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The Potential of Platelet Rich Plasma Injections and Stem Cell Therapy for Penile Rejuvenation

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Abstract

Penile concerns include erectile dysfunction (ED) and Peyronie disease (PD). Restorative therapies including Stem Cell Therapy (SCT) and Platelet Rich Plasma (PRP) injections are proposed to treat these concerns. SCT encompasses the harvesting and injection of mesenchymal stem cells or stromal vascular fractions from various tissue sources. PRP is derived autologously from a patient's plasma and is then injected into the penile tissue. These therapies repair damaged penile tissue and promote both new cellular and vascular growth, as demonstrated in basic science studies. Human trials on SCT and PRP for both ED and PD and have yielded promising results with few side effects. While encouraging, small cohort size and lack of blinding or placebo control limit these studies' external validity. Recently, the first double-blinded randomized controlled trial on PRP for ED was published, providing significant evidence of efficacy. With the rapid commercial availability of SCT and PRP for ED and PD, it is imperative to perform more randomized and placebo-controlled trials with standardized procedures and preparations to evaluate efficacy and safety. This narrative review will summarize the available literature on these penile restorative therapies to date.

Introduction

Disorders of penile appearance and function include insufficient erections and abnormal penile curvature. These conditions often carry a heavy toll in the psychosocial, functional, and intimacy domains of affected men's lives [1,2]. Etiologies are commonly multifactorial and include continued atrophy due to diabetes mellitus as well as neurovascular injuries after prostatectomy among many other causes. The damage to penile functioning can

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Author Contribution Statement:

JI was responsible for writing the protocol and report, conducting the search, screening potentially eligible studies, extracting and analyzing data, interpreting results, updating reference lists and creating 'Summary of findings' tables. SL was responsible for designing the review protocol and screening potentially eligible studies. He contributed to writing the report, providing feedback, extracting and analyzing data, interpreting results and creating 'Summary of findings' tables. IVE contributed to writing the report, screening potentially eligible studies, extracting and analysing data, and interpreting results. TM provided feedback on the report. RR helped design the review protocol, provided overall guidance, and supplied feedback on the report.

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be irreversible as vascular and neurological changes occur. Globally, disorders of penile function and curvature are insufficiently treated with traditional therapeutic modalities that do not reverse the underlying pathology.

Stem Cell Therapy (SCT) and Platelet Rich Plasma (PRP) therapy are potential restorative therapies for a host of urological issues ranging from Erectile Dysfunction (ED) and Peyronie Disease (PD) to hypogonadism [3]. SCT encompasses the injection of mesenchymal stem cells (MSCs) or stromal vascular fraction (SVF) from various tissue sources, including adipose tissue and bone marrow, into the penile cavernosa [4]. On the other hand, PRP is created from a patient's own blood. The blood is collected and centrifuged with a separator gel to create a product that contains more than four times the number of platelets as normal plasma; this product is then injected into the site to stimulate healing [5]. Both SCT and PRP may induce repair of damaged tissue and reverse pathology.

SCT and PRP are widely available treatments that are utilized globally for penile rejuvenation by both urologists and non-urologists alike [6]. However, the urological clinical utility of these restorative therapies is still not well understood due to a dearth of rigorous studies. The purpose of this narrative review is to review the evidence surrounding SCT and PRP use for penile rejuvenation in ED and PD.

Erectile Dysfunction and SCT/PRP

Erectile dysfunction (ED) is defined as the inability for a man to obtain and maintain an erect penis for satisfactory sexual intercourse [7]. ED is common, with a prevalence reaching 50% in men aged 40–70 [8]. Furthermore, ED is a common complication of cancer surgeries, including radical prostatectomy for prostate cancer and radical cystectomy for bladder cancer [9]. Additionally, as the global population ages, approximately 322 million men are expected to be diagnosed with ED by 2025, doubling the prevalence of the condition in 1995 [10]. Accordingly, novel therapeutics are of utmost importance in alleviating increasing disease morbidity.

