different mechanisms. These mechanisms that explain apoptosis include increased blood glucose levels, oxidative stress, and inflammation which ultimately cause ED. Recently many clinical trials have reported that those RNA molecules play a role in the stimulation or inhibition of apoptosis in ED.[23]

2-Fibrosis:

Fibrosis is considered a pathological process that occurs in the corpora cavernosa of the penis, causing ED. Fibrosis is associated with extensive proliferation factors that stimulate fibrosis and the production of a large amount of collagen. The authors reported that different miRNAs such as miR-101a, 138, 338 and 142 may be involved in fibrosis of the corpora cavernosa. No one can completely know exact way in which fibrosis is formed. The Wnt signaling pathway and The TGF-b signaling pathway may play a role in the production of fibrosis. [24]

3-Angiogenesis:

Recently miR- 126 was investigated upon as regard ED. Zou et al. reported on the mechanism by which miR- 126 stimulates angiogenesis. They approved that miR-126 stimulates angiogenesis, increasing penile erection. That occurs through the stimulation of many transcription factors that induce cell growth. [25]

Angiogenesis is regulated by many factors. One of these factors that are considered a maestro in angiogenesis is VEGF. VEGF is a molecule that enhances the development of new blood vessels. That occurs through stimulation of the growth and proliferation of endothelial cells. In an animal study in mice with neurogenic ED, it was reported that miR-200a has a role in VEGF. It was found that, miR-200a downregulates VEGF which in turn causes ED. (25)

5-NO/cGMP pathway:

As we know NO/cGMP pathway is considered a corner stone in the development of ED. As described above in the sector of physiology of erection, normal levels of NO & cGMP molecules have an essential role in occurrence of penile erection. Recently in the literature, many miRNAs can affect NO & cGMP molecules negatively affecting erection of the penis. Examples of miRNAs include miR-328, 200a,1, 203, 206, 18a, 155 and 146a. [15]

6-Other molecular mechanisms:

Also, miRNAs have a role in the occurrence of ED through multiple effects on neurotropic factors. Also, miRNAs can affect AGEs and other biological factors that play a direct or indirect role in the pathogenesis of ED. [15]

References:

1-McMahon CG. Narrative review. Current diagnosis and management of erectile dysfunction. MJA. 2019:10:469-476.

2-McCabe MP, Sharlip ID, Atalla E, Richard Balon, Alessandra D Fisher, Edward Laumann, Sun Won Lee, Ron Lewis, Robert T Segraves. Definitions of sexual dysfunctions in women and men: a consensus statement from the Fourth International Consultation on Sexual Medicine. J Sex Med 2015; 13: 135 - 144.

3-Feldman HA, Goldstein I, Hatzichristou DG, Krane RJ, McKinlay JB. Impotence and its medical and psychosocial correlates: results of the Massachusetts Male Aging Study. J Urol 1994; 151: 54–61.

4-Seftel AD, Rosette J de la, Birt J, Porter V, Zarotsky V, Viktrup L.Coexisting lower urinary tract symptoms and erectile dysfunction: a systematic review of epidemiological data. Int J Clin Pract 2013: 67: 32-45.

5-Seyam RM, Albakry A, Ghobish A, Arif H. Prevalence of erectile dysfunction and its correlates

in Egypt: A community-based study. International Journal of Impotence Research. 2003: 15 : 237-45.

6-Jackson G, Piero Montorsi, Michael A Adams, Tarek Anis, Ahmed El-Sakka, Martin Miner, Charalambos Vlachopoulos, Edward Kim. Cardiovascular aspects of sexual medicine. J Sex Med. 2010 :7: 1608-26.

7-Lee JC, Francois Bénard, Serge Carrier, Varun Talwar, Isabelle Defoy. Do men with mild erectile dysfunction have the same risk factors as the general erectile dysfunction clinical trial population? BJU Int. 2011: 107: 956-60.

8-Gandaglia G, Alberto Briganti , Graham Jackson , Robert A Kloner , Francesco Montorsi , Piero Montorsi , Charalambos Vlachopoulos. A systematic review of the association between erectile dysfunction and cardiovascular disease. Eur Urol. 2014 :65: 968-78.

