1 **Article**

2 **Relationship between response to PDE5 inhibitors and penil duplex doppler ultrasound**
3 **in erectile dysfunction**

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14 **Abstract:** Relationship between the results of penile duplex doppler ultrasound(PDDU) and
15 response to vardenafil was investigated in patients diagnosed with erectile dysfunction (ED).
16 Data of 148 patients with ED were analysed retrospectively. Patients who did not respond to
17 therapy were classified as Group I(n=32), those responded partially were classified as Group
18 II(n=40) and complete responders were classified as Group III(n=76). Age, comorbid
19 diseases, vascular and penile pathology were compared among the three groups. While
20 diabetes mellitus(DM) and dyslipedimia positivity adversely affect the response to treatment,
21 the presence of hypertension(HT), peyronie's disease and priapism increase the therapeutic
22 response to the treatment($p<0.05$). Arterial insufficiency was present in 20(30.3%),
23 25(37,9%) and 21(31.8%) of the patients in Group I, Group II and Group III,
24 respectively($p=0.001$). Venous insufficiency was observed in 3(14.3%) patients in Group I
25 and in 8(85.7%) patients in Group III($p=0.001$). Arterial/venous insufficiency was seen in

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9(30%), 14(46.7%) and 7(23.3%) of the patients in Group I, Group II and Group III, respectively(p=0.001). Response rate to treatment was highest in normal patients according to PDDU, followed by patients with venous insuffiency. Besides, it was found that DM decreased the response to treatment, whereas response was increased in cases with HT, priapism and Peyronie's disease.

Keywords: comorbid diseases; erectile dysfunction; penile duplex doppler ultrasound; penile pathology; phosphodiesterase type 5 inhibitors

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1. Introduction

ED is defined as the inability to achieve and maintain an erection sufficient for satisfactory sexual intercourse [1]. Organic and psychogenic factors are responsible for pathogenesis of ED. Because the penis has a important vascular bed, vascular pathologies are more frequent. Vascular pathologies may be arteriogenic, venogenic and/or mixed type [2]. In vasculogenic ED; advanced age, diabetes mellitus (DM), hypertension (HT), dyslipidemia and atherosclerosis are the main risk factors. Penile pathologies such as priapism and peyronie's disease can also cause ED [3,4]. The basic mechanism involved in vasculogenic ED pathophysiology is the reduction in nitric oxide (NO) synthesis and bioavailability. Furthermore, the interaction between NO and superoxide anion causes an increase in free oxygen radicals. Free oxygen radicals in turn lead to neuronal and endothelial damage. Endothelial damage is associated with endothelial dysfunction and atherosclerosis [5]. PDE5Is (sildenafil, tadalafil, udenafil, vardenafil, avenafil, etc.) are used in the current treatment of patients with vasculogenic ED [6]. However, diagnostic tests are recommended in patients who do not benefit from oral agents or when surgical treatment is planned. Most important of these tests is PDDU. In this imaging technique, a careful evaluation that is performed by providing functional penile erection following intracavenousal injection, ensures reliable information about penile arterial and venous system [7]. In this study, we aimed to investigate the relationship between PDDU results and the response to vardenafil in patients diagnosed with ED.

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2. Materials and Methods

Data of 260 patients who admitted to our clinic with history of ED that persisted for longer than 6 months between May 2009 and April 2015 were evaluated retrospectively. Sexual history, physical examination findings, International Index of Erectile Function-5 (IIEF-5) scores, systemic diseases that are potential risk factors for ED and PDDU data were obtained from the patient's files. Out of all patients who underwent PDDU, those with a history of major pelvic surgery such as radical prostatectomy, neurologic diseases such as degenerative neuropathies and history of pelvic or perineal trauma were excluded from the evaluation. Patients who developed priapism and were interfered after 4 hours were also excluded. Data of 148 patients who had severe ED according to IIEF-5 score were included in the study. Testosterone levels of patients included in the study were normal. PDDU which is standard in our clinic is performed following intracavernosal injection of 50 mg papaverine. Before the procedure, information about the complications of the disease was given and the patient's signed consent forms were obtained. Following tourniquet and tactile stimulation, procedure was performed on erected penis using ultrasound equipment with a superficial 12 MHz probe. 5, 10, 15 and 30 minutes waveforms were obtained from cavernousal artery through penoscrotal angle approach and peak systolic velocity (PSV), end diastolic velocity (EDV) and resistance index (RI) values were recorded. PSV values above 30 cm/sec and RI values above 0.80 were normal vascular responses. PSV is the best doppler indicator of arteriogenic ED. If PSV values were below 30 cm/sec and RI values were below 0.80, they were considered as indicators for arterial insufficiency. EDV is the best doppler indicator of venogenic ED. PSV values above 30 cm/sec and RI values below 0.80 were considered as venous insufficiency. Patients were started on vardenafil 10 mg orodispersible tablet (ODT), a PDE5Is. Dosage adjustment was done as twice a week orally, and patients were questioned following 12 weeks of treatment. In order to asses the response to treatment, IIEF-5