In recent years, SCT has garnered increasing interest as a potential ED treatment. SCT may directly repair and replace the damaged corpus cavernosal nerve and restore damage mediated by trauma, tobacco, or disease processes like diabetes, which harm the nervous system [11]. Repair occurs when stem cells differentiate into other cells including neuronal cells, smooth muscle cells, and endothelial cells [12]. Additionally, paracrine signaling may recruit other cells to aid in the repair of damaged penile tissue in ED. In this process, cell-repair cytokines release and stimulate endogenous repair systems. This mechanism enables stem cells that do not directly interact with the target to still exert healing effects [13]. The paracrine effect utilizes anti-apoptotic and pro-angiogenic molecules to stimulate nervous and vascular tissue repair, demonstrating that direct stem cell incorporation is not needed for therapy to be successful [13].

Several human studies investigating SCT for ED due to various etiologies have been conducted. The small cohort sizes of these studies and their non-blinded/non-controlled

nature limit clinical applicability. Additionally, these trials were all early stage, in phases I and II [4, 14–16].

ED is a common complication of diabetes mellitus (DM), and several studies of SCT for DM induced ED were conducted. Bahk et al. studied 10 diabetic patients, with seven receiving umbilical cord derived MSCs (UC-MSCs). These seven lacked morning erections or erections during sexual activity before treatment. After two months of treatment, 6 of the 7 UC-MSCs receiving patients had morning erections. With the administration of Phosphodiesterase 5 inhibitors (PDE5i), only 2 of the 7 achieved sufficient erections for intercourse [16]. A Jordanian phase 1 single arm clinical trial investigated bone marrow derived MSCs (BM- MSCs). All 4 diabetic patients had low pain scores to injection, and none had serious adverse effects. Of the 4 patients, 3 increased their International Index of Erectile Function-15 (IIEF-15) scores and all had increases in the erectile function and erectile hardness domains [17]. The benefit of SCT to DM patients with ED is of uncertain value, and further standardized study with larger cohorts and placebo control are needed.

Radical prostatectomy (RP) is a common surgery for addressing prostate cancer. ED is a frequent surgical side effect, and SCT has been studied for treating this. Yiou et al. conducted a clinical pilot trial studying intra-cavernosal injection of autologous bone marrow mononucleated cells (BM-MNCs). In 12 ED post-RP patients treated with BM-MNCs, significant improvement occurred in multiple domains of the International Index of Erectile Function (IIEF) and Erection Hardness Scale (EHS). No serious adverse events were noted, and clinical benefits were sustained after one year [4,18]. Similarly, Haahr et al. examined adipose-derived regenerative cells (ADRCs) for patients with ED following Radical Prostatectomy (RP) in an open label phase 1 clinical trial. The study included 17 patients, and 11 continent men had significant improvements in IIEF-5 scores while 6 incontinent men did not have improvements. 8 participants recovered erectile function with capacity to have intercourse. No serious adverse effects were reported besides minor transient liposuction harvesting and injection related discomfort [19]. The lack of serious adverse effects in these smaller scale studies encourage larger scale exploration, and the aspect of continence dependent improvement is interesting and may aid in individualized prognosis of treatment utility.

SCT has also been studied in a more general ED population. At a private clinic, Levy et al. conducted a study on SCT in ED using Placental Matrix Mesenchymal Stem Cells (PM- MSCs) derived from the chorionic placenta in 8 patients. Patients selected could not tolerate oral therapy and had all been using injectable therapy prior, which may indicate higher ED morbidity. The 8 study patients received trimix injections prior to the study. Between the six- week and three-month follow ups, peak systolic velocity (PSV) increased significantly. Three of the patients were able to achieve erection without the use of medications. No patients experienced adverse events, although three had some irritation at the injection site [15]. Limitations include small original sample size (8) and smaller sample size at 6 month follow up (5). To investigate complementary factors, Protogerou et al. studied the efficacy of Adipose Derived Mesenchymal Stem Cells (ADMSCs) and platelet lysate together, compared to platelet lysate alone in a pilot study of 8 patients with ED. Patients enrolled had organic ED due to DM, hypertension, hypercholesterolemia, or

Peyronie disease. IIEF-5 scores improved in all patients by the sixth month. No side effects were observed [20]. The small sample limits applicability of the study, but the similar results and improvements in each group are interesting for future study. In 2020, Ory et al. published the first post hoc metanalysis to investigate SCT impact on erectile function using randomized, placebo-controlled data [21]. Patients with ischemic cardiomyopathy were recruited for trans-endocardial SCT injection through cardiac catheterization. Overall, there were no significant increases in IIEF-15 scores; however, by 12 months there were significant IIEF-15 increases in men receiving higher cell counts or autologously sourced cells. While these results are promising, the wide ranges of tissue origin, protocols, and routes of SCT administration make this data hard to decipher when combined with the low cohort sizes, encouraging future studies to expand on these.

