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Regenerative Therapy in Erectile Dysfunction: A Survey on Current Global Practice Trends and GAF Expert Recommendations

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Purpose: This study aimed to examine current global practices in regenerative therapy (RT) for erectile dysfunction (ED) and to establish expert recommendations for its use, addressing the current lack of solid evidence and standardized guidelines.
Materials and Methods: A 39-question survey was developed by senior Global Andrology Forum (GAF) experts to comprehensively cover clinical aspects of RT. This was distributed globally via a secure online Google Form to ED specialists through the GAF website, international professional societies, and social media, the responses were analyzed and presented for frequencies as percentages. Consensus on expert recommendations for RT use was achieved using the Delphi method.
Results: Out of 479 respondents from 62 countries, a third reported using RT for ED. The most popular treatment was low-intensity shock wave therapy (54.6%), followed by platelet-rich plasma (24.5%) and their combination (14.7%), with stem cell therapy being the least used (3.7%). The primary indication for RT was the refractory or adverse effects of PDE5 inhibitors, with the best effectiveness reported in middle-aged and mild-to-moderate ED patients. Respondents were confident about its overall safety, with a significant number expressing interest in RT's future use, despite pending guidelines support.
Conclusions: This inaugural global survey reveals a growing use of RT in ED treatment, showcasing its diverse clinical applications and potential for future widespread adoption. However, the lack of comprehensive evidence and clear guidelines requires further research to standardize RT practices in ED treatment.

Keywords: Erectile dysfunction; Extracorporeal shockwave therapy; Platelet-rich plasma; Regenerative medicine; Stem cells; Surveys and questionnaires

INTRODUCTION

Erectile dysfunction (ED) is defined as the inability to attain or maintain erections sufficient for satisfactory sexual performance [1]. There has been a significant global increase in the prevalence of ED, partly due to the rapidly aging population [2]. ED is an important health concern that can affect men's psychosocial well-being as well as the interpersonal relationships of couples [3]. Furthermore, it is an independent risk factor for impending cardiovascular disease [4].

Phosphodiesterase 5 inhibitors (PDE5i) remain the first-line treatment for ED due to their efficacy and safety but are often not effective or have adverse side effects [5]. Intracavernosal injection of alprostadil, alone or in combination with phentolamine and papaverine, was approved by the FDA in 1996 and has good efficacy, but may cause prolonged erections or pain at the injection site, and occasionally fibrosis after long-term use [6]. Alternatively, intraurethral alprostadil has also been used but is less efficacious despite having fewer adverse effects [7]. ED patients can also use vacuum erection devices, but the erection is often unsatisfactory, and compliance is generally low [8]. Finally, refractory patients who do not respond to the aforementioned treatment modalities may be considered for penile prosthesis surgery which demonstrates superior efficacy with high satisfaction rates. However, patients should be carefully selected and counseled before this irreversible surgical treatment, and its complications, though few, include corporal perforation, cross-over displacement, urethral/bladder/bowel injury, soft glans syndrome, infection, mechanical malfunction, and erosion [9,10]. While all these treatments provide symptomatic relief, there is a need to develop new and efficacious treatment options that alter the progres-

sion of the disease and even restore normal physiologic erections.

Regenerative therapy (RT) has been suggested to aid in the repair and recovery of damaged tissues and local cell lines of dysfunctional organs [11]. Thus, RT aims to restore normal erections by attempting to regenerate erectile tissue, rather than merely relieve symptoms [12]. Emerging RT advances for ED include platelet-rich plasma (PRP), stem cells (SCs) therapy, and low-intensity shock wave therapy (LISWT).

PRP is an autologous centrifuged plasma that has more platelets than normal plasma and contains platelet-related growth components, tissue factors, plasma-derived fibrinogen, and several biologically active cytokines. Several studies have been carried out utilizing intracavernosal PRP infusion for ED, particularly for diabetic patients non-responsive to oral PDE5i [13], but more studies are needed that consider the quality and efficacy of PRP preparations and provide long-term outcomes [14].

SCs are undifferentiated cells that can divide into particular types of cell lines and tissues. Hence, SCs can replace worn-out or damaged tissues to obtain tissue- or organ-specific cells with specialized capacities [15]. Several sources of SCs have been identified, each with unique characteristics and potential applications. A limited number of studies have provided proof of their possible utility in treating ED. A meta-analysis study [16] suggested the efficacy of SC therapy for ED due to diabetic mellitus and the possible superiority of adipose tissue-derived SCs over bone marrow mesenchymal stromal cells in erection restoration and structure renovation. In addition, laboratory studies on rat models have shown the useful role of SCs and stromal vascular fraction in restoring erectile function and preventing penile fibrosis in various animal models of Peyronie's disease and ED [17]. However, solid evidence is still lacking in clinical settings, and there is insufficient data on suitable dosage, cell heredity, or its component of activity.

LISWT has been applied for treating vasculogenic ED in PDE5i non-responders, with few adverse effects. Animal studies have shown that LISWT significantly improves penile hemodynamics and might reverse some penile pathological changes in an animal model of induced diabetes [18]. It was proposed that LISWT repairs erectile tissues by stimulating vascular endothelial growth factor (VEGF) and different chemokine proteins, such as stromal cell-derived factor 1 (SDF-1), which can partially reverse pathological changes in the corpus cavernosum, endothelial dysfunction, and peripheral neuropathy [19-21]. According to a meta-analysis of seven randomized controlled trials (RCTs) involving men who received LISWT for ED, the International Index of Erectile Function (IIEF) and Erection Hardness Score (EHS) scores increased significantly in the treatment groups [22]. Patients with moderate and/or severe ED reported better improvements in IIEF scores. The lack of penile deformation at 5-year follow-up supports the long-term safety of LISWT in men with ED [23].

However, the selection criteria, techniques, and protocols for these various RT modalities in clinical practice lack evidence-based recommendations for the best clinical practice. Therefore, the aims of this study are, 1) to explore the current global practices of the use of RT in ED, and 2) to develop expert recommendations on various clinical aspects of this treatment modality using the Delphi method.

MATERIALS AND METHODS

A cross-sectional, worldwide, online survey for the global perception and practice of RT in ED was developed and distributed in accordance with the CHERRIES checklist (Supplement File 1) [24]. The initial survey questions were submitted by the senior members of Global Andrology Forum (GAF) and underwent several rounds of review to ensure that the questions and answers were unambiguous. The final list of questions was comprehensive and covered all clinical aspects of RT within the context of ED. The overall survey strategy is presented in Fig. 1.

The completed 39-item questionnaire comprised three sections: The first section (Q1–5) gathered demographic information such as age, years of experience, country, setting of practice, and specialty of the respondents. The questions in the second section (Q6–11) were about the workload of ED patients, patient assessment, and the present and future intentions regarding the overall utilization of RT. Section three of the questionnaire (Q12–39) focused on the different facets of RT utilization, including frequently employed modalities, prevalent indications, patient feedback, as well as the effectiveness and safety of treatments.