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questionnaire was used and ED was classified into five categories based on the scores: severe (5-7), moderate (8-11), mild to moderate (12-16), mild (17-21), and no ED (22-25). IIEF-5 score following the vardenafil ODT treatment was classified as: a score within severe ED range was non responder group (Group I (n:32)), a score within moderate ED range was partially responder group (Group II (n:40)) and those who were within mild ED or normal erectile function were classified as complete responder group (Group III (n:76)). Distribution of age, comorbidities such as DM, HT and dyslipidemia; if any, type of vascular pathology (arterial, venous, arterial and venous insufficiency), relationship between priapism and peyronie disease were compared among the groups.

This study was approved by the ethical committee of Giresun University Faculty of Medicine (approval no KAEK-01)

2.1. Statistical analysis

Data obtained in this study were analyzed with SPSS 20 package program. Because of unit numbers, Shapiro Wilks was conducted to check whether the variables came from a normally distributed population. When the differences among the groups were examined, Kruskal Wallis-H test was used in case variables did not come from normal distrubiton. If Kruskal Wallis-H test revealed significant differences, groups that held differences were detected by Post-Hoc Multiple Comparison Test. Chi-square test was conducted when relation of nominal variables were analyzed among the groups. Pearson Chi-Square test was performed in RxC tables. Statistical significance was accepted when $p<0.05$.

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128 **3. Results**

129 The average age of the patients was 56.3 (27-80 years). The average age was 57.7 (45-65
130 years) in Group I, 57.9 (33-80 years) in Group II, and 54.9 (27-79 years) in Group III
131 (p=0.404). (Table-1)

132 DM was present in 30 (93.7%) patients in Group I, in 38 (95%) patients in Group II and in
133 32 (42.1%) patients in Group III. It was found that distribution of patients with no DM was
134 significant in complete responder group (Group III) (p=0.001). HT was observed in 16
135 (50%) patients in Group I, in 27 (67.5%) patients in Group II and in 67 (88.1%) patients in
136 Group III. It was found that distribution of patients with HT was significant in Group III
137 (p=0.001). Dyslipedimia was found in 26 (81.2%) patients in Group I, in 39 (97.5%) patients
138 in Group II and in 45 (59.2%) patients in Group III. It was found that distribution of patients
139 with dyslipidemia was significant in Group III (p=0.001).

140 According to the results of PDDU, priapism was detected in 22 (14.8%) of the 148 patients.
141 All the patients with priapism were found in Group III. There was no priapism in any
142 patients in Group I and II (p=0.001). It was determined that endothelial dysfunction did not
143 develop in priapism in which intervention was performed within first 4 hours. Peyronie's
144 disease was present in 16 (50%) patients in Group I, in 9 (22.5%) patients in Group II and in
145 18 (23.6%) patients in Group III (p=0.013). Response to the vardenafil treatment in
146 peyronie's patients was significantly higher. (Table-2)

147 According to the results of PDDU; in Group I; the number of patients with arterial
148 insufficiency was 20 (30.3%), the number of patients with venous insufficiency was 3
149 (14.3%), and the number of patients with arterial and venous insufficiency was 9 (30%).
150 However, there was not any normal patient in this group (p=0.001). In Group II, the number

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of the patients with arterial insufficiency was 25 (62.5%), the number of patients with both arterial and venous insufficiency was 14 (35%) and the number of the normal patients was 1(3.2%) (p=0.001). Number of the patients with arterial insufficiency was 21 (27.6%) in Group III, while number of the patients with venous insufficiency was 18 (23.7%). Number of patients with both arterial and venous insufficiency was 7 (9.2%) in this group, whereas number of the patients with normal results was 30 (39.5%). Under light of these data, according to PDDU results, it was found that rate of patients with venous insufficiency as well as patients with normal results was statistically significantly higher in Group III compared to Group I and Group II (p=0.001). (Table-3)

Table-1. Age distribution of according to groups.

