IABJ. Volume 4 No 1. June 2023
Available online at https://e-journal.unair.ac.id/iabj

e-ISSN: 2746-4474
DOI=10.20473/iabj.v4i1.43832

INDONESIAN ANDROLOGY AND BIOMEDICAL JOURNAL

Literature Review

The Mechanism in which Sjogren's Syndrome Contributes to The Onset of Erectile Dysfunction

Ria Margiana* [1,2,3], **Azlansyah Azlansyah** [1]

[1] Dr. Soetomo General Hospital, Surabaya, Indonesia
[2]Department of Anatomy, Faculty of Medicine, Universitas Indonesia, Jakarta, Indonesia
[3] Master's Programme in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta

OPEN ACCESS

ARTICLE INFO

Received: March 02, 2023
Accepted: May 22, 2023
Published: June 10, 2023

*) Corresponding author:
e-mail:
ria.margiana11@gmail.com

Keywords:
Sjogren's Syndrome
Erectile Dysfunction
Endothelial Dysfunction
Autonomic Neuropathy
Reproductive Health

Abstract

Sjogren's Syndrome is an autoimmune disorder characterized by the loss of salivary and lacrimal glands, resulting in dry mouth and eyes. Erectile dysfunction (ED) is a prevalent complaint among people with Sjogren's Disease, however the underlying mpoiechanism is not yet known. The purpose of this article is to examine the mechanism through which Sjogren's Disease causes ED and to identify potential therapies. Using MEDLINE, EMBASE, and the Cochrane Library databases, a systematic review was done. Papers investigating the link between Sjogren's Syndrome and ED published between 1990 and 2021 were included in the study. The review paper discusses a number of potential mechanisms for the association between Sjogren's Disease and ED. They include low levels of testosterone, endothelial dysfunction, autonomic neuropathy, and psychosocial issues. The article also discusses potential treatments for ED caused by Sjogren's Disease, including inhibitors of phosphodiesterase type 5, testosterone replacement therapy, and psychological counseling. The research implies a connection between Sjogren's Disease and ED, although the underlying mechanisms remain unknown. It is necessary to conduct additional studies to better comprehend the relationship and develop targeted remedies.

Cite this as: Margiana R, Azlansyah A. The Mechanism in which Sjogren's Syndrome Contributes to The Onset of Erectile Dysfunction. Indonesian Andrology and Biomedical Journal. 2023 June 10;4(1):37-43. DOI: https://doi.org/10.20473/iabj.v4i1.43832

1. Introduction

The autoimmune condition known as Sjogren's Syndrome is characterized by the death of salivary glands as well as lacrimal glands, which results in dry mouth and eyes. According to estimates, between 0.2% and 3.0% of the general population suffers from the condition, with females and those over the age of 40 having a higher prevalence. Although the most obvious indications of Sjogren's Syndrome are dry mouth and eyes, many patients also have a wide range of systemic symptoms, including fatigue, joint pain, and muscle weakness. Erectile dysfunction, sometimes known as ED, is a common complaint among those who have Sjogren's Syndrome; however, the mechanism that causes this is not yet completely understood. The purpose of this review article is to research the mechanism by which ED is caused by Sjogren's Disease and to explore potential remedies for the condition. This study is both innovative and important since it does a full analysis of the existing research on the connection between Sjogren's Syndrome and ED and investigates the various potential treatment approaches.[1–7]

2. Review

A narrative review was conducted using the databases MEDLINE, EMBASE, and the Cochrane Library. The search was limited to papers published between 1992 and 2021. The following search terms were used: "Sjogren's Syndrome," "erectile dysfunction," "androgen," "endothelial dysfunction," "autonomic neuropathy," and "therapy." Studies were eligible for inclusion if they studied the association between Sjogren's Syndrome and ED, were published in English, and included human subjects. Animal models, case reports, and studies that did not evaluate the association between Sjogren's Disease and ED were excluded.[8–14]

The purpose of this review article was to research the mechanism by which Sjogren's Syndrome causes erectile dysfunction (ED), as well as explore potential remedies for the condition. Based on the findings, it appears that there may be more than one element contributing to the link between Sjogren's Syndrome and ED, and more than one mechanism may be at play.

