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Assessment of Sonographic Findings of Erectile Dysfunction and Role of Phosphodiesterase 5 Inhibitor: Systematic Review

Muhammad Shoaib¹, Nawaz Anjum¹, Zeshan Haider², Zobia Saleem², Syed Muhammad Yousaf Farooq², Rizwan Rashid² and Muhammad Zubair^{2*}

¹Radiology Research Section, Faculty of Allied Health Sciences, University of Lahore, Pakistan ²University Institute of Radiological Sciences and Medical Imaging Technologies, Faculty of Allied Health Sciences, University of Lahore, Pakistan

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Abstract: Background: Sonographic studies in the arena of erectile dysfunction had reduced in significance in the last 10 years with the introduction of the latest actual therapies and the acknowledgment that surgical of the penile arterial and venous inefficiency had poor long-term clinical results. The praise of phosphodiesterase type 5 inhibitor developed the therapeutics of erectile dysfunction and completely reformed the method in which men erectile dysfunction are evaluated and examined. Objective: The objective of our study was to assess the sonographic findings of erectile dysfunction and the role of phosphodiesterase-5 inhibitor. Methods: A systematic search was achieved of MEDICINE and EMBASE research databases such as Google Scholar, PubMed, and Crossref databases from 2000 to 2021. The keywords are including, Doppler erectile dysfunction, assessment of sonographic findings of erectile dysfunction, the role of phosphodiesterase-5 inhibitor, and penile color Doppler sonography. Results: A total of 193 studies were documented through the database search. Also, 05 studies were recognized through additional bases. Then, the selection was achieved and 43 records were removed due to repetition. More selection was performed for 150 articles and 62 studies were excluded due to lack of evidence. There were 48 studies excluded due to research conducted on animals because this study was only determined on human studies. Conclusions: Soon, color Doppler sonography might be used in favor of patients because it can detect even small vessels in the tissue and study their blood flow. Duplex sonography of the penile arteries must be performed to deliver a good selection of therapeutic options.

Key words: Phosphodiesterase-5 inhibitors, erectile dysfunction, penile color Doppler sonography, duplex ultrasound.

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INTRODUCTION

Erectile dysfunction had been well-defined by the National Institutes of Health as the consistent inability to achieve or maintain penile erections of adequate quality to allow suitable sexual activity [1]. It signifies a significant public health problem with studies signifying 52.0% of men aged 40 to 70 years' experience erectile dysfunction, with as several as 10.0% of the people suffering severe erectile dysfunction [2, 3]. The causes of erectile dysfunction are wide-ranging and penile vascular disorders are considered to be an important factor in organic malfunction. Approximately 30.0% of erectile dysfunction is due to the occurrence of systemic diseases that disturb the blood flow of the penis. Penile erection is accomplished by complex stability among the increased blood flow in the corporeal artery,

*Corresponding Author: Muhammad Zubair

sufficient veno-occlusive function, and reduction of the corporal smooth muscle. Due to a decrease in the blood flow in the penile arteries, arteriopathy causes erectile dysfunction in male patients over 50 years of age. In recent times, erectile dysfunction is an important issue in cancer survivors concerning the quality of life. In this case, the penile color Doppler ultrasonography is a proficient and suitable tool for the evaluation of post-operative erectile dysfunction [4].

Subsequently, increase demand for a less invasive procedure such as penile duplex sonography characterizes the 1st line imaging modality to examining the arterial influx and the veno-occlusive mechanism. Advances in the ultrasound technology of the transducer development, renal time display, color Doppler, and power Doppler real-time display had upgraded the diagnostic proficiency [5]. The role of the penile color Doppler flow imaging study in the examination of the penile diseases well recognized because the vasculogenic ineffectiveness accounts for 60.0—80.0% of the whole causes. High-resolution sonography with the combination of color and pulsedwave Doppler forms the basis of modern penile sonographic assessment. Furthermore, they also play important role in the diagnosis of coronary artery disease in men having erectile dysfunction [6]. Currently improvements in the elastography and contrast-enhanced sonography techniques may be helpful to deliver valued evidence on penile diseases [7].