								Kruskal Wallis H Test		
		n	Mean	Median	Min	Max	ss	Rank Avg.	H	p
Age	Group I	32	57,75	57	45	65	5,62	79,91	1,811	0,404
	Group II	40	57,9	57,5	33	80	10,39	78,91		
	Group III	76	54,91	55	27	79	12,64	69,9		
	Total	148	56,33	57	27	80	10,91			

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Table-2. Distribution of comorbidities according to the groups.

		Group I		Group II		Group III		Total		Chi-square test	
		n	%	n	%	n	%	n	%	Chi-square	p
Diabetes Mellitus	Positive	30	30	38	38	32	32	100	100	46,232	**0,001**
	Negative	2	4,2	2	4,2	44	91,7	48	100		
	Total	32	21,6	40	27	76	51,4	148	100		
Hypertension	Positive	16	14,5	27	24,5	67	60,9	110	100	18,519	**0,001**
	Negative	16	42,1	13	34,2	9	23,7	38	100		
	Total	32	21,6	40	27	76	51,4	148	100		
Dyslipidemia	Positive	26	23,6	39	35,5	45	40,9	110	100	21,16	**0,001**
	Negative	6	15,8	1	2,6	31	81,6	38	100		
	Total	32	21,6	40	27	76	51,4	148	100		
Priapism	Positive	0	0	0	0	22	100	22	100	24,481	**0,001**
	Negative	32	25,4	40	31,7	54	42,9	126	100		
	Total	32	21,6	40	27	76	51,4	148	100		
Peyronie	Positive	16	37,2	9	20,9	18	41,9	43	100	8,708	**0,013**
	Negative	16	15,2	31	29,5	58	55,2	105	100		
	Total	32	21,6	40	27	76	51,4	148	100		

Table-3. Distribution of the groups in terms of doppler ultrasonography results

		Group I		Group II		Group III		Total		Chi-square test	
		n	%	n	%	n	%	n	%	Chi-square	p
PDDU	Arterial insufficiency	20	30,3	25	37,9	21	31,8	66	100	56,605	**0,001**
	Venous insufficiency	3	14,3	0	0	18	85,7	21	100		
	Arterial/Venous insufficiency	9	30	14	46,7	7	23,3	30	100		
	Normal	0	0	1	3,2	30	96,8	31	100		
	Total	32	21,6	40	27	76	51,4	148	100		

PDDU: Penile duplex doppler ultrasonound

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4. Discussion

ED is the most common sexual disorder in men. For normal erectile function, psychosocial, hormonal, neurological, vascular and cavernousal factors should coordinate and defects in one or more of these factors leads to ED. Penile erection is a hemodynamic phenomenon that occurs through arteries and corpus cavernosum smooth muscle relaxation. The relaxation of smooth muscle in corpus cavernosum is arranged with the formation of cyclic guanosine monophosphate (cGMP) induced by NO. cGMP is hydrolyzed by isoenzyme of phosphodiesterase type 5 enzyme (PDE5) in cavernous tissue. Potent inhibition of PDE5 enzyme in the corpora cavernosa leads to increased levels of cGMP and NO and extends the smooth muscle relaxation [8]. Current selective PDE5Is include sildenafil, tadalafil, udenafil, vardenafil and avanafil. PDE5Is are also used in treatment of ED secondary to aging, DM, HT, dyslipidemia and atherosclerosis as well as in general population [9,10]. These etiologic factors cause impairment in the structure of corpus cavernosum and result in loss of erectile function.