The complete survey with the invitation letter are

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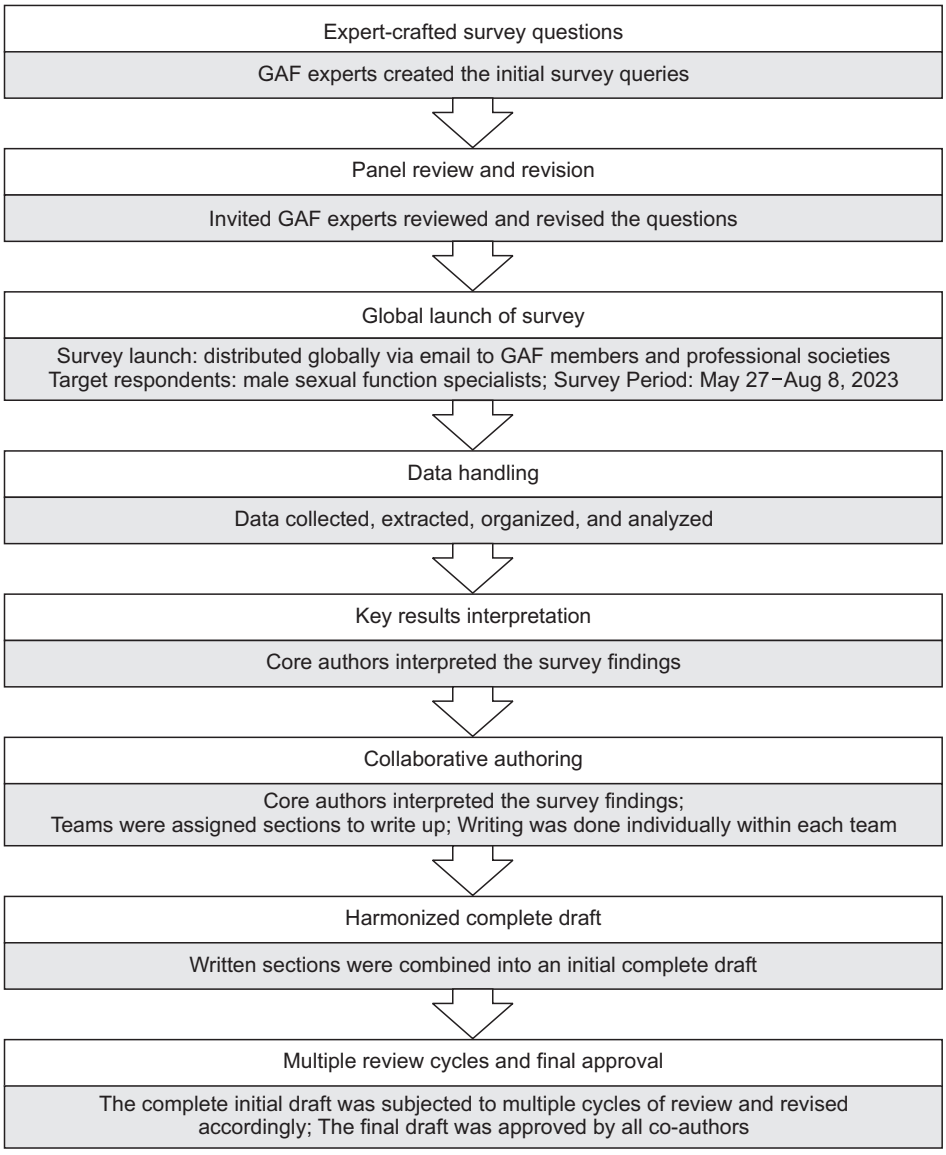


Fig. 1. A flow diagram of the research process. GAF: Global Andrology Forum.

provided in Supplement File 2. The respondents were given the option to skip questions about specific RT modalities if they did not have experience with that specific modality, thus avoiding potential answer bias. The survey was created and globally distributed using the secure Google Forms platform to ensure the confidentiality of the submitted responses. The survey was made accessible from May 27, 2023, to August 8, 2023. Clinicians worldwide treating ED were invited to participate in this study. They were informed about the nature and objective of the survey and requested to complete the online survey. The survey questions were provided in the English language and used standard medical terms. This survey was approved by the Ethics committee (approval number: IR-02-23-103).

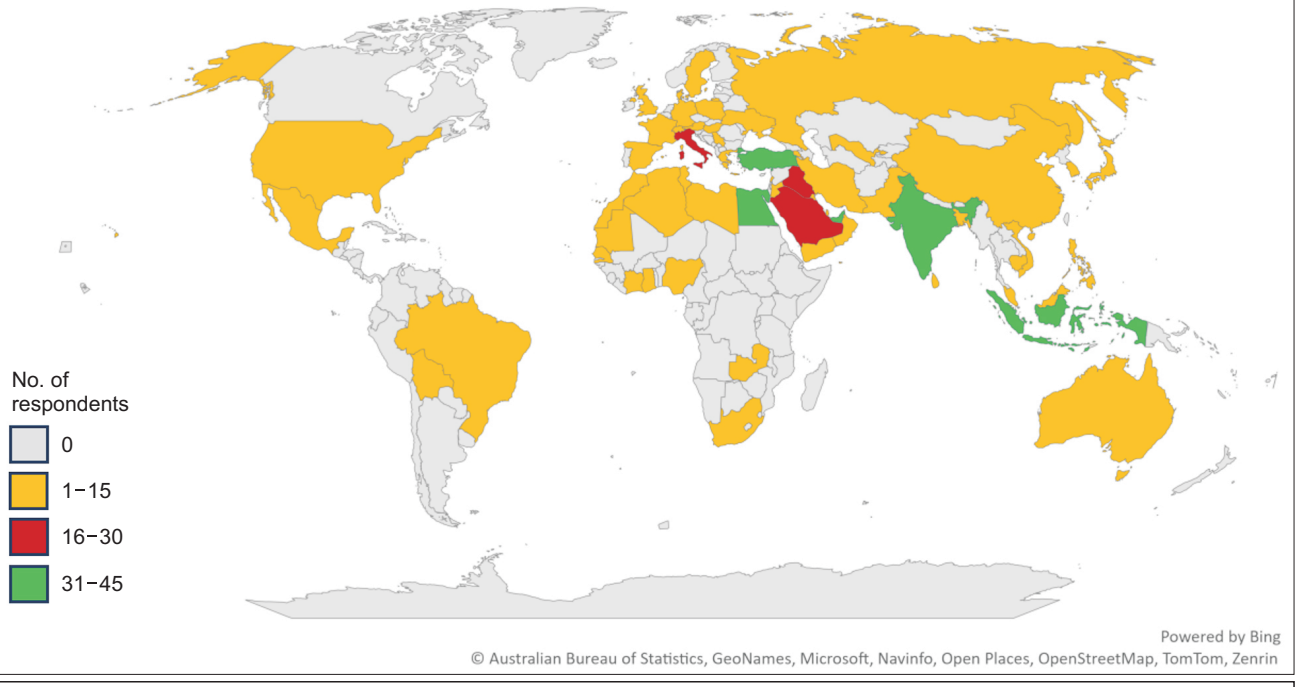
The answers to the questionnaire were described as numbers and percentages of each choice. For questions where the participant might choose more than one answer, each response frequency was calculated from the total number of participants. The R version 4.1.2 programming language (www.r-project.org) was used to create the bar charts (Supplement File 3).