The present non-surgical, effective, and safe treatment for erectile dysfunction is the use of oral phosphodiesterase type 5 inhibitors. The influence of long-term daily use of phosphodiesterase type 5 inhibitors on endothelial function had induced a short-term improvement in erectile function [8]. The 1st accepted compound to prevent phosphodiesterase type 5 was sildenafil, which had established effectiveness and safety in clinical trials for erectile dysfunction. More recently, the effectiveness and care of other inhibitors of phosphodiesterase type 5 such as tadalafil had been recognized and stated [9]. It is an effective, reversible, and selective phosphodiesterase type 5 inhibitor for the treatment of erectile dysfunction [10].

METHODS

This review was conducted according to the preferred reporting items for the systematic review statement. We searched MEDICINE and EMBASE research databases such as Google Scholar, PubMed, and Crossref databases from January 2000 to April 2021. The keywords are including, Doppler erectile dysfunction, assessment of sonographic findings of erectile dysfunction, the role of phosphodiesterase-5 inhibitor, and penile color Doppler sonography. The current study was surveyed the presently accessible literature of evaluation of sonographic findings of erectile dysfunction and role of phosphodiesterase-5 inhibitor at the time of writing in March and simplified in April 2021. To raise the affectability of the search the Google scholar was utilized with similar keywords, taking the newly available research articles in the sonography of erectile dysfunction. We included those articles whose are original research work and peerreviewed written in English. This literature review reclaimed studies including sample size, duration of the study, study design, and its complication (Table 1). The

variables included were as follows; the 1st author of the research study, sample size, clinical findings, Doppler findings, ultrasound finding of the cavernous artery (PSV), erectile dysfunction, P-value, and treatment.

RESULT

We review different studies including the newly available articles material worldwide to provide information regarding research on erectile dysfunction and the role of phosphodiesterase-5 inhibitor. We include articles published from 2000 to 2021 and there were only sonographic related studies in the English language. A total of 193 studies were documented through the database search. Also, 05 studies were recognized through additional bases. Then, the selection was achieved and 43 records were removed due to repetition. More selection was performed for 150 articles and 62 studies were excluded due to lack of evidence. There were 48 studies excluded due to research conducted on animals because this study was only determined on human studies. Based on this review, we include different studies; systematic review, original research, and observational studies. In our article review, we assess the penile anatomy, its sonographic technique, erectile dysfunction, and the role of phosphodiesterase-5 inhibitor (figure 1).

