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An updated narrative review on revolutionizing erectile dysfunction treatment: the crucial role of trophic factors in Adipose-Derived stem cell therapy

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Abstract

Erectile dysfunction (ED) is a pervasive condition projected to affect some 322 million men worldwide by 2025, profoundly impairing quality of life and psychosocial well-being. Current therapies—most notably phosphodiesterase-5 inhibitors and mechanical devices—offer only transient, symptomatic relief and do not repair the underlying vascular, smooth muscle, and neural degeneration driving ED, particularly in diabetic and neurogenic subtypes. Emerging non-cellular modalities (e.g. low-intensity pulsed ultrasound or shockwave therapy) likewise lack demonstrated long-term safety and durable efficacy. Adipose-derived stem cell (ADSC) therapy has emerged as a promising regenerative strategy. In preclinical models, ADSCs exert paracrine effects—secreting trophic factors (VEGF, IGF-1, SDF-1, NGF) and exosomal microRNAs—that stimulate angiogenesis, smooth muscle restoration, and nerve regeneration. Innovative delivery platforms (thermosensitive hydrogels, size-controlled spheroids, magnetic guidance) and genetic enhancements (iNOS or PEDF overexpression) further improve cell retention and functional outcomes. Early-phase clinical trials confirm ADSC safety and suggest improvements in International Index of Erectile Function scores, but are limited by small cohorts, heterogeneous protocols, and short follow-up. Critical gaps persist that hinder translation to routine practice: the long-term safety and efficacy of ADSC therapy remain unestablished; retention of transplanted cells in target tissues is inconsistent; methods for cell isolation, processing, dosing, delivery routes, and outcome monitoring are highly variable; and potential adverse effects—immunogenic responses or malignant transformation—have not been fully characterized. Moreover, standardized, mechanism-based biomarkers and regulatory frameworks are lacking. To bridge these gaps, next-generation approaches are under investigation: ADSC-derived exosomes as cell-free therapeutics; genetic or epigenetic modification of ADSCs to boost reparative potency; and combination regimens pairing ADSCs with adjunct modalities such as low-intensity shockwave therapy. Rigorous, well-powered phase II/III trials with standardized protocols, long-term follow-up, and mechanistic endpoints are urgently needed to validate efficacy,

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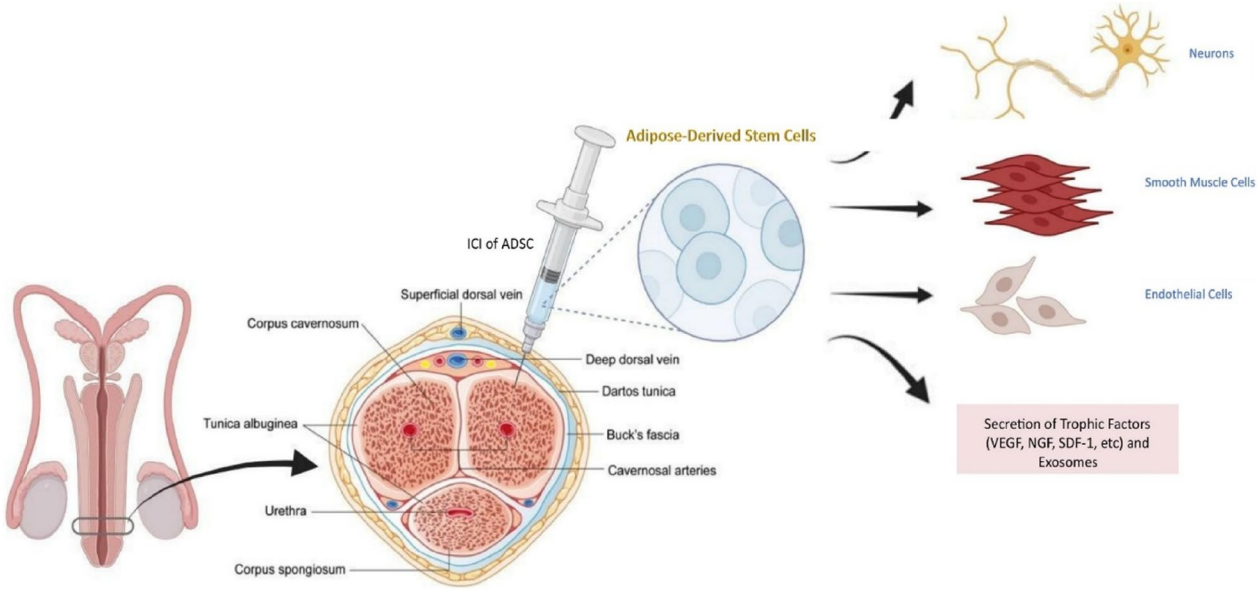
ensure safety, and establish best-practice guidelines. Addressing these unmet needs could shift ED management from palliative symptom relief toward true tissue regeneration and durable cure.