A set of expert recommendations was created through a collaborative process between senior GAF members with substantial academic expertise and clinical experience in the treatment of ED by RT. These statements comprised the critical facets of RT in ED treatment and were circulated among the experts to achieve consensus through the Delphi method [25] (Supplement File 4).

RESULTS

1. Demographics of participants

A total of 479 participants from 62 countries completed the survey. Participants from the United Arab



1. United Arab Emirates (n=44)
2. Egypt (n=42)
3. Indonesia (n=39)
4. India (n=38)
5. Türkiye (n=37)
6. Saudi Arabia (n=25)
7. Iraq (n=22)
8. Italy (n=20)
9. Austria (n=15)
10. Vietnam (n=14)
11. Iran (n=12)
12. Morocco (n=12)
13. Nigeria (n=9)
14. Greece (n=8)
15. Japan (n=8)
16. United States (n=8)
17. Armenia (n=7)
18. Libya(n=6)
19. Singapore (n=6)
20. Spain (n=6)
21. Bahrain (n=5)
22. Brazil (n=5)
23. Pakistan (n=5)
24. Russia (n=5)
25. United Kingdom (n=5)
26. Bangladesh (n=4)
27. Hong Kong (n=4)
28. Jordan (n=4)
29. Mexico (n=4)
30. Oman (n=4)
31. Algeria (n=4)
32. Germany (n=3)
33. Ghana (n=3)
34. Kuwait (n=3)
35. Malaysia (n=3)
36. Qatar (n=3)
37. Tunisia (n=3)
38. Australia (n=2)
39. France (n=2)
40. Korea, South (n=2)
41. Lebanon (n=2)
42. Serbia (n=2)
43. South Africa (n=2)
44. Switzerland (n=2)
45. Ukraine (n=2)
46. Uzbekistan (n=2)
47. Barbados (n=1)
48. Bolivia (n=1)
49. Cambodia (n=1)
50. China (n=1)
51. Cote d'Ivoire (n=1)
52. Denmark (n=1)
53. Hungary (n=1)
54. Mauritania (n=1)
55. Philippines (n=1)
56. Poland (n=1)
57. Senegal (n=1)
58. Sri Lanka (n=1)
59. Sweden (n=1)
60. West Bank (n=1)
61. Yemen (n=1)
62. Zambia (n=1)

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Fig. 2. Geographical distribution of the respondents.

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Emirates had the highest response rate (44/479, 9.19%), followed by those from Egypt (42/479, 8.77%) and Indonesia (39/479, 8.14%) as in Fig. 2. Most of the respondents were 35 to 44 years old (158/479, 33.0%), whereas less than 10% of the participants were older than 65 years. The survey was mostly composed of urologists, accounting for 84.3% (404/479). They were equally distributed between those primarily specializing in andrology and sexual medicine, and those whose primary focus was urology with some involvement in andrology and sexual medicine. Approximately half of the participants had worked in private practice and had more than 15 years of experience (Supplement File 5).

2. ED diagnosis and work-up

For 237/479 (49.5%) respondents, the workload with ED patients comprised >25% of their practice. A total of 279/479 (58.2%) expressed that combined etiology for ED was the foremost commonly diagnosed etiology in their practice, whereas vasculogenic ED was the next most common according to 75/479 (15.7%) respondents, followed by psychogenic causes (56/479, 11.7%). The respondents used different work-up protocols for the diagnosis of ED, but the majority (205/479, 42.8%) used history, examination, and hormonal testing, as shown in Fig. 3.

3. The current global trend of RT use in ED treatment

The majority of the respondents are not using RT for ED in their practice (316/479, 66.0%). This was mostly due to the lack of experience with this type of therapy (68/316, 21.5%) as shown in Fig. 4. However, some respondents expressed potential willingness to consider utilizing RT for ED in the future under certain conditions. These conditions included: if further studies demonstrated increased efficacy (121/316, 38.3%), if they were provided with adequate training (61/316, 19.3%), if it became accessible at their institution (48/316, 15.1%), if it received endorsement from guidelines (45/316, 14.3%), or if it was covered by insurance (41/316, 13.0%).

RT was used by 163 respondents (34.0%) (Table 1). Of these, 18/163 users (11.0%) applied RT in more than 50% of cases, another (29/163, 17.8%) utilized it in 25% to 50% of cases, while 61/163 (37.4%) used it in up to 25% of cases. Additionally, 55/163 (33.7%) incorporated it only occasionally (less than 10% of cases).

The respondents reported that the most available modality options for RT were penile LISWT (122/163, 74.8%), intracavernosal PRP (30/163, 18.4%), and intracavernosal SC (6/163, 3.7%). The first modality of RT chosen for the treatment of ED was monotherapy with LISWT by 89 out of 163 respondents (54.7%), trailed by intracavernosal PRP by 40 out of 163 (24.5%), and a combination of both therapies by 24 out of 163 (14.7%). A minority of respondents 6/163 (3.7%) were using in-

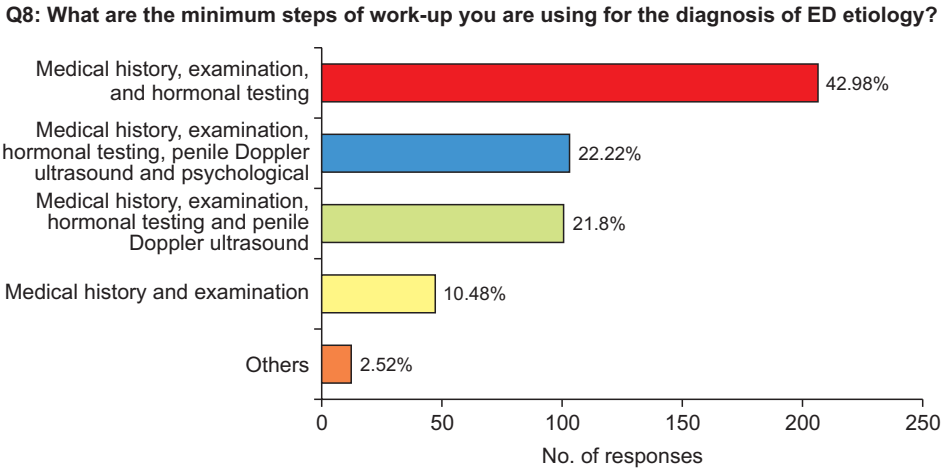

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Fig. 3. Minimal work-up pathways for erectile dysfunction (ED) diagnosis.