According to the findings of a study conducted by Azcarate (2014), which found an increased incidence of ED among guys with Sjogren's Disease, one plausible reason is lower testosterone levels.[10] In their study on Sjogren's Syndrome, Łuczak (2021) established the role of androgen shortage in endothelial dysfunction. This finding suggests that endothelial dysfunction may be another mechanism that contributes to the disease.[13] As indicated in a study by Koh (2017), autonomic neuropathy may potentially play a role. These researchers discovered that women with primary Sjogren's Syndrome had reduced autonomic nervous system function.[8]

According to Ugurlu (2014), who discovered a high prevalence of depression in Sjogren's Syndrome patients. This finding suggests that psychological factors may also contribute in Sjogren's Syndrome patients.[15] In addition, Tristano (2009) found that people suffering from rheumatologic disorders, such as Sjogren's Syndrome, had a significantly increased risk of experiencing sexual dysfunction.[12]

Although that the precise mechanisms that underlie the connection between Sjogren's Syndrome and ED are not completely understood, several different therapeutic strategies have been presented. According to Tincani et al. (2012), treatment of an underlying autoimmune disease with immunomodulatory drugs may improve sexual dysfunction in people with Sjogren's Syndrome.[11]

More research is required to completely understand the intricate association between Sjogren's Disease and ED, as well as to discover effective treatments for the condition. Nonetheless, the findings of this review article show that doctors should be aware of the potential for ED in Sjogren's Syndrome patients and should explore a multimodal strategy for treatment that addresses both physical and psychological issues. The relationship between Sjogren's Syndrome and ED can be seen in Figure 1.

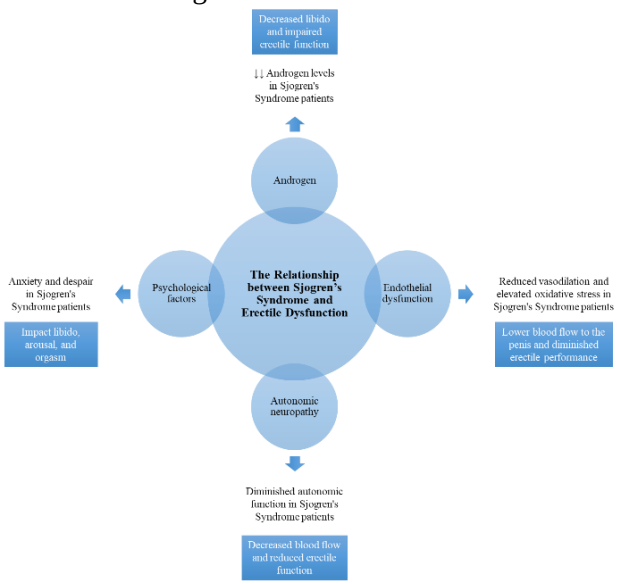

Figure 1. The Relationship between Sjogren's Syndrome and Erectile Dysfunction

Androgen:

Androgen deficiency has been identified as a potential mechanism underlying the association between Sjogren's Syndrome and erectile dysfunction (ED). Several studies have reported lower androgen levels in Sjogren's Syndrome patients compared to controls and these lower levels have been linked to a higher prevalence of ED in both men and women.

The previous study found that male Sjogren's Syndrome patients had lower total and free testosterone levels than controls, and that low testosterone levels were associated with a higher prevalence of ED.[10,14] Similarly, Valtysdottir (2003) reported that female Sjogren's Syndrome patients had lower levels of dehydroepiandrosterone (DHEA) and DHEA-sulfate than controls, and that low DHEA levels were associated with a higher prevalence of sexual dysfunction.[15]

While the exact mechanism by which androgen deficiency contributes to ED in Sjogren's Syndrome is not yet fully understood, it is thought that low androgen levels may lead to decreased libido and impaired erectile function. Androgen replacement therapy has been proposed as a potential treatment option for ED in Sjogren's Syndrome patients with androgen deficiency. However, further research is needed to evaluate the safety and efficacy of this approach.

In conclusion, the findings of this review suggest that androgen deficiency may play a role in the development of ED in Sjogren's Syndrome patients. Clinicians should consider evaluating androgen levels in patients with Sjogren's Syndrome and sexual dysfunction, and consider androgen replacement therapy as a potential treatment option.[10,14–16]

Endothelial Dysfunction:

Endothelial dysfunction, defined by poor vasodilation and elevated oxidative stress, has been linked to the development of erectile dysfunction (ED) in Sjogren's Syndrome and non-Syndrome Sjogren's patients. Sjogren's Syndrome is an autoimmune disorder that mostly affects the exocrine glands and is marked by dry eyes and mouth. ED is a common issue in both male and female patients with Sjogren's Disease, although the specific mechanism through which endothelial dysfunction contributes to ED in this population remains unknown.