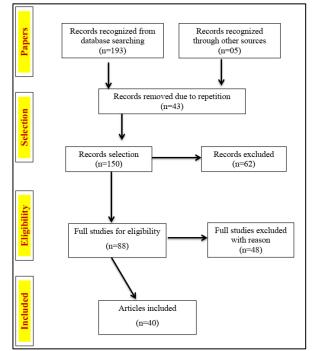


Fig-1: Flow diagram

References	P.Y	Country	al and Doppler S.D	N.P	C/F	US	D/F of C/A (PSVcm/s)	Erectile dysfunction	P-value	T.C weeks	Treatment
Aversa <i>et</i> <i>al</i> . [11]	2000	England	Prospective double-blind, placebo- controlled	20	B.P	*	*/*	**	<0.0001	12	P-5 Inhibitor
Kimura <i>et al</i> . [12]	2021	Japan	Propensity score matched analysis	79	*/*	*/*	*/*	**	< 0.05	4-24	P-5 Inhibitor
Bari <i>et al</i> . [13]	2017	Pakistan	Cross sectional	70	D.M	*	*/*	**	*/*	2	*/*
Mutnuru <i>et</i> al. [14]	2006	India	Prospective longitudinal	73	D.M, HPT	*	25.0	**	< 0.001	*/*	*/*
Rogers et al. [15]	2012	USA	Prospective, multicenter	30	RH.MI	*	22.5±23.7	**	*/*	4	P-5 Inhibitor
Arslan <i>et</i> <i>al</i> . [16]	2001	Turkey	Various methods of hemodynamic studies	42	HA, TC	*	19.79±1.32	**	*/*	24	*/*
Khanzada <i>et al</i> . [2]	2017	Pakistan	Retrospective cross sectional	97	Anxiety	*	46.22±18.4	**	< 0.022	*/*	*/*
Musa <i>et al</i> . [17]	2020	Egypt	Prospective	55	HPT, D.M	*/*	*/*	**	0.83	12-48	P-5 Inhibitor
Palmieri et al. [18]	2020	Italy	Prospective	109	D.M, HPT	*/*	22.07±5.2	**	< 0.0001	3	P-5 Inhibitor
Shamloul <i>et al</i> . [19]	2013	Canada	*/*	*/*	D.M, HPT	*	*/*	**	*/*	*/*	P-5 Inhibitor
Montorsi et al. [20]	2004	Italy	Randomized, double-blind	1173	D.M, HPT	*/*	*/*	**	*/*	28-48	T/ P-5 Inhibitor
Hatzichris- tou <i>et al</i> . [21]	2001	Italy	*/*	179	D.M, HPT	*/*	*/*	**	*/*	*/*	T/ P-5 Inhibitor
Brock <i>et al</i> . [10]	2002	Australia	Integrated analysis	1112	D.M CAD	*/*	*/*	**	< 0.001	12	T/ P-5 Inhibitor
Cannarella et al. [22]	2021	Italy	Cross sectional	80	Anxiety	*	25.0	**	< 0.01	*/*	NA
Mohan <i>et</i> <i>al</i> . [23]	2021	Switzerland	Cohort	239	NA	*	30.0	**	NA	*/*	Alprostadil
Corona <i>et</i> <i>al</i> . [24]	2008	Italy	Consecutive series	1346	MI, D.M	*	<25.0	**	< 0.0001	*/*	*/*
Xuan <i>et al</i> . [25]	2015	China	Correlation	164	D.M, HPT	*	38.47±8.54	**	< 0.001	24	Lidocaine, sildenafil
Lewis <i>et al</i> . [26]	2001	USA	Randomized, double-blind	247	M.I, D.M	*	*/*	**	< 0.001	12	Sildenafil
Rosen <i>et al</i> . [27]	2004	USA	Randomized, double-blind	75	D.M, HPT	*/*	*/*	**	0.02	12	T/ P-5 Inhibitor
Padma- Nathan [28]	2003	USA	Randomized, double blind, and placebo controlled	61	*/*	*/*	*/*	**	0.001	12	T/ P-5 Inhibitor
Allen D. Seftel. [29]	2004	USA	*/*	38	H.A D.M, HPT	*/*	*/*	**	< 0.001	*/*	T/ P-5 Inhibitor
Keitz <i>et al</i> . [30]	2004	Germany, Spain and USA	Randomized, double-blind, crossover	219	D.M, CAD, HPT	*/*	*/*	**	<0.001	12	T/ P-5 Inhibitor
Rosen et at. [31]	2003	USA	Randomized, Double-blind, Parallel Trial Multicenter	179	D.M, HPT	*/*	*/*	**	<0.003	3	T/ P-5 Inhibitor
Giuliano <i>et al</i> . [32]	2002	U.K	Randomized, Double-blind, Parallel Trial	1112	D.M, HPT,	*/*	*/*	**	<0.001	*/*	T/ P-5 Inhibitor
G.A Stuckey[33]	2002	Australia	Parallel Trial Randomized, Double-blind, Parallel Trial Phase 3	804	CAD D.M, HPT, CAD	*/*	*/*	**	<0.001	12	T/ P-5 Inhibitor