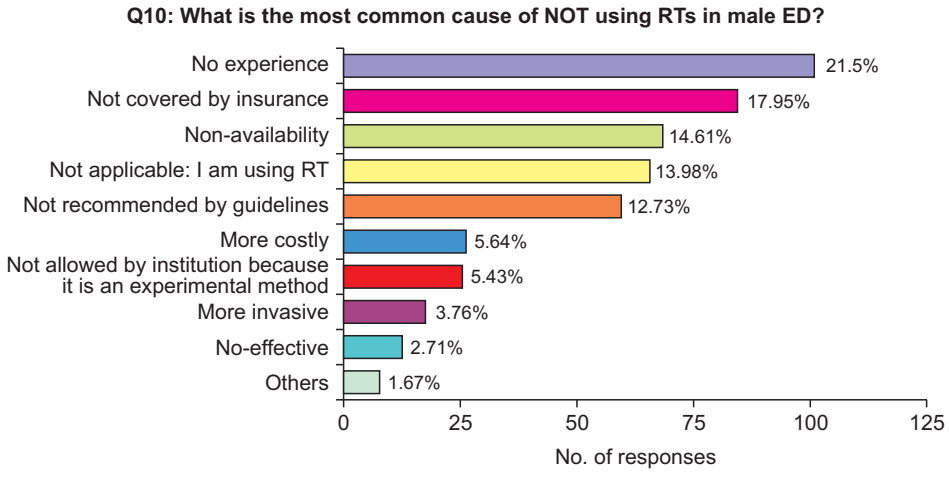

Fig. 4. The causes of not using regenerative therapy (RT) in erectile dysfunction (ED) treatment.

Table 1. The first, second, and third most commonly used modalities of regenerative therapy

Modality	First most common	Second most common	Third most common
Penile LISWT	89 (54.7)	23 (14.1)	15 (9.2)
Intracavernosal PRP	40 (24.5)	37 (22.7)	18 (11.0)
Combination of PRP+LISWT	24 (14.7)	26 (16.0)	23 (14.1)
Intracavernosal SCs	6 (3.7)	4 (2.4)	10 (6.2)
Combination of Intracavernosal SCs+LISWT	0 (0)	2 (1.2)	9 (5.3)
Others (not specified)	4 (2.4)	3 (1.9)	5 (3.1)
I don't use another modality	0 (0)	68 (41.7)	83 (51.0)
Total	163 (100)	163 (100)	163 (100)

Values are presented as number (%).
LISWT: low-intensity shock wave therapy, PRP: platelet-rich plasma, SCs: stem cells.

Table 2. The three most common indications for using regenerative therapy in erectile dysfunction

Indication	First-most common indication	Second-most common indication	Third-most common indication
Non-responders to other modalities	104 (63.8)	33 (20.2)	38 (23.3)
Patients request	23 (14.1)	42 (25.8)	53 (32.5)
To have a long-term cure	20 (12.3)	26 (16.0)	28 (17.2)
Adverse effects of other modalities	11 (6.8)	57 (35.0)	37 (22.7)
Others	5 (3.0)	5 (3.0)	7 (4.3)
Total	163 (100)	163 (100)	163 (100)

Values are presented as number (%).

tracavernosal SCs and 4/163 (2.4%) were using other not specified modalities. The second or third most frequently offered modalities of RT varied depending on their availability in the respective institutes, as illustrated in Table 1.

The majority of the respondents (100/163, 61.3%) did not offer RT as a first-line therapy and stated that they always tried established options such as PDE5i first, while the remaining respondents used RT as the first option in some selected patients (51/163, 31.3%) or

always (12/163, 7.4%).

The predominant indication cited by the participants for employing RT in ED included non-responsiveness to standard treatments of ED (104/163, 63.8%), patients expressing interest in exploring this novel approach (23/163, 14.1%), the pursuit of a lasting cure (20/163, 12.3%), encountering adverse effects from other treatments (11/163, 6.75%), and miscellaneous reasons (5/163, 3.07%). Additionally, Table 2 highlights the second and third most prevalent indications for using RT to treat ED.

Of those who used RT, 82.2% of respondents (134/163) used them in combination with other treatment modalities, while the remaining of respondents (29/163, 17.8%) offered RT as sole treatment. The most common combination was offered with PDE5i in 82.8% of respondents (135/163) and the remaining was with a vacuum erection device, intra-cavernosal alprostadil, or others.

4. Patient satisfaction, time to and duration of improvement

Approximately half of the respondents from the group utilizing RT (82 out of 163, 50.3%) indicated that their patients exhibited moderate satisfaction with the effectiveness of RT. Other respondents noted that their patients were either mildly satisfied (40 out of 163, 24.5%) or highly satisfied (33 out of 163, 20.2%). A small minority (8 out of 163, 5.0%) reported that their patients were unsatisfied with RT.

On the flip side, only 24.5% of respondents stated that >50% of their treated patients demonstrated notable objective improvement and attained the desired objectives of RT treatment (Fig. 5).

Regarding the timeframe for enhanced erectile function following RT, responses were notably consistent: a majority of participants (152/163, 93.2%) indicated that their patients exhibited a clinical response within 6 months post-treatment. The remaining patients either cited a requirement for more than 6 months (5/163,

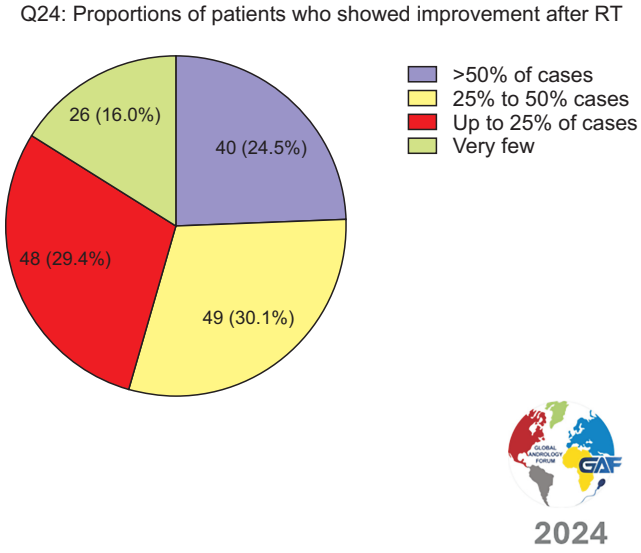

Fig. 5. Proportions of patients who showed objective improvement after regenerative therapy (RT).

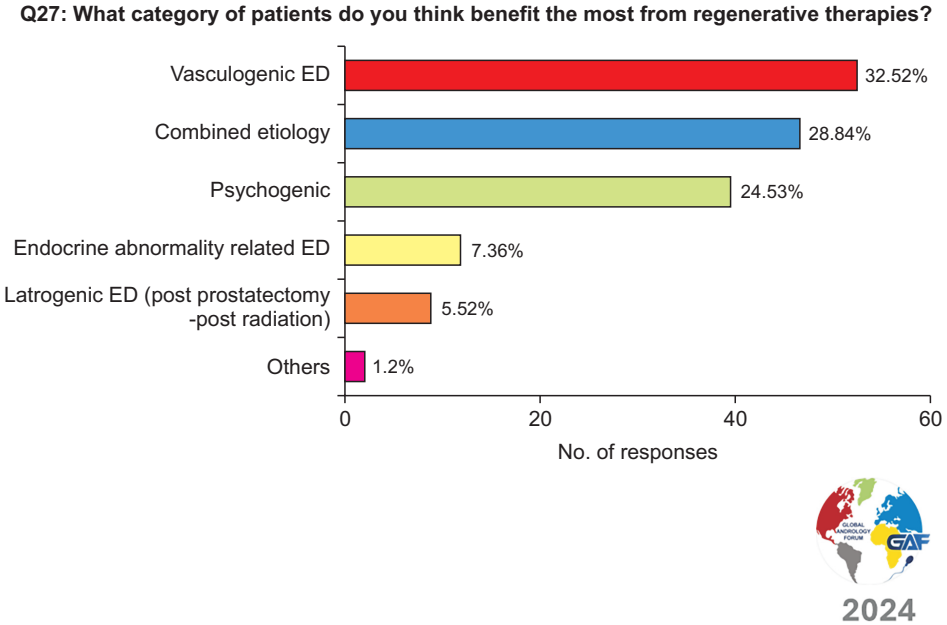

Fig. 6. The erectile dysfunction (ED) etiologies that best responded to regenerative therapy.