PRP utilizes the patient's own blood to create a concentrated product rich in growth factors and cytokines that are normally stored within platelets and plasma. During normal wound healing, biologically active molecules are released from platelets. The delivery of concentrated and regenerative bioactive molecules to healing sites explains the rationale for using PRP. Once administered, the growth factors and cytokines stored in PRP interact with the surrounding cells, the intracellular matrix, and mediators at the site of injection to recruit the body's natural healing capacity. Importantly, appropriate activation of PRP prior to administration may be crucial to this process. PRP is divided into two categories: activated PRP (AA-PRP) and non-activated PRP (A-PRP). AA-PRP is produced by introducing an exogenous activator such as calcium and is thought to contain higher concentrations of growth factors and cytokines [22]. Some of these growth factors include vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), insulin-like growth factor (IGF), and fibroblast growth factor (FGF) [23]. Preclinical and clinical trials demonstrate that these molecules improve erectile function [24]. The mechanism of this is unclear although it may be related to growth factors stimulating repair of cavernosal nerve as well as enhanced angiogenesis, ameliorating both neuronal and vasculogenic ED etiologies.

Early work by Epifanova et al. focused on the mechanisms of PRP [23]. Subsequently, they conducted a randomized clinical study assessing the efficacy of various PRP modalities in ED. Patients were randomly divided into three groups. The first group consisted of 30 patients who received injections of PRP activated by a 10% CaCl2 solution, the second group comprised 30 patients who received injections identical to the first group with the addition of PDE5I injections, and the final group contained 15 patients who received inactivated PRP. There were statistically significant improvements in PSV and IIEF-5 scores after PRP administration [23,25]. The lack of both a true placebo group and long-term results limit the impact of this study. Furthermore, Alkhayal and Lourdes administered intra-cavernosal PRP injections to men with ED. In total, 267 patients with organic ED received injections, with full data collected on 61 patients. Exact procedures followed are unclear, and the authors note that they followed an established protocol from the American Cellular Medicine Association. Patients had significant improvements in IIEF-5, and 48 patients (78%) achieved successful intercourse. No adverse effects were reported in any patient in this prospective observational trial [26]. Missing information on inclusion criteria, as well as the lack of a placebo group or blinding all limit the influence of this study.

In a pointed study, Tas et al. investigated the effectiveness of autologous PRP application in treating ED in patients with metabolic syndrome. They studied 31 patients with ED, as qualified by IIEF-EF. Patients showed a significant increase in the mean IIEF-EF scores compared to baseline in the first, third, and sixth month after procedure [27]. Despite this, the median value remained within the mild-moderate classification, indicating minimal clinical improvement. The lack of placebo group and small cohort size encourage more large and blinded trials before PRP can be validated as an ED treatment modality. Additionally, one patient developed a fibrotic plaque, which may be a concern for injections. No other side effects were reported. Matz et al. focused on PRP safety while using it to treat both ED and PD. The 4 ED patients showed no decrease in IIEF-5 evaluations, and the measure increased on average by 4.14 points in the mixed cohort of ED and PD patients. Four minor adverse events were reported amongst 17 total treated patients with various urological conditions, including mild penile bruising [5]. This study was notable for attempting a new formulation of PRP while detailing the preparation process to allow replication. Limitations include lack of a control group and small sample size, encouraging further study.

Recently, the first randomized controlled trial (RCT) to evaluate PRP for ED was published [28]. This study followed a double blinded placebo-controlled design, with two separate groups of 30 patients comprising treatment and control groups. All patients were men with mild to moderate ED who received two intra-cavernosal injections one month apart. The study utilized Minimal Clinically Important Difference (MCID) in the IIEF-EF scale to measure outcomes at time points of 1 month, 3 months, and 6 months. They found that 76% of the PRP patients achieved MCID at 1 month vs. just 25% of the control group ($p < 0.001$). Furthermore, although baseline IIEF-EF questionnaires and Sexual Encounter Profile (SEP) diaries did not differ, PRP injections led to statistically significant improvements in both parameters at each follow up point compared to placebo [28]. This study was much needed in validating PRP efficacy and safety clinically. Its status as the first RCT on PRP for ED combined with the statistically significant clinical improvements and complete lack of serious adverse effects helps lay the scientific bedrock for PRP as treatment, and the authors should be commended for their pioneering work. Several limitations of the study encourage further investigation. Firstly, the patient population excluded those with more severe ED who represent some of the patients with the greatest need. Furthermore, surgical causes of ED were excluded. Finally, the single center nature of the trial limits the ability to apply the results widely.