Keywords Adipose-derived stem cells, Trophic factors, Erectile dysfunction

Graphical abstract

Intra-cavernosal injection (ICI) of adipose-derived stem cells (ADSCs) ameliorates erectile dysfunction via multiple synergistic mechanisms. ADSCs differentiate into neurons, smooth muscle cells, and endothelial cells, thereby contributing directly to tissue regeneration. In addition, their paracrine activity results in the secretion of numerous trophic factors and exosomes that stimulate angiogenesis, neurogenesis, and nerve regeneration while concurrently suppressing inflammation. Collectively, these effects culminate in enhanced erectile function



Background: penile structure and function

The penis comprises three erectile columns: two dorsally positioned corpora cavernosa and a single ventrally located corpus spongiosum, the latter enclosing the urethra. Each erectile body is surrounded by a dense fibrous sheath known as the tunica albuginea, while all three are collectively enclosed by Buck's fascia [1, 2] The corpora cavernosa consist of endothelial-lined sinusoidal lacunae interspersed with trabeculae composed of smooth muscle and elastic fibers, enabling substantial engorgement. The tunica albuginea then maintains intracavernosal pressure (ICP) by facilitating veno-occlusion.

In contrast, the corpus spongiosum—distinguished by smaller sinusoidal spaces and a thinner tunica albuginea—expands distally to form the glans penis and serves to maintain urethral patency during erection [3–5]. The tunica albuginea consists of an inner circular layer and an outer longitudinal layer; its biomechanical strength limits cavernosal distension, thereby sustaining ICP through a veno-occlusive mechanism [6, 7].

The initiation of penile erection involves the release of nitric oxide (NO) into the penile vasculature, resulting in vasodilation, increased cavernosal blood flow, and subsequent veno-occlusion. NO is synthesized by isoforms of nitric oxide synthase (NOS), primarily endothelial NOS (eNOS) and neuronal NOS (nNOS). eNOS regulates basal vascular tone, whereas nNOS is responsible for the neurogenic initiation of erection [8, 9].

Once released from non-adrenergic, non-cholinergic nerve terminals and endothelial cells, NO diffuses into corpus cavernosum smooth muscle cells (CCSMCs), where it activates soluble guanylate cyclase (sGC), catalyzing the conversion of guanosine triphosphate (GTP) to cyclic guanosine monophosphate (cGMP). Elevated cGMP levels serve as second messengers that activate cGMP-dependent protein kinase (protein kinase G, PKG). PKG facilitates intracellular calcium reduction by promoting potassium channel opening and inhibiting voltage-gated calcium channels. This sequence leads to smooth muscle relaxation, increased arterial inflow, and penile tumescence [10–14]. The maintenance of erection depends on continuous NO-mediated cGMP synthesis. Phosphodiesterase type 5 (PDE5) subsequently degrades cGMP, initiating detumescence if not pharmacologically inhibited. PDE5 inhibitors—including sildenafil, tadalafil, and vardenafil—act by preventing cGMP hydrolysis,

thereby sustaining its action and promoting prolonged erection [10, 15].