3.2%) or expressed uncertainty (6/163, 3.6%) regarding the duration of improvement.

The participants noted variations in the duration of improved erectile function following RT. Specifically, 19/163 respondents (11.7%) reported sustained enhancement for 1–3 months, 39/163 (23.9%) for 3–6 months, 53/163 (32.6%) for 6–12 months, and 26/163 (16.0%) for over 12 months. Furthermore, 29/163 (17.8%) expressed uncertainty regarding the exact duration.

5. The best patient category to benefit from RT in ED treatment

The respondents reported that the most common ED etiology to benefit from RT is vasculogenic and combined etiology, as shown in Fig. 6.

6. Comparison of RT response to PDE5i

Opinions regarding the comparison between RT and PDE5I are varied. A significant proportion of respondents highlighted RT's higher cost (53/163, 32.5%), its superior long-term effects (28/163, 17.2%), better efficacy, and reduced adverse effects (each noted by 19/163, 11.7%). Only a small fraction (13/163, 8.0%) considered this treatment more cost-effective, while 6.7% (11/163) reported it as less effective. The remainder either observed no discernible difference in their patients (9/163, 5.5%) or expressed uncertainty (11/163, 6.7%).

7. The assessment of RT response and the best-responding patient population

The evaluation of effectiveness appears largely subjective among the surveyed clinicians, with 95 out of 163 (58.3%) assessing the effectiveness of RT based on overall patient satisfaction, while only 31/163 (19.0%) utilized the IIEF questionnaire. Objective methods, such as penile Doppler ultrasound, were employed by just 20.9% (34/163) of respondents to evaluate erectile function. A small minority (3/163, 1.8%) utilized alternative criteria like partner satisfaction.

The participants observed that the effectiveness of RT varies depending on the age of the patient and the severity of ED. Middle-aged patients (100/163, 61.3%) and those with moderate ED (102/163, 62.6%) were identified as the most responsive target population for RT, as shown in Fig. 7 and 8.

8. The impact of insurance coverage and country regulations on RT utilization, along with physician assessment of existing evidence and therapeutic delivery of RT

Most survey participants indicated that if insurance covered RT, it would likely result in higher demand for RT. This could stem from physicians being more inclined to prescribe RT (51/163, 31.3%) or from more patients consenting to or seeking out RT (66/163, 40.5%). On the other hand, a minority (46/163, 28.2%) reported

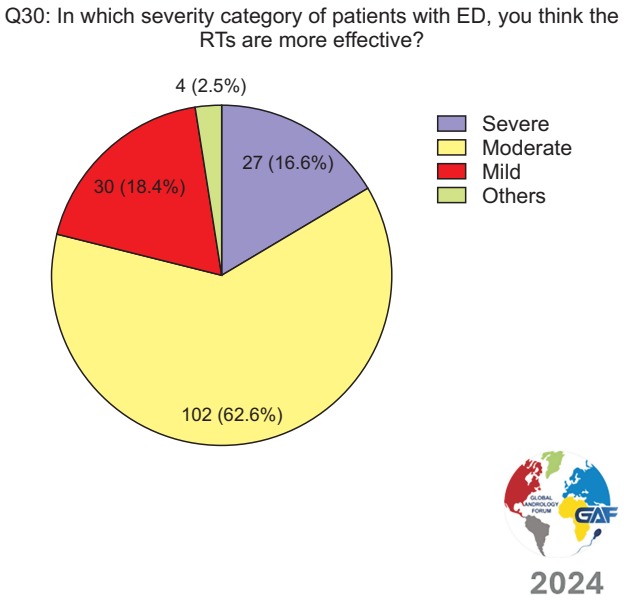

Fig. 7. Stratification by erectile dysfunction (ED) severity clusters responding to regenerative therapy (RT).

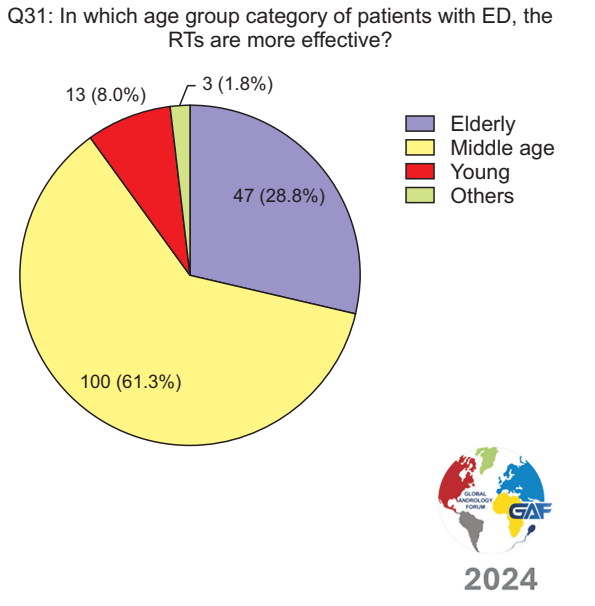

Fig. 8. Response to RT based on the patients' age group. ED: erectile dysfunction, RT: regenerative therapy.

that the availability of insurance coverage did not influence either the physicians' or patients' choices. Out of the respondents surveyed, just 39 out of 163 (23.9%) were knowledgeable about any particular regulations about this treatment in their respective countries. Conversely, the majority either lacked awareness of such regulations (93/163, 57.1%) or expressed uncertainty regarding their existence (31/163, 19.0%).

The approach to presenting RT to patients varied among the respondents: nearly half (78/163, 47.9%) regarded RT as a conventional therapeutic choice, while the other half primarily utilized RT within experimental contexts (43/163, 26.4%), clinical trials (36/163, 22.1%), or unspecified alternative options (6/163, 3.6%).

Respondents exhibit diversity in their classification of the existing evidence and recommendations regarding RT in the treatment of ED. Approximately 46.6% of respondents (76/163) characterized the evidence and recommendations as moderate, while 38.0% (62/163) deemed them poor. Merely 9.2% (15/163) of respondents regarded the evidence as strong, with a minority of 6.2% (10/163) denying the existence of any pertinent evidence.