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Wanshou et al. [34]	2019	China	Randomized, Double-blind, Parallel Trial Multicenter	120	D.M, HPT,	*	*/*	**	<0.05	12	P-5 Inhibitor
Carneiro et al. [35]	2019	Brazil	Randomized	40	D.M, HPT,	*	65.7 ± 22.2	**	0.768	12	P-5 Inhibitor
Joshua <i>et</i> <i>al</i> . [36]	2021	Nigeria	Consecutive	35	C.M	*	42.88 ±18.7	**	0.481	*/*	*/*
Hartmut <i>et al</i> . [37]	2003	Germany	Randomized, Double-blind, Parallel Trial Multicenter	348	C.M, H.A	*	*/*	**	<0.001	4	T/ P-5 Inhibitor
Skoumal <i>et</i> <i>al.</i> [38]	2004	Czech Republic	Randomized, Double-blind, Parallel Trial Multiple center	443	D.M, HPT	*/*	*/*	**	<0.001	4	T/ P-5 Inhibitor
Tajada <i>et</i> al. [39]	2002	Spain	Randomized	216	D.M, HPT, H.A	*/*	*/*	**	<0.001	*/*	T/ P-5 Inhibitor
Wang <i>et al.</i> [40]	2019	China	Self-Control	357	C.M HPT	*	31.2±5.1	**	<0.001	*/*	*/*
Pathak <i>et</i> al. [41]	2020	North Carolina	Retrospective Review	2043	D.M, HPT	*	>35.0	**	0.002	*/*	T/ P-5 Inhibitor
Ogreden et al. [42]	2018	Turkey	Retrospective	260	D.M, HPT	*	<30.0	**	0.404	*/*	P-5 Inhibitor
Butaney <i>et</i> al. [43]	2018	USA	Electronic Survey	30	D.M	*	<25.0	**	0.01	*/*	*/*
Li Chen <i>et</i> <i>al</i> . [44]	2019	China	Prospective	53	D.M, HPT	*	48.36±9.88	**	< 0.05	*/*	*/*
Michele et al [45]	2020	Italy	*/*	*/*	*/*	*	*/*	**	*/*	*/*	P-5 Inhibitor
Handarini <i>et al.</i> [46]	2020	Indonesia	Prospective observation	30	D.M, HPT	*	14.3 ± 3.6	**	0.030	*/*	*/*
Yamacake et al. [47]	2018	Brazil	Double blinded, Prospective, Randomized, sham Controlled trial	20	D.M, HPT	*	50.8	**	0.853	12	*/*
Altinbas <i>et al</i> . [48]	2018	Turkey	Prospective	88	D.M, HPT	*	56.1±23.9	**	< 0.001	*/*	P-5 Inhibitor

Abbreviations: N.P= Number of patients, B.P=Blood pressure, C/F= Clinical findings, US=Ultrasound, D/F= Doppler findings, S.D=Study design, C/A= Cavernous artery, PSV= Peak systolic artery, D/S= Duration of symptoms, D.M= Diabetic mellitus, HPT=Hypertension, C.A= Coronary artery, P.V=Peripheral vascular, RH.MI=Relevant history of myocardial infarction. H.A= Headache, TC=Tachycardia, A.I= Arterial insufficiency, CAD=, Coronary artery disease, V.L= Venous leak, A.D= Arterial dysfunction, P-5= Phosphodiesterase-5, T.C=Treatment course, T/P-5=Tadalafil Phosphodiesterase-5, */*=Not available, *=Performed, **=Present. C.M= Cigarette smoking.

DISCUSSION

Sonographic inspection can be used to observe the penile structure and vasculature with the help of color Doppler flow imaging allowing for the detection of the cavernosal and dorsal penile arteries. It was recognized as an inspective technique and recently had advanced through the use of phosphodiesterase type-5 inhibitors such as tadalafil. The use of tadalafil drugs causes increased blood flow into the corpora cavernosa, relaxation of the smooth muscle, and vasodilatation. A suitable reaction to the experiment of this drug confirms sufficient arterial supply, veno-occlusive mechanism, and prevents the need for further additional research. Therefore, penile duplex sonography should be performed on those patients with slight or no reaction to the 1st line medications, and arterial or venous insufficiency is assumed [49].