Erectile dysfunction (ED): etiology, prevalence, and impact

Erectile dysfunction (ED) is defined as the persistent inability to achieve or maintain an erection sufficient for satisfactory sexual intercourse for at least three months. The etiology of ED is multifactorial, encompassing vascular, neurological, hormonal, and psychological components. Additional contributors include general health status, obstructive sleep apnea, and mental health disorders [16–20].

Vascular factors are the leading cause of ED and are frequently associated with cardiovascular disease, atherosclerosis, hypertension, hyperlipidemia, low high-density lipoprotein levels, obesity, smoking, diabetes mellitus (DM), and insulin resistance. These conditions induce endothelial dysfunction and impair vasodilation, thereby reducing penile blood flow and compromising filling of the corpora cavernosa [15, 21–24]. Persistent inflammation and oxidative stress—particularly in the context of obesity and diabetes—further exacerbate vascular injury and diminish erectile function [15, 25]. Lifestyle factors such as physical inactivity, obesity, smoking, and excessive alcohol consumption significantly increase the risk of ED by promoting vascular dysfunction, hormonal imbalances, and the development of metabolic syndrome [22].

Neurogenic ED, which accounts for approximately 10–19% of cases, arises from disruption of central or peripheral neural pathways, as observed in spinal cord injury, multiple sclerosis, Parkinson's disease, stroke, and diabetic or other peripheral neuropathies [23, 24].

Hormonal dysregulation—including hypogonadism, hyperprolactinemia, thyroid disorders, and Cushing's syndrome—impairs erectile function through effects on libido, vascular tone, and smooth-muscle responsiveness [23, 26–28]. Structural abnormalities of the penis, such as Peyronie's disease—which involves fibrous plaque formation within the tunica albuginea—can lead to painful, curved erections and hinder maintenance of a functional erection due to both mechanical distortion and associated pain [27]. Traumatic injuries, for example penile fracture (rupture of the tunica albuginea with resultant hematoma and scarring), can damage erectile tissues by reducing blood flow and compromising cavernosal expansion and vascular integrity, often precipitating ED [23].

In the oncological setting, radical prostatectomy and other pelvic surgeries for prostate or colorectal cancer frequently result in ED due to cavernous nerve injury (CNI) sustained during nerve-sparing procedures, with reported post-prostatectomy ED incidence ranging from 20 to 93.9%, reflecting variability in surgical technique and patient factors [29–31]. Similarly, cystectomy and other pelvic operations may inadvertently damage the neurovascular structures essential for erection [32]. Psychological contributors—such as anxiety, depression, stress, relationship difficulties, and performance anxiety—can disrupt both the psychological and physiological processes required for sexual arousal, further exacerbating ED [33, 34]. Finally, numerous medications—including antihypertensives, antidepressants, antipsychotics, antiandrogens, luteinizing hormone-releasing hormone agonists, certain antihistamines, opioids, and illicit substances—are recognized to induce or worsen ED [27, 35].

Erectile dysfunction (ED) is highly prevalent among men aged 40 years and older, with rates that rise sharply with advancing age and the presence of comorbid conditions [36]. Recent estimates suggest that global ED prevalence spans from approximately 3–76.5%, largely reflecting differences in assessment tools (for example, the International Index of Erectile Function versus Massachusetts Male Aging Study questionnaires) and the demographic and clinical characteristics of study populations. Epidemiological projections suggest that by 2025, around 322 million men worldwide will be affected by ED [37, 38]. The incidence of ED increases disproportionately in men with DM, metabolic syndrome, psychiatric disorders, and hypertension [39]. Although ED is not directly fatal, it substantially reduces sexual activity, impairs health-related quality of life, and diminishes work performance. Men with ED exhibit significantly higher rates of workplace absenteeism and presenteeism, translating into notable economic burdens for individuals, employers, and healthcare systems. Beyond somatic effects, ED adversely impacts mental health and emotional well-being, contributing to anxiety, depression, irritability, poor self-image, guilt, insecurity, relationship dissatisfaction, and impaired intimacy [40, 41].