Numerous research have studied the association between endothelial dysfunction and erectile dysfunction (ED) in Sjogren's Syndrome patients. Pattanaik utilized flow-mediated dilation (FMD) of the brachial artery to evaluate the endothelial function of male erectile dysfunction patients. The study indicated that male erectile dysfunction patients exhibited impaired FMD relative to healthy controls, and that FMD was adversely linked with the severity of erectile dysfunction. This indicates that poor vasodilation in response to increased blood flow may contribute to the development of ED.[17]

Similarly, Łuczak (2021) explored the association between endothelial impairment and sexual dysfunction in female Sjogren's Syndrome patients. The study indicated that female Sjogren's Syndrome patients exhibited impaired FMD and elevated oxidative stress in comparison to healthy controls, and that these characteristics were related to a higher prevalence of sexual dysfunction. Our findings indicate that poor vasodilation and increased oxidative stress may contribute in female Sjogren's Disease patients.[13]

In Sjogren's Syndrome, the precise mechanism through which endothelial dysfunction contributes to erectile dysfunction is still unknown. It is believed, however, that reduced vasodilation and elevated oxidative stress may result in lower blood flow to the penis and diminished erectile performance. Endothelial dysfunction may potentially contribute to the development of atherosclerosis and other cardiovascular illnesses, known risk factors for erectile dysfunction.[18]

Several research have examined potential therapeutic approaches for endothelial dysfunction in patients with Sjogren's Syndrome and ED. The previous studies reported that individuals with primary Sjogren's Syndrome had considerably higher levels of endothelial dysfunction indicators than healthy controls. They discovered that Sjogren's Syndrome patients exhibited elevated levels of oxidative stress and lower levels of nitric oxide, both of which are indicative of endothelial dysfunction. It is still unknown how endothelial dysfunction leads to ED in Sjogren's Syndrome, although it is believed that reduced vasodilation and increased oxidative stress may lead to decreased blood flow to the penis and impaired erectile function. These results imply that early intervention to restore endothelial function may prevent or treat sexual dysfunction in Sjogren's Syndrome patients.[13,19]

Endothelial dysfunction is a probable mechanism driving the development of erectile dysfunction in both male and female Sjogren's Disease patients. Inadequate vasodilation and elevated oxidative stress may lead to erectile dysfunction by lowering blood flow to the penis and affecting erectile function. Pharmacological approaches aiming at enhancing endothelial

function, like as antioxidant therapy and phosphodiesterase type 5 inhibitors, may be effective therapies for ED in Sjogren's Syndrome patients.[13,17–19]

Autonomic Neuropathy:

Autonomic neuropathy has been found as a probable mechanism explaining the link between erectile dysfunction (ED) and Sjogren's Syndrome. ED is a prevalent symptom in Sjogren's Syndrome patients. Autonomic neuropathy is a disorder of the autonomic nervous system that can affect several organs, including the penis. This discussion will examine the data relating autonomic neuropathy to ED in Sjogren's Disease patients.

Many research have studied the correlation between autonomic neuropathy and ED in Sjogren's Disease patients. Using heart rate variability and sympathetic skin response, Baldini et al. conducted a study to assess the autonomic function of male Sjogren's Syndrome patients.[3] Compared to healthy controls, male Sjogren's Syndrome patients had diminished autonomic function, according to the study. This shows that autonomic neuropathy may have a role in the development of erectile dysfunction in male Sjogren's Disease patients.[20,21]

Using heart rate variability and baroreflex sensitivity, Koh (2017) examined the autonomic function of female Sjogren's Syndrome patients. The study discovered that female Sjogren's Syndrome patients showed diminished autonomic function in comparison to healthy controls. This shows that autonomic neuropathy may also play a role in the development of erectile dysfunction in female Sjogren's Disease patients.[8]