9. Physicians' attitudes toward RT, their training in RT, and safety concerns surrounding its use

The participants presented diverse reasons behind their patients' reluctance to undergo RT for ED treatment. Most commonly, the cost (119/163, 73.0%) was mentioned, followed by apprehensions regarding its experimental nature (29/163, 17.8%). A smaller fraction of respondents highlighted patient's concerns about its invasive nature (7/163, 4.3%), past negative experiences (4/163, 2.5%), or other unspecified factors (4/163, 2.5%) as factors leading patients to decline RT options for treating ED.

Regarding the respondent's confidence in the role of RT in ED treatment, two-thirds (106/163, 65.0%) believed in its effectiveness in treating ED. About 17.8% (29/163) were uncertain about its efficacy but chose to integrate it into their clinical practice to enhance their knowledge. However, 12.2% (20/163) did not believe in its efficacy, often citing patient-driven decisions. The remaining 5.0% (8/163) selected it for other unspecified reasons.

Just 44.2% (72/163) of the participants had received formal training for practicing RT in ED. Meanwhile, the remaining individuals either relied on instruction manuals provided by industrial companies (76/163, 46.6%), learned from colleagues or believed that certain RT modalities did not necessitate formal training (15/163, 9.2%).

Most respondents (148/163, 90.8%) expressed optimism about the safety of RT modalities, considering them either safe or very safe. A smaller portion of respondents either expressed concerns about significant side effects (7/163, 4.3%) or were uncertain about its long-term safety (8/163, 4.9%).

10. Guidelines and recommendations for RT in ED treatment

Numerous clinical trials have investigated a variety of RT regimens for ED treatment. However, due to the lack of regulatory approval, there was significant heterogeneity in these trials in terms of methodology, patient populations, treatments, and clinical outcomes [26]. This variability or diversity in studies can indeed pose challenges to formulating clear, evidence-based guidelines and recommendations.

To date, although there is some evidence to support the use of LISWT, the majority of professional societies' guidelines advise against using SC or PRP therapies outside of clinical trials [27]. The recommendations provided by major urology and sexual medicine societies are summarized in Table 3 [1,28-33].

The Fig. 9 summarizes the current research on RT for ED, highlighting its strengths, weaknesses, opportunities, and threats.

11. Expert recommendations of the Global Andrology Forum

Currently, the existing guidelines from relevant societies lack precise instructions for practitioners regarding RT in ED, primarily due to limited research and its classification as low evidence. Therefore, the GAF has created statements of expert consensus and recommendations regarding different aspects of RT in ED, aiming to guide the practitioners on the most debated points in this field. Statements of recommendation were proposed based on the survey results, professional society guidelines and recommendations, available evidence in the literature, and experts' clinical practice.

The statements considered all the important aspects of RT in ED treatment and were subsequently sent to the experts to reach a consensus using the Delphi method, as shown in Fig. 10. The statements were sub-

Table 3. Societies guidelines and recommendations for regenerative therapy (RT) in erectile dysfunction (ED) treatments

Society	Recommendation
American Urology Association (AUA) Guidelines, 2018 [28]	Penile LISWT and intracavernosal SCs should be considered investigational (Conditional recommendation) (Grade C evidence level). Intracavernosal PRP therapy is regarded as an experimental expert opinion.
Sexual Medicine Society of North America (SMSNA) Position Statement, 2021 [29]	There is an absence of robust clinical data supporting the efficacy of RT for the treatment of ED. However, technologies such as LISWT have established relative safety.
The Asia-Pacific Society for Sexual Medicine Position Statement, 2021 [30]	Supports the use of LISWT to improve penile erectile hemodynamics based on convincing basic science evidence (Level 2, Grade B). Clinical evidence on LIPUS is accruing and should have similar biological effects as LISWT. Since ED is often multifactorial in pathogenesis, further studies across various animal models of ED should be conducted. Correct patient selection is important for treatment success; younger patients with mild-moderate ED, minimal cardiovascular comorbidities, and absence of diabetes or cavernous nerve injury are likely to have recovery and spontaneous erection (Level 2, Grade B). Adjunctive measures like combination with PDE5i may enhance LISWT effects and erectile function recovery (Level 2, Grade C). LISWT improves erectile function scores and penile hemodynamic parameters in men with vasculogenic ED (Level 1, Grade B). However, the long-term outcome is uncertain. Evidence suggests benefits for up to 12 months after treatment (Level 2, Grade B). LISWT and LIPUS for treatment of ED should be restricted to men with mild-moderate vasculogenic ED, either responder or non-responders to PDE5i, and be performed in highly specialized centers (Level 2, Grade B). LISWT is a safe and well-tolerated procedure without clinically significant adverse events (Level 1, Grade A).
Canadian Urological Association (CUA) Guidelines, 2021 [31]	Conditionally recommends against LISWT as a treatment for ED patients. Additional studies are required.
The Italian Society of Andrology and Sexual Medicine (SIAMS) Guidelines, 2023 [32]	Suggests the use of LISWT in patients with mild vasculogenic ED not responding to PDE5i (weak recommendation, very low-quality evidence). No clear recommendations on the use of SC and PRP therapies can be provided given the limited data.
European Association of Urology (EAU) Guidelines, 2024 [1]	LISWT may be offered to patients with vasculogenic ED, although they should be fully counseled before treatment. More studies are needed to define treatment protocols and the effectiveness of LISWT for ED. Despite some studies showing successful outcomes with PRP and SC therapies for ED, further studies are needed to achieve adequate evidence-based and clinically reliable recommendation grades [32].
European Society for Sexual Medicine (ESSM) position statements, 2024 [33]	CT for ED should be considered a treatment under investigation and not offered outside of clinical trials (Good Clinical Practice Statement). Patients should be informed regarding the limited evidence on the efficacy and safety of CT for ED (Level 3, Grade C).

LISWT: low-intensity shock wave therapy, PRP: platelet-rich plasma, SCs: stem cells, CT: cell therapy, LIPUS: low-intensity pulsed ultrasound shock wave therapy.

sequently sent to 56 experts in male sexual dysfunction (MSD) and RT, all of whom were members of the GAF, of whom 2/3 were urologists and 1/3 were andrologists. More than 2/3 of the participating experts had >10 years of experience in treating MSDs. The recommendations of GAF experts are summarized in Table 4.

DISCUSSION

This is the first global survey aimed at identifying the global practices and attitudes of sexual medicine practitioners toward the use of RT for ED treatment.