Evolution of ED treatment modalities

Early approaches to ED were empirical, encompassing animal-derived aphrodisiacs, herbal preparations, and rudimentary mechanical aids. Mid-20th-century mechanical solutions—including penile splints, vacuum-constriction devices, and basic penile prostheses—offered only partial symptomatic relief [42, 43]. The late 1990 s introduction of PDE5 inhibitors transformed ED management by targeting vascular dysfunction via the NO–cGMP pathway. However, their efficacy is diminished in diabetes-related ED (DMED), and adverse events—such as headache, flushing, dyspepsia, altered color vision, back pain, priapism, hypotension, dizziness, non-arteritic anterior ischemic optic neuropathy, and rare hearing loss—may limit their use [44–48]. Moreover, emerging non-cellular modalities like low-intensity pulsed ultrasound (LIPUS) have shown promise in preclinical and small-scale clinical studies by enhancing

penile-tissue perfusion [49]. Despite these advances, most interventions remain symptomatic and do not restore native tissue architecture [50, 51]. This therapeutic plateau has driven interest in regenerative strategies—such as stem-cell therapies and tissue engineering—to achieve durable repair of the corpus cavernosum rather than transient functional improvement.

Regenerative approaches: ADSCs as a novel therapy

Stem cells are defined by their unique capacity for both long-term self-renewal and differentiation into multiple specialized cell types, properties collectively referred to as potency and essential for development, homeostasis, and tissue repair [52–54]. Mesenchymal stem cells (MSCs) are a population of non-hematopoietic, plastic-adherent stromal cells originally identified in bone marrow that exhibit multipotent differentiation potential into mesenchymal lineages including bone, cartilage, muscle, tendon, ligament, and adipose tissue [55]. Although MSCs can be isolated from diverse tissues—such as adipose tissue, bone marrow, umbilical cord, and dental pulp—their yield and proliferative capacity vary by source, and extensive in vitro expansion may alter their phenotype and potency [56–58]. Adipose tissue generally yields a higher quantity of MSCs than bone marrow, whereas umbilical cord-derived MSCs exhibit superior proliferative capacity and purity. These distinctions may significantly impact their therapeutic potential, particularly in the treatment of ED. ADSCs are frequently preferred due to their abundant availability and ease of extraction, while bone marrow-derived MSCs (BMSCs) are regarded as the gold standard owing to their extensive characterization in scientific research [59].

Adipose-derived Stem Cells (ADSCs/ASCs), a subset of MSCs, have emerged as one of the most promising therapeutic candidates for ED in preclinical studies. In animal models, these cells have been shown to stimulate angiogenesis, promote the regeneration of smooth muscle tissue, and restore nerve function. This novel approach addresses the condition by targeting the underlying tissue dysfunction rather than merely alleviating symptoms, offering a potentially more durable solution [56, 60–63]. Figure 1 depicts the microenvironmental architecture of adipose tissue.

ADSCs: characteristics and advantages

ADSCs are increasingly important in regenerative medicine because they can be obtained in large numbers through minimally invasive procedures. Compared to BMSCs, which require painful iliac-crest aspiration and carry higher infection risk, ADSCs are harvested by liposuction, resulting in lower morbidity and faster recovery [64–69] (Table 1). Following tumescent or ultrasound-assisted liposuction, adipose tissue undergoes washing, enzymatic digestion with collagenase, and centrifugation to isolate the stromal vascular fraction (SVF). When