By affecting the blood vessels and nerves of the penis, autonomic neuropathy can reduce erectile function. The autonomic nervous system plays a vital role in controlling blood flow to the penis, and malfunction in this system can result in decreased blood flow and erectile dysfunction. In addition, autonomic neuropathy can reduce penile sensitivity, making it more difficult to attain and sustain an erection.[22]

Many potential therapeutic approaches exist for autonomic neuropathy in Sjogren's Disease and ED patients. In this demographic, medicines that improve autonomic function, such as alpha-blockers and phosphodiesterase type 5 inhibitors, may be effective ED treatments. Nevertheless, changes in lifestyle, such as regular exercise and a nutritious diet, may enhance autonomic function and minimize the risk of ED.[23]

Autonomic neuropathy may have a role in the development of ED in Sjogren's Disease patients. In both male and female Sjogren's Disease patients, reduced autonomic function, as shown by lower heart rate variability and sympathetic cutaneous response, has been noted. A malfunction of the autonomic nervous system can reduce erectile function and blood flow to the penile region. Medication and lifestyle modifications that improve autonomic function may be helpful therapies for erectile dysfunction in persons with Sjogren's Syndrome.[10,20–23]

Psychological Factors:

Sjogren's Syndrome is an autoimmune condition that mostly affects the exocrine glands, causing eyes and mouth dryness. Psychological issues such as worry and despair have been connected to sexual dysfunction in patients with Sjogren's Disease. This discussion part tries to examine the data linking psychological aspects to sexual dysfunction in Sjogren's Disease patients, as well as potential treatments.

Many research have examined the correlation between psychological factors and sexual dysfunction in Sjogren's Disease patients. The study discovered that female Sjogren's Syndrome patients had a higher prevalence of anxiety and depression than controls and that these traits were connected with a higher frequency of sexual dysfunction. Furthermore, the study showed that psychological factors such as anxiety and fatigue were significantly associated with sexual dysfunction in individuals with Sjogren's Disease of both sexes.[9,16]

Although the precise process by which anxiety and depression contribute to sexual dysfunction is not entirely understood, it is believed that these psychological issues may impact libido, arousal, and orgasm. In addition, anxiety and depression may result in low self-esteem and body image problems, which can contribute to sexual dysfunction.[27]

Psychotherapy, including cognitive-behavioral therapy and sex therapy, may be useful for treating sexual dysfunction in Sjogren's Syndrome patients caused by psychological causes. Cognitive-behavioral therapy can assist patients in identifying and altering negative thought patterns that contribute to anxiety and depression, whereas sex therapy can assist patients in addressing particular sexual issues and improving communication with their partners.[28]

Psychological factors including anxiety and despair have been associated with sexual dysfunction in Sjogren's Disease patients. Sexual dysfunction caused by psychological causes may be treatable with psychotherapy, including cognitive-behavioral therapy and sex therapy. To discover the most effective treatment techniques

for this population, additional study is required.[9,16,27,28]

Treatment:

Phosphodiesterase type 5 (PDE5) inhibitors, testosterone replacement therapy, and psychological counseling are some of the potential treatment options for erectile dysfunction (ED) caused by Sjogren's Syndrome.[9,16,17,29–31]

PDE5 inhibitors:

PDE5 inhibitors, such as sildenafil and tadalafil, are frequently used to treat ED in people with and without Sjogren's Syndrome. These drugs work by boosting blood flow to the penis, hence enhancing erectile function. Hatzimouratidis (2006) discovered that sildenafil improved erectile function in male patients with erectile dysfunction.[31] Similarly, Coward (2008) discovered that tadalafil improved erectile function in patients with sexual dysfunction.[29] The use of PDE5 inhibitors in patients with Sjogren's Syndrome should be closely monitored due to the possibility of adverse consequences, especially in patients with underlying medical disorders. For instance, people with Sjogren's Syndrome may be at a higher risk for cardiovascular disease, and PDE5 inhibitors may interact with some cardiovascular drugs. PDE5 inhibitors such as sildenafil and tadalafil can effectively cure sexual dysfunction in Sjogren's Syndrome patients. Nonetheless, the usage of these medications should be closely managed, especially in patients with preexisting illnesses. To evaluate the long-term safety and efficacy of PDE5 inhibitors in this population, additional research is required.[17,29,31]