ED is a worldwide health problem and its incidence increases with age. In developed countries, improved life expectancy also increases the general incidence of ED in general population. Epidemiological data obtained to date have shown that worldwide prevalence and incidence of ED are 69.2% and 34.5%, respectively [11]. With increasing age, atherosclerosis occurring in the vascular structures also affects penile vascular structures and can lead to ED. Atherosclerosis impairs the blood flow in cavernosal arteries and leads to accumulation of oxygen free radicals in the tissues [12]. In our study, rate of patients with arterial insufficiency was higher in non-responder group compared to partially or completely responder groups.

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It was shown in several studies that duration and severity of risk factors increase the lesion in vascular structure [12-14]. Especially the relation between duration of diabetes and severity of ED was well established. Poor metabolic control in diabetes shortens the time between onset of diabetes and development of ED [14]. Arterial structures are affected earlier compared to trabecular smooth muscle structures and venous system. Long duration of diabetes, poor metabolic control and on-going atherosclerosis cause atrophy in penile smooth muscle structures, loss of myofilament, shrinking in cell size, increase in collagen fibers and decrease in "gap junction" structures, impairment in relaxation of trabecular smooth muscle structures and venous leak [15]. This, in turn hampers the treatment of ED associated with DM. In a retrospective study conducted by Blonde L. [15], rate of the patients who responded to treatment was reported as 62% and they concluded that PDE5Is treatment was effective in achieving and maintaining erectile function ($p<0.0001$). In our study it was calculated that the rate of patients with diagnosis of DM who responded partially or completely to PDE5Is treatment was 70%. We believe that this difference could be related to the fact that treatment dose was not standard and a different PDE5Is preparation was used in Blonde's study. In vitro studies report that vardenafil is 10 times potent than sildenafil [16]. This study too shows that different active substances could have different effects. In a study comparing various doses of sildenafil, it was shown that 100 mg sildenafil is more effective [17]. Lack of dose standardization might have understated the total effect. Besides, in development of ED in diabetic cases, accompanying neurologic component along with vascular pathology contributes to decrease in response to treatment. In cases where no response is obtained with vardenafil 10 mg, increase in dosage and evaluation of the patient in terms of peripheral neuropathy can be beneficial.

HT is considered to be a major risk factor for ED. ED is present in approximately 30% of hypertensive patients. The mutual mechanism between HT and ED is endothelial

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dysfunction. ED can develop due to hemodynamic changes of high blood pressure and increased atherosclerosis, such as a result of antihypertensive treatment [18]. Although HT is a major risk factor for ED, in a meta-analysis it was shown that compared to placebo, vardenafil provided significant improvement in patients with ED. In the same study it was reported that vardenafil displayed similar effect in patients with or without HT [19].

Dyslipidemia is a well known risk factor for atherosclerosis. Dyslipidemia leads to occlusion by increasing the lipid accumulation in vascular lesions and accelerating the atherosclerotic process. Besides this, endothelial dysfunction is held responsible for the main pathology. Atherosclerotic lesions extend through internal pudendal and cavernosal arteries, and decrease penile blood flow. Although statin group drugs are used in first step treatment of dyslipidemia, studies showed that these type of agents can cause ED. As a result of this, treatment of patients with dyslipidemia diagnosis involves PDE5Is [20]. In our study, response rate of patients with dyslipidemia to PDE5Is treatment was 81.2% in Group I, 97.5% in Group II and 59.2% in Group III, respectively (p=0.001). It was observed that response to PDE5Is was diminished in patients with dyslipidemia. Besides, rate of patients with arterial and both arterial and venous insufficiency was higher in group where no response to treatment was achieved compared to other treatment groups. In treatment group with prominent venous insufficiency, response to PDE5Is treatment was favorable.

Priapism is a rare pathology defined as painful erection which lasts for more than 4 hours without any sexual desire or stimulation [21]. Decrease in basal levels of PDE5 enzyme causes uncontrolled erection (priapism). In this condition, mechanisms of erection are entirely normal but there appears to be a lack of mechanisms controlling returning of penis to its flaccid state. Therefore prolonged uncontrolled erections are seen in priapism [22]. Histopathologic studies showed that erectile tissue damage is dependent on time in priapism and irreversible damage occurs after 6 hours [23]. The goal in priapism treatment is to empty

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anoxic blood, decompressing corpus cavernosum and providing perfusion. Hence alleviating pain, ischemia, necrosis, fibrosis, formation of penile deformity and probability of erectile dysfunction is aimed [24]. In our study, all of the cases with priapism were treated before 4 hours and erectile tissue damage was avoided. Therefore, a complete response to PDE5Is treatment was achieved in all patients who developed priapism.