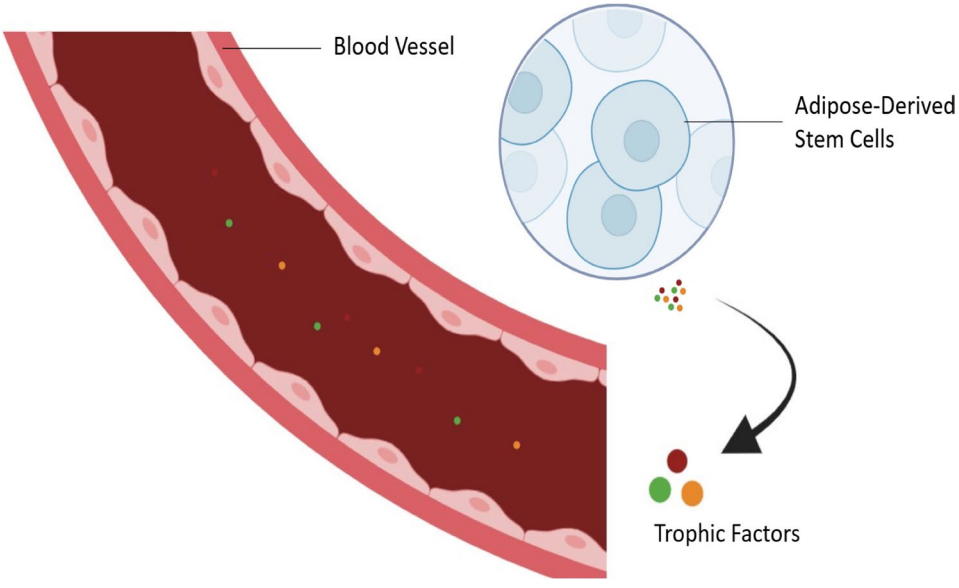


Fig. 1 The adipose tissue microenvironment represents a dynamic, intricate network that underlies both physiological homeostasis and pathological processes, including tissue regeneration and tumor progression. This microenvironment encompasses mature adipocytes as well as a stromal–vascular fraction composed of preadipocytes, adipose-derived mesenchymal stromal cells (ADSCs), immune cells, endothelial cells, and fibroblasts (with other cell types omitted for clarity). Among these components, ADSCs are particularly noteworthy due to their robust regenerative capabilities. These multipotent cells are capable of differentiating into diverse lineages—such as adipocytes, osteoblasts, chondrocytes, and myocytes—underscoring their versatility in regenerative medicine. Furthermore, ADSCs exert their therapeutic effects primarily through paracrine signaling by secreting a broad spectrum of bioactive molecules, including growth factors (indicated by red circles), cytokines (green circles), and extracellular vesicles (orange circles), which collectively facilitate tissue repair, stimulate angiogenesis, and mitigate inflammatory responses

Table 1 Features of ADSCSs vs. BMSCs

Aspect	Adipose-Derived Stem Cells (ADSCs/ASCs)	Bone Marrow-Derived Stem Cells (BMSCs)
Source and Yield	Harvested from adipose tissue; high yield	Harvested from bone marrow; lower yield
Proliferation Rate	High	Moderate
Differentiation Potential	Strong adipogenic differentiation	Strong osteogenic and chondrogenic differentiation
Immunomodulatory Properties	Yes	Yes
Clinical Applications	Cosmetic surgery, wound healing, cardiovascular treatments	Bone and cartilage repair, hematological treatments
Age-Related Changes	Less decline with age	Decline with age
Surface Markers	Typical Markers: High CD49d, low Stro-1	
	Primary Positive Markers: CD90, CD44, CD29, CD105, CD13, CD34, CD73, CD166, CD10, CD49e and CD59.	Positive Markers: CD73, CD90, CD105
	Negative markers: CD31, CD45, CD 14, CD11b, CD34, CD19, CD56, CD146.	Negative Markers: CD45, CD34, CD14, CD11b, CD19, CD79a, HLA-DR
	Additional Positive Markers: HLA-ABC, HLA-DR, SH2, SH3, STRO-1, VEGF2, vWF, ABCG2, SSEA-1 (CD15), PDGFR, alpha- SMA, c-Kit (CD117), $OCT4^+$ and CCR5X (CD195).	
Ease of Harvest	Less invasive (liposuction)	More invasive (bone marrow aspiration)