Testosterone Replacement Therapy*:*

Testosterone replacement treatment, often known as TRT, has been shown to be beneficial in treating erectile dysfunction (ED) in men who have naturally low levels of testosterone. TRT may also be useful in treating ED in male Sjogren's Syndrome patients who have naturally low levels of androgen. TRT was found to be beneficial in improving erectile function in male Sjogren's Disease patients who had ED and low testosterone levels. Unfortunately, it is not yet known whether or not TRT is safe and effective over the long term for people with Sjogren's Syndrome.[30]

Psychological counseling:

Patients with Sjogren's Syndrome who also have underlying psychological concerns, such as anxiety and depression, may benefit from psychotherapy to alleviate sexual dysfunction. In a previous study, they discovered that psychological factors, such as anxiety and exhaustion, were significantly associated with sexual dysfunction in Sjogren's Syndrome patients of both sexes. This study demonstrates that psychological counseling can improve sexual function in people with Sjogren's Disease who have underlying psychological issues such as anxiety and sadness.[9,16]

Cognitive-behavioral therapy can assist patients in identifying and altering negative thought patterns that contribute to anxiety and depression, whereas sex therapy can assist patients in addressing particular sexual issues and improving communication with their partners. Psychotherapy can be an integral aspect of the treatment for people with Sjogren's Disease, especially those experiencing sexual dysfunction due to psychological issues.[9,16]

3. Summary

The information that is now available implies that there is a connection between Sjogren's Disease and ED; however, the underlying mechanisms continue to be unknown. A drop in testosterone levels, problems with endothelial function, autonomic neuropathy, and even psychological causes are all possibilities for what might be going on. PDE5 inhibitors, testosterone replacement therapy, and psychological counseling are all potential treatment options for erectile dysfunction that is caused by Sjogren's syndrome. However, additional research is required to better understand the connection between Sjogren's Syndrome and ED, as well as to develop treatments that are specifically geared toward treating this condition.

Acknowledgment

Many thanks to everyone on the andrology program staff and to the residents who have provided continuous support and unique insights to ensure that this work was able to be completed effectively.

Author's Contributions

RM and AZ have made a substantial contribution to the concept or design of the article; RM the acquisition, analysis, or interpretation of data for the article, drafted the article or revised it critically for important intellectual content, drafted the article or revised it agreed to take responsibility for all parts of the work, including making sure that any questions regarding the accuracy or integrity of any component of the work are examined and

handled acceptably. RM and AZ approved the version to be published.

Conflict Of Interest

Because it is a review article, there is no potential for a conflict of interest to arise.

Funding Information

The funding for this study came only from Ria Margiana; no other organization or branch of the government contributed any resources toward its production.