Overall, the low rate of serious adverse effects shows that PRP is very safe. It is evident that there is a great deal of heterogeneity among studies with regards to numbers of injections, volumes, activation status, and leukocyte rich/poor determinations of the injectables used. This limits the interpretability and translation of these works. However, the recent RCT contributes evidence-based data for tangible PRP benefits to patients and should be followed up with similar studies, some of which are already underway [29].

Peyronie Disease and SCT/PRP

Peyronie disease (PD) causes abnormal, pathological penile curvature that affects both young and old patients. Named after Francois Gigot de la Peyronie, surgeon to King Louis

XV of France [30], PD is a localized and slowly progressive connective tissue disorder of the tunica albuginea of the penis [31]. PD was previously estimated to affect between 0.3–1% of males [32], but recent reports estimate numbers as high as 3.2% [33]. PD is relatively rare below the age of 30 and is most common in men over 40 [34]. The disorder is emotionally troubling and makes penetrative intercourse difficult [2]. The condition is theorized to stem from localized inflammation in the tunica albuginea, resulting in a hardened, thickened, inelastic collagen plaque. As the plaque develops, penile curvature and shortening result which may be associated with painful erections and ED [35]. For PD diagnosis and management, recent studies highlight the benefits of ultrasound compared to other modalities. These include no radiation, easy detection of calcification and plaques, and familiarity to urologists [36]. Ultimately, detection and effective treatment of PD remain at the crux of urology.

Despite the lack of cure for PD, many treatments have been evaluated throughout the years. These include traction therapy and vacuum devices to encourage scar tissue remodeling [37], anti-inflammatories and colchicine to reduce swelling [38], Potassium amino-benzoate (Potaba) to reduce plaque size (but not curvature) [39], pentoxifylline (TGFb1 inhibition) [40], L-arginine and PDE-5 inhibitors such as tadalafil to counteract fibrosis [41], and both verapamil [42] and interferon alfa-2b for intralesional injections [43].

The only FDA-approved treatment for PD since 2013 involves an intensive series of intralesional injections of collagenase clostridium histolyticum (CCH, brand name Xiaflex) [44]. Xiaflex is recommended for patients with a penile curvature of >30 and <90 degrees. Surgical interventions are employed as well, including penile plication, plaque incision and grafting [45], and penile prosthesis placement in cases of either solitary or simultaneous ED/PD [46,47]. Surgery is not always preferable and may result in penile shortening [45]. The past few years have yielded several new investigational treatments for PD that quickly gained popularity. These are SCT penile injections, extracorporeal shockwave therapy (ESWT), platelet-rich plasma (PRP), and combinations of these modalities [48–50].

Stromal vascular fraction (SVF) comprises stem cells isolated from adipose tissue. SVF has regenerative, anti-inflammatory, immunomodulatory, and scar reducing properties [48]. This makes it uniquely interesting as a treatment PD, a disorder of plaques with excessive fibrin and collagen deposition [51]. The anti-inflammatory properties of SVF may hasten healing and diminish collagen over-deposition. This is supported by literature indicating that inflammatory regulation can prevent scar formation [52]. Similarly, Adipose Derived Stem Cells (ADSCs) have prevented fibrosis and elastosis in the tunica albuginea and corpora cavernosum of rat models [53]. The PD fighting properties of ADSCs also include decreasing expression of tissue inhibitors of metalloproteinases [54]. These combined properties propel SCT to among the forefront of experimental therapies for treatment of PD.

The use of ESWT for PD has appeared to generate beneficial effects including and not necessarily limited to pain relief. However, the mechanism remains uncertain and there are various schools of thought. ESWT may directly damage and remodel the plaque, and it may

also increase local circulation due to the heat of ESWT which promotes inflammation and increased macrophage activity that culminates in plaque destruction and resorption [55].