Peyronie's disease, a disorder playing a role in ED, is an inflammatory process characterized by fibroblast proliferation and fibrous plaque formation in tunica albuginea. Peyronie's disease is associated with ED in 20-40% of the cases [25]. Ozturk et al. [26] investigated the effectiveness of sildenafil in 39 patients who had Peyronie's disease and accompanying ED. They showed that a significant improvement occurred in IIEF-5 in sildenafil-received group (p=0.028). In our study, partial or complete response rate to treatment in 43 patients with Peyronie's disease was 62.8%. In a study, following PDE5Is treatment, complete or partial satisfaction rate was reported as 70.8%. In the same study 90% of the patients who had venous insufficiency according to PDDU finding, were satisfied with the treatment [27]. In our study, rate of patients with venous insufficiency in responder group was 85,7%.

It is known that approximately 35% of the cases do not respond to PDE5 inhibitors in treatment of ED. Major reasons of this failure include is reported as DM, severe neurologic and vascular disorders [28]. In our study non response rate to PDE5Is was 21.6%, a figure lower than that is found in the literature. We believe that the reason for this is the exclusion of potential conditions that could lead to neurologic ED.

Mulhall et al. [29] reported that response rate was 25% in ED patients who had venous insufficiency. This figure was 85.7% in our study. Success rate in ED has an inverse correlation with venous insufficiency. It is reported that response to treatment decreases in

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patients with high degree of insufficiency [30]. We did not grade the degree of venous insufficiency, so this could be considered as a limitation to our study.

5. Conclusion: In the light of consequences of our study, we found that rate of patients with arterial insufficiency is higher in group of patients who did not respond to PDE5Is. Response rate to the treatment was highest in normal patients according to PDDU findings, followed by the patients with venous insufficiency. Besides this, it was found that DM decreases the respond to treatment, response was improved in the patients who had HT, priapism and Peyronie's disease.

6. Patients

Conflicts of interest

The authors declare no conflict of interest.

Author Contributions

Conception and design: Ercan Öğreden and Ural Oğuz. Administrative support: Orhan Yalçın, Erhan Demirelli. Provision of study material or patients: Ercan Öğreden, Ural Oğuz, Erhan Demirelli, Orhan Yalçın and Alptekin Tosun. Collection and assembly of data: Ercan Öğreden and Erhan Demirelli. Data analysis and interpretation: Ural Oğuz and Alptekin Tosun. Manuscript writing: All authors. Final approval of manuscript: All authors.

Appendix

Table-1. Age distribution of according to groups.

Table-2. Distribution of comorbidities according to the groups.

Table-3. Distribution of the groups in terms of doppler ultrasonography results.

References

1. Viigimaa, M.; Vlachopoulos, C.; Lazaridis, A.; Doumas, M. Management of erectile dysfunction in hypertension: Tips and tricks. World J Cardiol. 2014, 26, 908-915, DOI: 10.4330/wjc.v6.i9.908.
2. Persu, C.; Cauni, V.; Gutue, S.; Albu, E.S.; Jinga, V.; Geavlete, P. Diagnosis and treatment of erectile dysfunction a practical update. J Med Life. 2009, 2, 394-400.
3. Martin-Morales, A.; Sanchez-Cruz, J.J.; Saenz de Tejada, I.; Rodriguez-Vela, L.; Jimenez-Cruz, J.F.; Burgos-Rodriguez, R. Prevalence and independent risk factors for erectile dysfunction in Spain: results of the Epidemiologia de la Disfuncion Erectil Masculina Study. J Urol. 2001, 166, 569-575. DOI: 10.1016/S0022-5347(05)65986-1.
4. Tanik, S.; Sarikaya, S.; Zengin, K.; Albayrak, S.; Yilmaz, Y.K.; Akyol, L. Cardiometabolic risk factors in patients with erectile dysfunction. ScientificWorldJournal. 2014, 22,1-4, DOI: 10.1155/2014/892091.
5. Bivalacqua, T.J.; Usta, M.F.; Champion, H.C.; Kadowitz, P.J.; Hellstrom, W.J. Endothelial dysfunction in erectile dysfunction: role of the endothelium in erectile physiology and disease. J Androl. 2003, 24, 17-37, DOI: 10.1002/j.1939-4640.2003.tb02743.x.
6. Yuan, J.; Zhang, R.; Yang, Z.; Lee, J.; Liu, Y.; Tian, J.; Qin, X:, Ren, Z.; Ding, H.; Chen, Q.; Mao, C.; Tang, J. Comparative effectiveness and safety of oralphosphodiesterase type 5 inhibitors for erectile dysfunction: a systematic review and network meta-analysis. Eur Urol. 2013, 63, 902-912, 10.1016/j.eururo.2013.01.012.
7. Pezzoni, F.; Scroppo, F.I. Penile vascular diagnostic categorization using penile duplex Doppler ultrasound: Differences in vascular hemodynamics parameters by