References

1. Fox RI. Sjögren's syndrome. *Lancet (London, England)* 2005; 366: 321–331.
2. Ramos-Casals M, Brito-Zerón P, Sisó-Almirall A, et al. Primary Sjögren syndrome. *BMJ* 2012; 345: 1–7.
3. Baldini C, Ferro F, Elefante E, et al. Biomarkers for Sjögren's syndrome. *Biomark Med* 2018; 12: 275–286.
4. Kobak S, Saracoglu M. Peyronie's disease in a patient with primary Sjogren's Syndrome. *Int J Rheum Dis* 2014; 17: 116–117.
5. Yildiz Ç, Karakuş S, Bozoklu Akkar Ö, et al. Primary Sjögren's Syndrome Adversely Affects the Female Sexual Function Assessed by the Female Sexual Function Index: A Case-Control Study. *Arch Rheumatol* 2017; 32: 123–128.
6. Baudouin C, Aragona P, Messmer EM, et al. Role of hyperosmolarity in the pathogenesis and management of dry eye disease: proceedings of the OCEAN group meeting. *Ocul Surf* 2013; 11: 246–258.
7. Cheng H, Niu Z, Xin F, et al. A new method to quantify penile erection hardness: real-time ultrasonic shear wave elastography. *Transl Androl Urol* 2020; 9: 1735–1742.
8. Koh JH, Kwok SK, Lee J, et al. Autonomic dysfunction in primary Sjogren's syndrome: A prospective cohort analysis of 154 Korean patients. *Korean J Intern Med* 2017; 32: 165–173.
9. Ugurlu GK, Erten S, Ugurlu M, et al. Sexual Dysfunction in Female Patients with Primary Sjögren's Syndrome and Effects of Depression: Cross-Sectional Study. *Sex Disabil* 2014; 32: 197–204.
10. Azcarate PM, Venincasa VD, Feuer W, et al. Androgen deficiency and dry eye syndrome in the aging male. *Invest Ophthalmol Vis Sci* 2014; 55: 5046–5053.
11. Tincani A, Andreoli L, Cavazzana I, et al. Novel aspects of Sjögren's syndrome in 2012. *BMC Med* 2013; 11: 93.
12. Tristano AG. The impact of rheumatic diseases on sexual function. *Rheumatol Int* 2009; 29: 853–860.
13. Łuczak A, Małecki R, Kulus M, et al. Cardiovascular Risk and Endothelial Dysfunction in Primary Sjogren Syndrome Is Related to the Disease Activity. *Nutrients*; 13. Epub ahead of print June 2021. DOI: 10.3390/nu13062072.
14. Brandt JE, Priori R, Valesini G, et al. Sex differences in Sjögren's syndrome: a comprehensive review of immune mechanisms. *Biol Sex Differ* 2015; 6: 19.
15. Valtysdottir ST, Wide L, Hallgren R. Mental wellbeing and quality of sexual life in women with primary Sjögren's syndrome are related to circulating dehydroepiandrosterone sulphate. *Ann Rheum Dis* 2003; 62: 875–879.
16. van Nimwegen JF, Arends S, van Zuiden GS, et al. The impact of primary Sjögren's syndrome on female sexual function. *Rheumatology (Oxford)* 2015; 54: 1286–1293.
17. Pattanaik S, Kaundal P, Mavuduru RS, et al. Endothelial Dysfunction in Patients With Erectile Dysfunction: A Double-Blind, Randomized-Control Trial Using Tadalafil. *Sex Med* 2019; 7: 41–47.
18. Foocharoen C, Tyndall A, Hachulla E, et al. Erectile dysfunction is frequent in systemic sclerosis and associated with severe disease: a study of the EULAR Scleroderma Trial and Research group. *Arthritis Res Ther* 2012; 14: R37.
19. Bartoloni E, Alunno A, Bistoni O, et al. Characterization of circulating endothelial microparticles and endothelial progenitor cells in primary Sjögren's syndrome: new markers of chronic endothelial damage? *Rheumatology (Oxford)* 2015; 54: 536–544.
20. Dessein PH, Joffe BI, Metz RM, et al. Autonomic Dysfunction in Systemic Sclerosis: Sympathetic Overactivity and Instability. 1992; 93: 143–150.
21. Davies K, Ng WF. Autonomic Nervous System Dysfunction in Primary Sjögren's Syndrome. *Front Immunol* 2021; 12: 1–7.
22. Yang CC, Jiang X. Clinical autonomic neurophysiology and the male sexual response: an overview. *J Sex Med* 2009; 6 Suppl 3: 221–228.
23. Lu Y, Kang J, Li Z, et al. The association between plant-based diet and erectile dysfunction in Chinese men. *Basic Clin Androl* 2021; 31: 11.

24. Davies K, Ng W-F. Autonomic Nervous System Dysfunction in Primary Sjögren's Syndrome. *Front Immunol* 2021; 12: 702505.
25. Dessein PH, Joffe BI, Metz RM, et al. Autonomic dysfunction in systemic sclerosis: sympathetic overactivity and instability. *Am J Med* 1992; 93: 143–150.
26. Fan F, He Z, Kong L-L, et al. Pharmacological targeting of kinases MST1 and MST2 augments tissue repair and regeneration. *Sci Transl Med* 2016; 8: 352ra108.
27. Wheeler LJ, Guntupalli SR. Female Sexual Dysfunction: Pharmacologic and Therapeutic Interventions. *Obstet Gynecol* 2020; 136: 174–186.
28. McCabe M, Althof SE, Assalian P, et al. Psychological and interpersonal dimensions of sexual function and dysfunction. *J Sex Med* 2010; 7: 327–336.
29. Coward RM, Carson CC. Tadalafil in the treatment of erectile dysfunction. *Ther Clin Risk Manag* 2008; 4: 1315–1330.
30. Rastrelli G, Corona G, Maggi M. Testosterone and sexual function in men. *Maturitas* 2018; 112: 46–52.
31. Hatzimouratidis K. Sildenafi l in the treatment of erectile dysfunction: an overview of the clinical evidence. *Clin Interv Aging* 2006; 1: 403–414.