According to Aversa et al. [11] sildenafil 100 mg is a precise inhibitor of phosphodiesterase-5 and characterize an influential therapy for male erectile dysfunction of different pathologies. They enrolled 20 patients for three months of the time of the study. Duplex sonography was also performed for the resistive index of the coronary artery respectively. According to Kimura et al. [12] there is an advantage from penile rehabilitation using a phosphodiesterase type 5 inhibitor. They enrolled a total of 158 patients, of which 79 patients in the penile rehabilitation group and 79 patients in the non-penile rehabilitation. For penile therapy tadalafil 20.0 mg phosphodiesterase type 5 inhibitor was administrated two times a week for 1-6 months post-operatively. In the end, they concluded that significant improvement in the erectile retrieval percentage in the penile rehabilitation group. Bariet et al. conducted a study on erectile dysfunction; the purpose of his study was to evaluate the role of Doppler ultrasonography in the assessment of erectile dysfunction. They enrolled a total of 70 patients with an age range from 24 to 70 years, of which 2 patients had primary erectile dysfunction with arterial insufficiency on color Doppler ultrasonography and 68 patients had developed this problem after a period of normal sexual activity [13]. Mutnuru et al. reported that the patients that had erectile dysfunction are only 5 out of 73 patients [14]. Rogers et al. [15] reported that, erectile dysfunction is a common situation and is often facilitated by atherosclerosis. They enrolled 30 patients and the mean age of patients was 60.1 years and the mean peak systolic velocity was 22.5±23.7 cm/sec. Arslan et al. [16] enrolled 42 patients, Of which 22(52.3%) patients had erectile dysfunction. Difficulties due to papaverine and sildenafil management are severe pain 8(19.0%), tachycardia 2(4.0%), and ecchymosis 2(4.0%). Khanzada et al. [2] enrolled 97 patients, of which the mean age of patients was 37.0±11.5 years, range between 19 to 69 years. The patients that had normal penile Doppler sonographic findings are 50(51.5%). The peak systolic velocity of the cavernosal artery is 46.22±18.41 cm/sec, 24(24.7%) patients had arterial insufficiency, 15 (15.5%) patients had a venous leak. Musa et al. [17] also reported that 22 patients who had oral phosphodiesterase type-5 inhibitors had able to complete an erection sufficient and 19 patients had poor response to it. A similar study was conducted by Palmieri et al. [18], they enrolled 109 patients. The age range between 21 to 78 years. Mild erectile dysfunction are noted in 2(1.8%), mild to moderate erectile dysfunction are in 29(27.3%), moderate erectile dysfunction are 38(35.9%), and severe erectile dysfunction are 75(35.0%). According to Rany and Hussein [19], substantial progress had happened in the understanding of the pathophysiology of erectile dysfunction that eventually led to the growth of successful oral therapy such as phosphodiesterase-5 inhibitor.

Montorsi et al. [20] in 2004 studied the long safety and acceptability of period tadalafil (phosphodiesterase-5 inhibitor) in the management of erectile dysfunction. This study was conducted in a multicenter and the total numbers of patients are 1173 men with erectile dysfunction. The mean age of patients was 57 and range between 23 to 83 years. Of 1173 patients only 493(42.0%) patients had completed 24 months of treatment. In the end, they concluded that tadalafil in long-term use is safe and well-tolerated. A similar study in 2001 show the effectiveness and safety of on request dosing of tadalafil (phosphodiesterase-5 inhibitor) 2 to 25 mg in 179 men with erectile dysfunction was evaluated in a multicenter, presenting a significant development in 88.0% of men given tadalafil reported improved erections [21]. Another similar study was conducted in 2002 [10], the purpose of his study was to integrated analysis of the effectiveness and safety of tadalafil, a strong selective phosphodiesterase-5 inhibitor for the treatment of erectile dysfunction.

According to his study tadalafil 20 mg significantly enhanced all efficacies than placebo. According to the Cannarella et al. [22] penile color Doppler sonography is the gold standard for the detection of arterial erectile dysfunction. Xuan et al. [25] examined the correlations between hemodynamic parameters and the therapeutic effects of phosphodiesterase-5 inhibitors by using color Doppler sonography. They enrolled 164 patients; the mean age of the patient was 44, and the range between 22 to 71 years. All patients were given oral sildenafil with a minimum dose of 50 mg and a maximum of 100 mg. The penile vessels were diagnosis through color Doppler sonography. A similar study in 2019 [34] shows that low-intensity pulsed ultrasound is a therapeutic device that improves erectile function because it is safe and effective to treat patients. They concluded that the 1st line erectile dysfunction therapeutic approach is a phosphodiesterase-5 inhibitor and the 2nd choice is intracavernosal injection therapy. Rosen et al. [27] reported the initial period to erectogenic consequence leading to the successful association within 30 mints after taking tadalafil 10 mg and 20 mg.

CONCLUSION

In the era of phosphodiesterase type-5 inhibitor, penile color Doppler evaluation had reduced its significance however, it remains to have an important role in the assessment of particular patients having erectile dysfunction. While color Doppler sonography might be used in favor of patients because it can detect even small vessels in the tissue and study their blood flow. Duplex sonography of the penile arteries must be performed to deliver a good selection of therapeutic options.

Conflict of Interests

The authors have declared no conflict of interest.

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