plated, ADSCs adhere and proliferate rapidly, often reaching clinically relevant quantities within days. The SVF is estimated to contain approximately 0.02–0.06% adipose-derived MSCs, whereas bone marrow mononuclear cells comprise only 0.001–0.01% bone marrow-derived MSCs [70]. These cells maintain high viability, exhibit multipotency and secrete a diverse array of paracrine factors, including vascular endothelial growth factor (VEGF) and hepatocyte growth factor (HGF), as well as immunomodulatory cytokines such as interleukin-6 (IL-6) and transforming growth factor-beta (TGF-β) [71]. ADSCs also demonstrate lower senescence rates and maintain phenotype through more passages than BMSCs, enabling extensive in vitro expansion without loss of function [72, 73].

A comprehensive literature search was conducted across multiple databases, including PubMed/MEDLINE, EMBASE, Web of Science, Scopus, and Google Scholar. The search was restricted to studies published between 2015 and 2025, encompassing both preclinical (animal model) investigations and clinical trials evaluating the therapeutic potential of adipose-derived stem cells (ADSCs) for erectile dysfunction (ED). The inclusion criteria emphasized studies that elucidated mechanistic insights, efficacy, and translational feasibility, thereby providing a robust foundation for assessing ADSC-based interventions. In the subsequent sections, we critically examine how ADSCs contribute to ED improvement, focusing on their paracrine effects, regenerative capacity, and optimization of delivery strategies.

Therapeutic efficacy and mechanistic insights of ADSCs in ED: in vivo and in vitro perspectives

Animal models, particularly rodents such as rats and mice, are indispensable for elucidating the pathophysiology of ED and for preclinical evaluation of novel therapies (e.g., cavernous nerve crush, diabetic or hyperlipidemic models). These models replicate diverse etiologies of ED, including traumatic CNI, metabolic derangements (diabetes, hyperlipidemia), hormonal deprivation (castration), and lifestyle-related insults (smoking, hypertension). While such studies offer controlled, reproducible settings, they must contend with species-specific differences in penile anatomy and concerns regarding animal welfare [74–76].

In most preclinical investigations of ADSC therapy for ED, ADSCs are administered via intracavernosal injection (ICI). The standard ICI protocol entails retracting the prepuce and delivering cells into the lateral corpora cavernosa at a depth of approximately 3–4 mm, followed by manual compression of the dorsal penile vein for one minute to prevent cell efflux. Alternative delivery methods explored include periprostatic implantation (PPI) near the major pelvic ganglion (MPG) or direct injection into cavernous nerves (CNs), strategies intended to enhance local retention and neural tropism [77–79].

Functional recovery is quantitatively assessed by measuring ICP in response to standardized cavernous nerve electrical stimulation (5 mA, 20 Hz, 0.2 ms pulse width for 60 s) and normalizing to mean arterial pressure (MAP). Key endpoints comprise peak ICP, ΔICP, and the ratios of ΔICP/MAP or peak ICP/MAP [80, 81].

Researchers have also investigated various methods to augment the therapeutic efficacy of ADSCs. These modifications include genetic enhancements, combinatorial therapies with agents such as flavonoids, low-intensity shock wave therapy, and oral medications, as well as the incorporation of advanced delivery systems like scaffolds, exosomes, and nanotechnology. Each of these strategies aims to bolster the regenerative potential of ADSCs and improve clinical outcomes [79].