All the respondents to this survey were actively involved in the management of ED but the majority of respondents reported that ED represented less than 25% of their clinical work. Several studies have reported that the percentage of ED patients in outpatient clinics ranges from 21.1% to 81.5% [34-36]. A study by [37] grouped the patients who declared ED as their primary or secondary symptom as 'very early treatment seekers' (VETS) and 'early treatment seekers' (ETS) respectively. The patients who hid their ED until

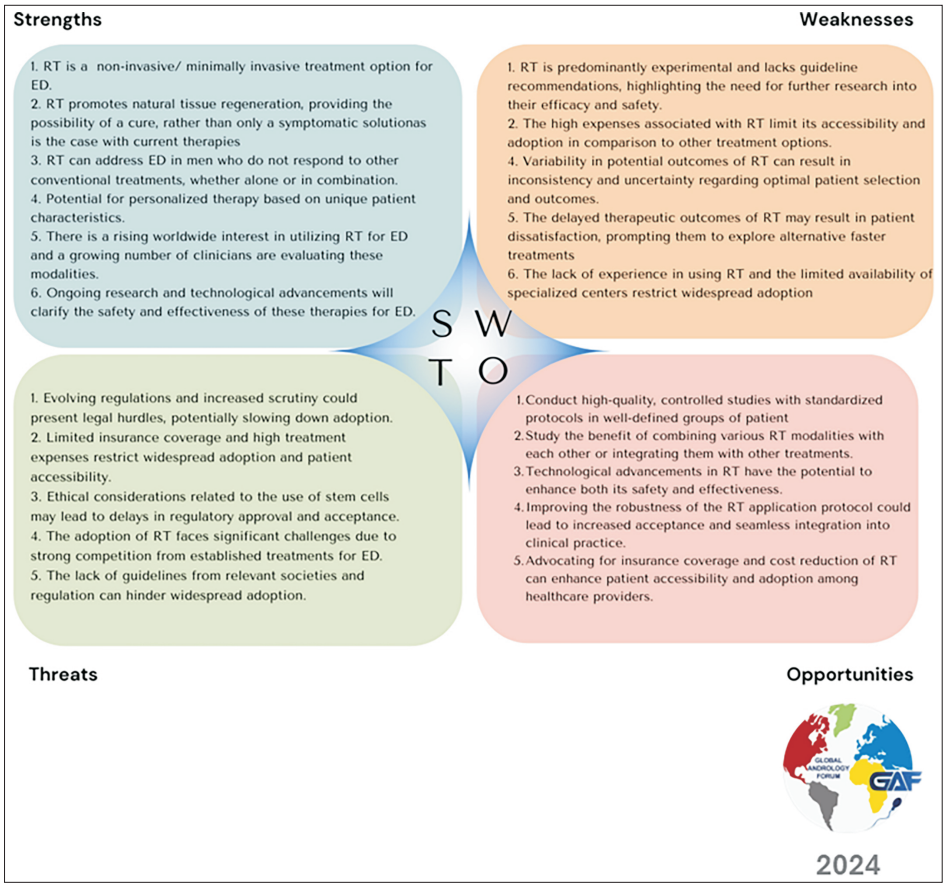

Fig. 9. Strengths, Weaknesses, Opportunities, and Threats (SWOT) of the regenerative therapy (RT) in erectile dysfunction (ED).

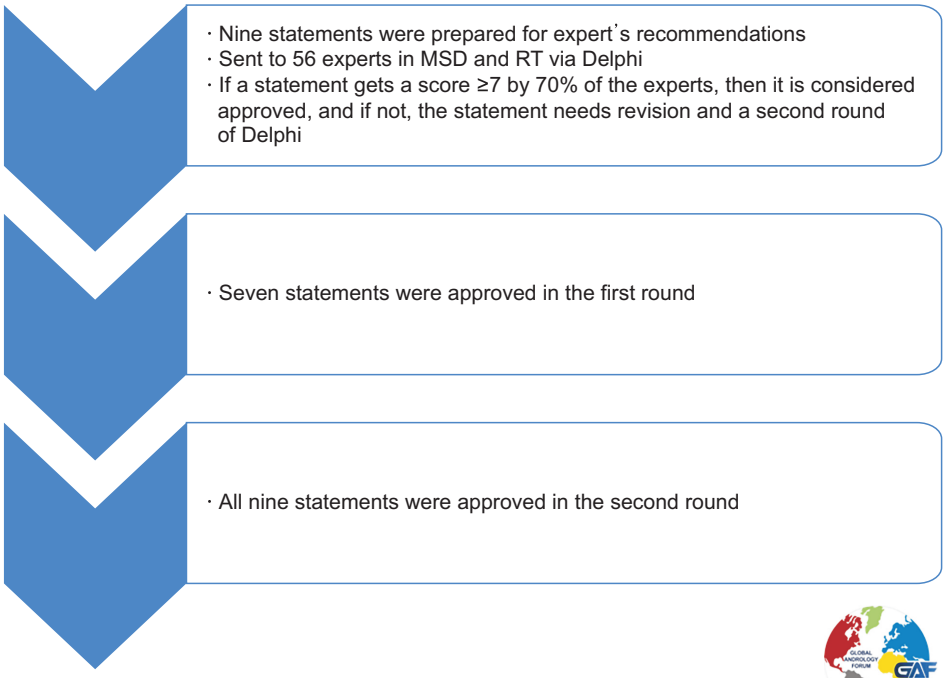

Fig. 10. Global Andrology Forum's pathway in assessing the statements created regarding the use of regenerative therapy (RT) in erectile dysfunction using the Delphi approach. MSD: male sexual dysfunction.

Table 4. Global Andrology Forum experts' recommendations about regenerative therapy (RT) in erectile dysfunction (ED)

Global Andrology Forum Expert's recommendations about RT for the treatment of ED
1. RT should not be considered the standard of care for treating ED and should be offered to patients with informed consent according to its current limitations.
2. RT appears to be more effective in patients with vasculogenic ED compared to other types of ED.
3. RT appears to be most effective in men with mild-to-moderate ED.
4. Young and middle-aged males, appear to derive the most benefits from RT for the treatment of ED.
5. RT can be used in combination with other ED treatment modalities or as a solo treatment in males for whom standard treatments have failed, or who wish to try and regain natural erections.
6. A limited proportion of patients treated with RT for ED report satisfaction with treatment.
7. Current evidence is unclear as to the duration of significant improvement in erectile function after RT.
8. Although RT is associated with high short-term safety and minimum adverse effects, the long-term safety of RT is still unidentified.
9. Currently, there is more evidence to support the efficacy of low-intensity shock wave therapy compared to other modalities of RT.

directly questioned and the patients whose ED was diagnosed with an IIEF-5 questionnaire were grouped as 'late treatment seekers' (LTS) and 'very late treatment seekers' (VLTS) respectively. The rate of severe ED was significantly higher in the VETS group, whereas the rate of mild ED was significantly higher in the VLTS group. These authors concluded that most of the patients would not seek help for their ED until the clinician directly or indirectly questioned them.

The causes of ED are multifactorial and include both psychogenic factors and organic factors. In this survey, most participants reported that multiple factors were the primary cause of ED, with isolated vasculogenic factors being the second most common. Although previously believed to be predominantly psychogenic in origin, ED in young men is now acknowledged to involve several organic risk factors. Vasculogenic and structural alterations, such as focal arterial occlusive disease, subclinical endothelial dysfunction, and Peyronie's disease (PD), can obstruct arterial flow or induce veno-occlusive dysfunction, thus contributing to ED [38]. Desvaux et al [39] (2004) reported a mix of organic and psychogenic ED in 67.1% of men with ED constituting a vicious cycle. Additionally, Huang et al [40] (2012) reported that 73.1% of patients with psychogenic ED could have endothelial dysfunction, confirming the high rate of ED with multiple etiologies or somehow erroneous diagnosis.