Pursuing a combination of strategies, Lander et al. carried out a pilot study on safety and subjective outcomes in a small number of PD patients using both autologous SVF isolated from lipoaspirate and penile shock wave therapy. No serious adverse events were reported. Of the eleven PD patients, all of them reported subjective reduction in plaque size and curvature, while seven reported improved erectile function. Scores improved on both Mean Peyronie Disease Questionnaire and Mean Erectile Hardness Grading scores [48]. No placebo group and small sample size limit the study's generalizability. Additionally, the patients selected had no pain associated with their plaques, and since PD pain is a major driver for pursuing treatment, this too may limit the interpretability of the results. Levy et al. injected MSCs derived from placental matrix into 5 patients with PD. In total, 10 plaques were treated, 7 of which completely disappeared by the 3-month follow up. One patient developed priapism and an additional plaque. Beyond this, no significant adverse events were reported. This was among the first studies to use SCT to manage PD in humans, and the positive response warrants further exploration despite the small sample size and lack of a control group [56].

Autologous PRP has been shown to help heal tissues in orthopedic, maxillo-facial, plastic, and reconstructive surgery [57]. The potent mix of platelet growth factors and cytokines may diminish PD plaques and improve penile curvature. Molecules in platelets include PDGF, VEGF, TGF-b, IGF, FGF and others that can lead to vigorous tissue repair by inducing the inflammatory and proliferative phases of wound healing [23]. These molecules regulate cell growth and division and stimulate the production of extracellular matrix in tissue healing. Additionally, the plasma contains proteins such as fibrinogen, vitronectin, and fibronectin that play integral roles in regulating cell-cell interactions and the spatial organization of cells [58]. PRP alone or in conjunction with added stem cell products has been used to treat PD, sometimes in combination with a penile pump [59]. Aside from the growth factors that help spur angiogenesis, PRP is hypothesized to aid in the repair of PD plaques by downstream collagenase action and tissue regeneration (via epithelial cell mitogenesis) [60].

Studies on PRP for PD are few and limited by small cohorts and lack of placebo control. Marcovici published a case report on using PRP in PD combined with daily penile pump use in which the penile angle of curvature significantly improved after two months [59]. While interesting and encouraging, the sample size of one begets further study with larger cohorts.

Combinations of complementary molecules are also of interest in optimizing PRP. Okabe et al. demonstrated experimentally that hyaluronic acid (HA) enhances PRP's regenerative action by acting as a biological scaffold [57]. Virag et al. evaluated a combination of autologous PRP and HA in treating PD, which showed significant improvement in TA deformation and thickening one month after 4 sessions were completed and at last follow up. 28 patients had calcified plaques, and 6 of these experienced decrease in plaque density on ultrasound. These improvements increased with more sessions and were significant after 4 sessions [58]. A few patients had ecchymosis or hematoma, as well as transient hypotension from anesthesia. No serious adverse events were reported. In a separate preparation, Matz

et al. studied the effect of Platelet Rich Fibrin-Matrix (PRFM) injections in treating PD in a cohort of 11 patients. No PD patients reported worsening of IIEF-5 score, and IIEF-5 score increased by 4.14 from baseline in the combined PD/ED cohort. Decreased penile angle curvature was reported by 80% of the PD patients. A few patients experienced mild pain or bruising. No serious adverse events were reported [5]. Standardization and publishing of the composition and dosages of each injection will inform future research in this promising area, as well as increasing cohort sizes and controlling with placebo. Further randomized, double blinded, placebo-controlled crossover studies are already underway [61].

Discussion

SCT and PRP injection therapies continue to grow in popularity among both physicians and patients alike as possible restorative remedies to ubiquitous urological ailments. These encompass disorders of function including ED and PD. Early trials have been conducted on humans with promising efficacy and safety (Table 1), yet the lack of power, standardization, controls, and randomization in these studies necessitates deeper investigation into the true efficacy of these treatments. Although further randomized clinical trials have not yet been completed, there has been a rapid adoption and marketing of these procedures by medical clinics. This is problematic because the evidence is not yet there for widespread adoption as first line treatment.

FDA oversight of human cells, tissues, and cellular and tissue-based products (HCT/P's) is avoidable, should clinics utilize the appropriate exemption as per the Code of Federal Regulations Title 21 part 1271. The "same surgical procedure" exemption applies to solely autologous harvesting and transplantation of HCT/P's in a single procedure, and allows clinics to avoid FDA regulation of these products and therapies [62]. This exemption would not apply if the products were sent to an outside lab or taken elsewhere for processing, or if the patient were to leave after product harvesting and before it was administered.