differences in anatomic sampling location. Arch Ital Urol Androl. 2016, 5, 88, 183-185, DOI: 10.4081/aiua.2016.3.183.

8. Corbin, J.D.; Francis, S.H. Pharmacology of phosphodiesterase-5 inhibitors. Int J Clin Pract. 2002, 56, 453-459.
9. Montorsi, F.; Adaikan, G.; Becher, E.; Giuliano, F.; Khoury, S.; Lue, T.F.; Sharlip, I.; Althof, S.E.; Andersson, K.E.; Brock, G.; Broderick, G.; Burnett, A.; Buvat, J.; Dean, J.; Donatucci, C.; Eardley, I.; Fugl-Meyeri K.S.; Goldstein, I.; Hackett, G.; Hatzichristou, D.; Hellstrom, W.; Incrocci, L.; Jackson, G.; Kadioglu, A.; Levine, L.; Lewis, R.W.; Maggi, M.; McCabe, M.; McMahon, CG.; Montague, D.; Montorsi, P.; Mulhall, J.; Pfaus, J.; Porst, H.; Ralph, D.; Rosen, R.; Rowland, D.; Sadeghi-Nejad, H.; Shabsigh, R.; Stief, C.; Vardi, Y.; Wallen, K.; Wasserman, M. Summary of the recommendations on sexual dysfunctions in men. J Sex Med. 2010, 7, 3572-3588, DOI: 10.1111/j.1743-6109.2010.02062.x.
10. Derby, C.A.; Mohr, B.A.; Goldstein, I.; Feldman, H.A.; Johannes, C.B.; McKinlay, J.B. Modifiable risk factors and erectile dysfunction: can lifestyle changes modify risk? Urology. 2000, 56, 302-306, DOI: http://dx.doi.org/10.1016/S0090-4295(00)00614-2.
11. Nicolosi, A.; Moreira, E.D. Jr.; Shirai, M.; Bin Mohd Tambi, M.I.; Glasser, D.B. Epidemiology of erectile dysfunction in four countries: cross-national study of the prevalence and correlates of erectile dysfunction. Urology. 2003, 61, 201-206, DOI: http://dx.doi.org/10.1016/S0090-4295(02)02102-7.
12. Moreland, R.B. Pathophysiology of erectile dysfunction: the contributions of trabecular structure to function and the role of functional antagonism. Int J Impot Res. 2000, 12, 39-46.