In the current survey, 43.0% of the participants utilized a combination of medical history, examination, and hormonal testing in the diagnostic work-up of ED etiology, and 44.0% of them also used penile Doppler ultrasound. This is following the EAU Guidelines of Sexual and Reproductive Health established in 2023 [1]. The objectives of the assessment are to conduct a thorough evaluation of erectile function, utilizing RigiScan to monitor Nocturnal Penile Tumescence and Rigidity (NPTR), which serves as a valuable diagnostic instrument for psychogenic ED. Meanwhile, penile Doppler ultrasound facilitates an initial assessment of the functional anatomy and offers real-time evaluation of the dynamic alterations essential to differentiating between the vascular and nonvascular causes of ED and therefore determining appropriate management of the patient [41,42].

The current survey revealed that the majority of the respondents (66.6%) are not using RT for ED in their practice. However, approximately one-third of physicians who treat patients with ED worldwide employ RT as a treatment modality, with more than half (54.6%) preferring LISWT. Our results surpass those of Fode et al [43] (2017) whose survey of 2017, found that only 14.1% of participants had utilized LISWT. This result suggests that RT has gained in popularity in recent years.

Established treatments for ED include oral medications, intracavernosal injections, vacuum erectile devices, and penile prostheses [8]. However, these conventional treatments cannot reverse the pathophysiological issues of ED. This point might be the cause of observing that young practitioners, in the current survey, were more interested in the novel lines of ED treatment, such as RT, than older practitioners.

According to the EAU Guidelines, in 2024, most of the studies have suggested that LISWT can significantly increase IIEF and EHS scores in patients with mild vasculogenic ED, although this improvement appears modest, and the rates of patients reporting a

satisfactory improvement range between 40%–80% [1]. A recent RCT reported that 3 months after treatment with LISWT, 79% of the treatment group of patients with moderate ED attained a minimal clinically important difference (MCID) in IIEF-EF score *vs.* 0% in the sham group [44]. Likewise, previous study [20] pointed out that penile LISWT may improve erectile function, to a modest extent, in patients who do not respond to PDE5i, making it an alternative for vascular ED patients that reject more invasive therapies. Combination treatment with LISWT and once-daily tadalafil led to a 20% higher rate of patients achieving MCID three months after treatment compared to LISWT alone [45]. However, more prospective RCTs with longer follow-ups are required to provide clinicians with more confidence regarding the effectiveness of LISWT for ED. This point has been emphasized by many society guidelines as well as the GAF expert opinion.

After LISWT, the respondent's second choice was intracavernosal PRP (24.5%), followed by a combination of both therapies (14.7%), and a minority reported using intracavernosal SCs (3.68%). In this context, intracavernosal PRP has been investigated lately in several trials [13,46]. Available findings suggest favorable outcomes of PRP injections in terms of IIEF-5 and Sexual Encounter Profile (SEP) scores and peak systolic velocity on penile-duplex ultrasound. In a prospective interventional study, 41% of men with diabetes non-responders to oral PDE5i showed improved EHS response with daily oral tadalafil 5 mg plus on-demand vardenafil 20 mg tablets and 3 doses of intracavernosal PRP [47]. However, most of the current studies are limited by the low number of patients including the lack of placebo comparison and heterogeneity in terms of the modality of PRP preparation. Besides, the concentration of platelets and growth factors vary according to the different preparation protocols. Therefore, all society guidelines as well as our expert recommendations state that intracavernosal PRP for the treatment of ED should be used only in a clinical trial setting.

The survey presented limited data on the use of SC therapy as only 3.68% of the participants were using it, probably due to its unavailability, high cost, and possible need for certain regulations. A recently published systemic review of 18 studies involving 373 patients with organic ED suggested that SC therapy shows promise as an innovative and safe treatment for organic ED. However, the lack of standardized protocols and controlled groups in many studies hampers the ability to evaluate and compare these studies [48]. The recent European Society for Sexual Medicine guidelines stated that SC therapy for ED should be considered a treatment under investigation and not offered outside of approved clinical trials and the patients should be informed regarding the limited evidence on its efficacy and safety [33].

The current survey revealed three major factors limiting the utilization of RT in the management of ED including; lack of experience, non-coverage by insurance, and non-availability. Based on these findings, respondents indicated a willingness to use RT in the future if subsequent studies demonstrated increased efficacy, RT was endorsed by professional guidelines, and adequate training in the use of RT was available. The results of the current survey strongly highlight the need for further studies and RCTs to validate these initial promising findings and qualify RT for inclusion in international guidelines. Additionally, training and coverage by insurance could also assist in the broader use of RT in ED treatment.

This study has some limitations. Some of the responses of the survey participants were based on subjective criteria rather than objective measures, whether in the initial evaluation of ED patients (like history, examination and hormonal testing rather than basline penile Doppler ultrasound) or for the evaluation of the efficacy of RT in ED (like the use of overall patient satisfaction rather than IEEF or Doppler ultrasound). Also, the limited number respondents who are using penile SCs therapy, most propably, due to its high cost, the need for institutional approval, or the unavailability of this modality of RT.

CONCLUSIONS

This is the first global survey aimed at identifying the clinical practice patterns and attitudes of sexual medicine practitioners toward the use of RT for ED treatment. The current results revealed that one-third of respondents utilized different modalities of RT, and LISWT was the most commonly used, followed by PRP and a combination of both. Most of these techniques are used for non-responders or patients with adverse effects in combination with other ED treatment modalities, and they are commonly used with PDE5i.

The majority of respondents indicated that the best

responses to RT were seen in middle-aged patients and those with mild-to-moderate ED severity, and almost all of them confirmed the overall safety of RT. Moreover, the respondents were diverse and uncertain about the currently available evidence and recommendations for the best clinical practice and protocols for different RT modalities.

GAF experts' recommendations for RT in ED provide practitioners with clearer guidance in areas where clinical guidelines are lacking. However, robust conclusions can only be made based on future randomized clinical trials.

Overall, RT has the potential for treating ED in the future, but it is important to acknowledge the limitations and ongoing research efforts before it becomes a basic tool in the armamentarium of ED treatment.

Conflict of Interest

The authors have nothing to disclose.

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Author Contribution

Conceptualization: MAH, GMP. Statistical analysis: AH. Supervision: AA, R Shah. Writing – original draft: MAH, GMP, TM, AR, TH, R Shah, EC, AH, MA, TT, OR, CG, PB, LB, YJ, PK, RV, BH, AVH, WA, SG, CRC, DK, AF, NG, AZ, CCKH, MSAM, MM, GIR, AR, GMB, EK, HJP, SC, R Saleh, OR, DSK, GC, R Smith, MR, AK, QN, KB, AES, CT, HMA, HA, AA, Writing – review & editing: all authors. All authors have read and agreed with the findings reported in this manuscript.

Supplementary Materials

Supplementary materials can be found via https://doi.org/10.5534/wjmh.240086.

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