Despite the limited scope of previous clinical studies on SCT/PRP efficacy, the popularity of these treatments has boomed in the last decade. There is no standardized cost, and the price of PRP/SCT injections can range from $500-$2000 per treatment. Adding SCT to PRP may further increase the cost of therapy, and it may also depend on the location of the facility and expertise of the physician [63]. The AUA Guidelines for Management and Treatment of Erectile Dysfunction consider SCT and PRP as investigational (conditional recommendation; evidence level: grade C) and experimental (expert opinion) respectively [64]. Additionally, the AUA guidelines for PD were last published in 2015 and neglect to mention these therapies, perhaps due to their recent and rapid upswing in popularity [65].

Limitations abound in interpreting contemporary research into restorative therapies for penile function and curvature. Current human studies are very limited in cohort size, with cohorts generally comprising only a handful of patients. With such low patient numbers, it is difficult to interpret many of the positive results reported for patients treated with SCT or PRP. Whether the statistically significant results in these small cohorts are clinically significant remains unknown. Furthermore, these studies have inherent structural issues. Most studies lack a control/placebo arm and long-term follow-up, and there is

also a lack of standardization between dosage, preparation, and treatment regimens for SCT/PRP injections. This calls into question the safety of new formulations and those that do not follow the methods demonstrated largely safe in these trials. Large randomized and standardized controlled trials are necessary before these restorative therapies can be considered safe and effective for therapeutic use.

Conclusion

SCT and PRP injections are investigational restorative therapies that are in clinical use for the treatment of ubiquitous penile issues including ED and PD. Limited data exists in the current literature even though these therapies are commercially available. Results thus far are promising, and more studies with proper controls and follow-up are urgently needed to evaluate the efficacy and safety of these treatments in the urological arena.

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Table 1:

Summary of Studies on SCT/PRP for Disorders of Penile Appearance

Treatment/ Condition	Study/Year	Cohort	Injection type	Primary endpoint	Results	Serious adverse events
SCT for Erectile Dysfunction	Bahk et al. 2010 [16]	10	UC-MSCs	Erectile function	Improved subjective outcomes. 6/7 diabetic treatment patients with morning erections at 2 mo. 2/7 treatment patients able to achieve penetrative sex with PDE5I. No change 3 diabetic controls.	None
	Al Demour et al. 2018 [17]	4	BM-MSCs	Safety and tolerability	4/4 diabetic patients tolerated procedure well. Significant IIEF-15 improvements in 3/4 pts, all 4 significant EHS.	None
	Yiou et al. Phase 1: 2016 Phase II: 2017 [4,18]	12	Autologous BM-MNCs 2×10^9 1×10^9 2×10^8 2×10^7 cells	Tolerance	Significant improvements in IIEF-15 and EHS in post- RP patients. Greater improvements with higher doses.	None
	Haahr et al. 2015 [19]	17	ADRCs	Adverse events	11/17 post-RP patients reported improved erectile function. This was not seen in the incontinent group. 8 participants recovered erections capable of intercourse.	None
	Levy et al. 2015 [15]	8	PM-MSCs	Penile vascular changes	3/8 pts achieved erections at 3 months. PSV overall showed significant improvements.	None
	Protogerou et al 2019 [20]	8	Group 1: ADMSCs and platelet lysate Group 2: Platelet lysate	Efficacy	IIEF-5 scores improved in all pts at 6 mo. No statistically significant difference in scores between groups. Improved penile triplex and morning erections in all patients.	None
	Ory et al. 2020 [21]	Data from multiple trials	Allogeneic BM-MSCs vs. Autologous BM-MSCs	IIEF scores	Significantly better erectile function in men using autologous cell sources (p=0.03) or receiving 200 million cells (p=0.014) at 12 month follow up.	None noted
PRP for Erectile Dysfunction	Epifanova et al. 2017, 2020 [23,25]	75: 30 Group 1 30 Group 2 15 Group 3	Study 1: Qualitative/ quantitative analysis of growth factors/platelets from patients with/ without ED Study 2: Group1- AA- PRP, Group 2- AA PRP +PDE5I Group 3: Inactivated PRP	Efficacy of PRP, through PSV and Resistance index (RI)	Study 1: Significant difference in platelet concentration between groups, more growth factors after freezing/thawing. Study 2: Group 1: increase in PSV (P=0.005), RI (P=0.001), IIEF (P=.046), and SEP (P=0.001). Group 2: PSV (P=0.028), RI (P=.129), IIEF (P=0.046) and SEP (P<0.05). Group 3: IIEF-5 and SEP scores (P<0.05) and PSV and RI (P>0.05)	None
	Alkhayal and Lourdes 2019 [26]	267 Full data on 61	Intracavernosal PRP following American cellular medicine association protocol	Efficacy, measured by IIEF, GAQ, SEP	Mean IIEF improved pre to post treatment (P<.001), 88.5% (54/61) patients report improved GAQ (erection hardness), 78% achieved successful intercourse (SEP).	None
	Tas et al. 2021 [27]	31	Autologous PRP for ED in metabolic syndrome	IIEF-EF	Significant increase in mean IIEF scores compared to baseline	1 patient developed non-