13. Azadzoi, K.M.; Saenz de Tejada, I. Diabetes mellitus impairs neurogenic and endothelium-dependent relaxation of rabbit corpus cavernosum smooth muscle. J Urol. 1992, 148, 1587-1591, DOI: http://dx.doi.org/10.1016/S0022-5347(17)36975-6
14. El-Sakka, A.I.; Lin, C.S.; Chui, R.M.; Dahiya, R.; Lue, T.F. Effects of diabetes on nitric oxide synthase and growth factor genes and protein expression in an animal model. Int J Impot Res. 1999, 1, 123-32.
15. Blonde, L. Sildenafil citrate for erectile dysfunction in men with diabetes and cardiovascular risk factors: a retrospective analysis of pooled data from placebo-controlled trials. Curr Med Res Opin. 2006, 22, 2111-2120, DOI: 10.1185/030079906X148256.
16. Bischoff, E.; Schneider, K. A conscious-rabbit model to study vardenafil hydrochloride and other agents that influence penile erection. Int J Impot Res 2001, 13, 230-235, DOI:10.1038/sj.ijir.3900703.
17. Li, H.; Bai, G.; Zhang, X.; Shi, B.; Liu, D.; Jiang, H.; Ji, Z.; Davis, M.R.; Zhu, Z.; Fang, Y. Effects of Two Different Dosages of Sildenafil on Patients With Erectile Dysfunction. Am J Mens Health. 2015 Dec 3, DOI: 10.1177/1557988315620467.
18. Nunes, K.P.; Labazi, H.; Webb, R.C. New insights into hypertension-associated erectile dysfunction. Curr Opin Nephrol Hypertens. 2012, 21, 163-70, DOI: 10.1097/MNH.0b013e32835021bd.
19. Shabsigh, R.; Duval, S.; Shah, M.; Regan, T.S.; Juhasz, M.; Veltry, L.G. Efficacy of vardenafil for the treatment of erectile dysfunction in men with hypertension: a meta-analysis of clinical trial data. Curr Med Res Opin. 2007, 23, 2453-2460, DOI: 10.1185/030079907X219616.

20. Vrentzos, G.E.; Paraskevas, K.I.; Mikhailidis, D.P. Dyslipidemia as a risk factor for erectile dysfunction. Curr Med Chem. 2007, 14, 1765-1770, DOI : 10.2174/092986707781058931.

21. Broderick, G.A.; Kadioglu, A.; Bivalacqua, T.J.; Ghanem, H.; Nehra, A.; Shamloul, R. Priapism: pathogenesis, epidemiology, and management. J Sex Med. 2010,7, 476-500, DOI: 10.1111/j.1743-6109.2009.01625.x.

22. Anele, U.A.; Le, B.V.; Resar, L.M.; Burnett, A.L. How I treat priapism. Blood. 2015, 125, 3551-3558, DOI: 10.1182/blood-2014-09-551887.

23. Ralph, D.J.; Garaffa, G. Muneer, A.; Freeman, A.; Rees, R.; Christopher, A.N.; Minhas, S. The immediate insertion of a penile prosthesis for acute ischaemic priapism. Eur Urol. 2009, 56, 1033-1038, DOI: 10.1016/j.eururo.2008.09.044.

24. Huang, Y.C.; Harraz, A.M.; Shindel, A.W.; Lue, T.F. Evaluation and management of priapism: 2009 update.Nat Rev Urol. 2009, 6, 262-271,DOI: 10.1038/nrurol.2009.50.

25. Chow, K.; Payne, S. The pharmacological management of intermittent priapismic states. BJU Int. 2008, 102, 1515-1521, DOI: 10.1111/j.1464-410X.2008.07951.x.

26. Ozturk, U.; Yesil, S.; Goktug, H.N.; Gucuk, A.; Tuygun, C.; Sener, N.C.; Nalbant, I.; Imamoglu, M.A. Effects of sildenafil treatment on patients with Peyronie's disease and erectile dysfunction. Ir J Med Sci. 2014, 183, 449-453, DOI: 10.1007/s11845-013-1036-5.

27. Levine, L.A.; Latchamsetty, K.C. Treatment of erectile dysfunction in patients with Peyronie's disease using sildenafil citrate. Int J Impot Res. 2002,14, 478-482, DOI: 10.1038/sj.ijir.3900912.

28. Shamloul, R.; Ghanem, H. Erectile dysfunction. Lancet. 2013, 381, 153-165, DOI: 10.1016/S0140-6736(12)60520-0.

 doi:10.20944/preprints201801.0196.v1

400 29. Mulhall, J.; Barnas, J.; Aviv, N.; Anderson, M.; Parker, M. Sildenafil citrate response
401 correlates with the nature and the severity of penile vascular insufficiency. J Sex
402 Med. 2005, 2, 104-108, DOI: 10.1111/j.1743-6109.2005.20110.x.
403 30. McMahon, CG. Nonsurgical treatment of cavernosal venous leakage. Urology. 1997,
404 49, 97-100, DOI: 10.1016/S0090-4295(96)00389-5.

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