9-Vlachopoulos C, Graham Jackson, Christodoulos Stefanadis, Piero Montors. Erectile dysfunction in the cardiovascular patient. Eur Heart J. 2013.34(27):p.2034-46.

10-Gupta BP, M Hassan Murad, Marisa M Clifton, Larry Prokop, Ajay Nehra, Stephen L Kopecky. The effect of lifestyle modification and cardiovascular risk factor reduction on erectile dysfunction: a systematic review and meta-analysis. Arch Intern Med. 2011 :171: 1797-803.

11-Rosen R, Altwein J, Boyle P, Roger S Kirby, B Lukacs, Meuleman E, O'Leary MP, Puppo P, Robertson C, Giuliano F. Lower urinary tract symptoms and male sexual dysfunction: the multinational survey of the aging.male (MSAM-7). Prog Urol. 2004; 14: 332–344.

12-Yafi FA, Jenkins L, Albersen M, Corona G, Isidori AM, Goldfarb S, et al. Erectile dysfunction. Nat Rev Dis primers 2016 :2:16003.

13-Matsui H, Sopko NA, Hannan JL, Bivalacqua TJ. Pathophysiology of erectile dysfunction. Curr Drug targets. 2015 : 16:411–9.

14-Roushias S, Ossei-Gerning N. Sexual function and cardiovascular disease: what the general cardiologist needs to know. Heart (British Cardiac Society). 2019: 105:160–8.

15-Song J, Wang J, Liu K, Xu W, Sun T, Liu J. The role of microRNAs in erectile dysfunction: From pathogenesis to therapeutic potential. Frontiers in Endocrinology J. 2022:14: 22-30.

16-Mazzilli F. Erectile Dysfunction: Causes, Diagnosis and Treatment: An Update. J. Clin. Med. 2022, 11, 6429 – 39.

17-Gratzke C, Javier Angulo, Kanchan Chitaley, Yu-Tian Dai, Noel N Kim, Jaw-Seung Paick, Ulf Simonsen, Stefan Uckert, Eric Wespes, Karl E Andersson, Tom F Lue, Christian G Stief. Anatomy, physiology, and pathophysiology of erectile dysfunction. J Sex Med. 2010: 7: 445-75.

18-Hatzimouratidis K., Eardley I., Giuliano F., Moncada I., Salonia A. Guidelines on Male Sexual Dysfunctio. Erectile dysfunction and premature ejaculation. European Association of Urology. 2015: 1-38.

19-Ha M, Kim VN. Regulation of microRNA biogenesis. Nat Rev Mol Cell Biol. 2014 : 15:509–24.

20-Lee RC, Feinbaum RL, Ambros V. The c. elegans heterochronic gene lin-4 encodes small RNAs with antisense complementarity to lin-14. Cell. 1993: 75:843–54.

21-Sadiq S, Crowley TM, Charchar FJ, Sanigorski A, Lewandowski PA. MicroRNAs in a hypertrophic heart: from foetal life to adulthood. Biol Rev. Cambridge Philos Society.2017 :92:1314–31.

22-Lu TX, Rothenberg ME. MicroRNA. J Allergy Clin Immunol. 2018: 141:1202–7.

23-Wang H, Zhang K, Ruan Z, Sun D, Zhang H, Lin G, et al. Probucol enhances the therapeutic efficiency of mesenchymal stem cells in the treatment of erectile dysfunction in diabetic rats by prolonging their survival time via Nrf2 pathway. Stem Cell Res Ther. 2020: 11:302.

24-Cui K, Tang Z, Li CC, Wang T, Rao K, Wang SG, et al. Lipoxin A4 improves erectile dysfunction in rats with type I diabetes by inhibiting oxidative stress and corporal fibrosis. Asian J andrology. 2018: 20:166–72.

25-Apte RS, Chen DS, Ferrara N. VEGF in signaling and disease: Beyond discovery and development. Cell. 2019: 176:1248–64.