Treatment/ Condition	Study/Year	Cohort	Injection type	Primary endpoint	Results	Serious adverse events
					in 1st, 3rd, and 6th month after procedure (p<0.001)	symptomatic fibrotic plaque. No other effects
	Matz et al. 2018 [5]	4	PRFM	Safety	No decline in post vs pre IIEF-5 evaluations. Only 4 minor adverse events.	None
	Poulios et al. 2021 [28]	60	PRP	MCID in IIEF-EF	22/29 MCID in PRP group vs 7/28 in placebo (p <0.001) at 1 month. 20/29 MCID in PRP group vs. 7/26 placebo (p <0.001) at 6 months. Statistically significant improvement in Sexual Encounter Profile (SEP) diaries and IIEF-EF scores at each follow up in PRP group compared to placebo.	None
SCT for PD	Lander et al. 2016 [48]	11	SVF injections with shock wave treatment	Safety and subjective outcomes	All patients had subjectively better penile curvature and perceived reduction in plaque size. 7/11 report improved erectile function. Mean erectile hardness grading score increased from 2.7 to 3.5 and mean PDQs scores decreased from 15.0 to 8.7.	None
	Levy et al. 2015 [56]	5	MSCs from placental matrix	Plaque reduction, PSV	7/10 treated plaques were completely gone at 3 months. Statistically significant increase in PSV on doppler.	One patient developed priapism and additional plaque
PRP for PD	Marcovici 2019 [59]	1	2 PRP injections 4 weeks apart into maximal penile curvature, and 2x daily penile pump use for 6 weeks	Angle of curvature	After two months angle of curvature significantly reduced.	None noted
	Virag et al. 2017 [58]	90	PRP combined with HA	Penile curvature/ deformation and maximum thickness	Angulation and thickening significantly improved after 4sessions and at last follow-up. Significantly decreased US density of calcified plaques in 6/28 pts after 4 sessions and further improvement with more sessions (p<0.001).	None
	Matz et al. 2018 [5]	11	PRFM injections	IIEF-5 scores and penile angle curvature	IIEF-5 scores increased by 4.14from baseline in combined group of ED and PD patients and decreased penile angle curvature reported by 80% patients.	None

Table Abbreviations:

SCT= Stem Cell Therapy

PRP= Platelet Rich Plasma

ED= Erectile Dysfunction

PD= Peyronie Disease

UC-MSCs= Umbilical Cord derived Mesenchymal Stem Cells

BM- MSCs= Bone Marrow derived Mesenchymal Stem Cells

IIEF=International Index of Erectile Function

IIEF-EF= International Index of Erectile Function- Erectile Function

EHS= Erectile Hardness Score

BM-MNCs= Bone Marrow Mononucleated Cells

ADRCs= Adipose-Derived Regenerative Cells

PM-MSCs= Placental Matrix Mesenchymal Stem Cells

PSV= Peak Systolic Velocity

ADMSCs= Adipose Derived Mesenchymal Stem Cells

AA-PRP= Activated PRP

PDE5I= Phosphodiesterase Type 5 Inhibitors

RI= Resistance Index

SEP= Sexual Encounter Profile

GAQ= Global Assessment Questions

PRFM= Platelet Rich Fibrin-Matrix

MCID= Minimal Clinically Important Difference

SVF= Stromal Vascular Fraction

PDQ= Peyronie Disease Questionnaire

MSCs= Mesenchymal Stem Cells

HA= Hyaluronic Acid

US= Ultrasound