Paracrine activity as a therapeutic mechanism of ADSC therapy: comparative insights into direct differentiation and paracrine-mediated effects

Initial expectations that transplanted ADSCs would engraft and directly replace damaged endothelium or nerves have largely given way to the paracrine paradigm. In ED models, only a minimal fraction of transplanted cells persist long-term within penile tissue, yet significant functional recovery is observed [82]. This finding underscores that MSCs—particularly ADSCs—exert their therapeutic effects primarily through the secretion of bioactive factors and extracellular vesicles. Key secreted molecules include pro-angiogenic cytokines (VEGF, HGF, FGF [Fibroblast Growth Factor], IGF-1 [Insulin-like Growth Factor 1], PDGF [Platelet-Derived Growth Factor]), neurotrophic factors (NGF [Nerve Growth Factor], BDNF [Brain-Derived Neurotrophic Factor]), and anti-apoptotic/anti-fibrotic mediators (TSG-6 [TNF-stimulated gene 6 protein], IL-10) [83]. These factors are well-documented contributors to penile tissue repair: VEGF stimulates cavernous angiogenesis and inhibits apoptosis [84, 85]; HGF exhibits both angiogenic and neurotrophic properties; in diabetic ED models, it restored endothelial and smooth muscle integrity while promoting nerve regeneration [86]; IGF-1 supports smooth muscle integrity and enhances endothelial NO-cGMP signaling [85, 87]; basic FGF (FGF-2) increases smooth muscle mass while upregulating endogenous VEGF expression [85, 88]; NGF plays a critical role in cavernous nerve regeneration, facilitating reflex erectile recovery after nerve injury [89]. Another mechanism involves the neurotrophic effects of ADSCs mediated by pigment epithelium-derived factor (PEDF), which activates the PI3K/Akt pathway [90]. PEDF may reduce high-glucose-induced Toll-like receptor 4 expression and NADPH oxidase (NOX1/4) levels, markers indicative of active immune responses and oxidative stress, respectively. Furthermore, PEDF overexpression in ADSCs enhances cell viability by mitigating oxidative stress and decreasing levels of cleaved caspase-3 protein, thereby restoring the expression of cleaved poly(ADP-ribose) polymerase (PARP) under high-glucose conditions. PEDF also significantly upregulates expression of BDNF, NGF, and nNOS, while downregulating pro-inflammatory cytokines (e.g., tumor necrosis factor-α [TNF-α], IL-6, and IL-1β) [91]. Collectively, ADSC-based therapies harness a trophic milieu that targets the neurovascular and fibrotic pathophysiology underlying ED, making paracrine signaling the dominant mechanism of action.

The secretome of ADSCs has been characterized using multiple analytical techniques. Cytokine antibody arrays and proteomic screening of conditioned media allow for the simultaneous profiling of dozens of secreted factors. For example, a multiplex cytokine array performed on ADSC microtissue lysates in a rat model revealed high expression of VEGF, NGF, and the anti-inflammatory mediator TSG-6 [92]. Enzyme-linked immunosorbent assays (ELISA) have confirmed that cultured ADSCs secrete particularly high levels of VEGF and bFGF [85]. Similarly, transcriptomic analyses (RNA-seq) demonstrate upregulated expression of trophic genes in ADSCs [93]. To investigate how ADSCs improve erectile function in DMED rats, researchers conducted both in vivo and in vitro experiments. Erectile function was assessed in diabetic rats following ADSC administration, while cell co-culture assays were performed to examine the effects of ADSCs on CCSMCs. A cytokine microarray screening identified key molecular targets, and co-immunoprecipitation assays were used to determine the interaction between Neuropilin 1 (NRP1) and solute carrier family 7 member 11 (SLC7A11). The findings revealed that ferroptosis plays a significant role in erectile dysfunction in DMED rats, with ADSC treatment markedly restoring erectile function and improving ferroptosis-related markers. In vitro analyses demonstrated that CCSMCs exposed to ADSCs exhibited enhanced resistance to ferroptotic damage, showing reduced levels of ROS compared to cells treated with the ferroptosis inducer Erastin. Mechanistic investigations confirmed that NRP1 in CCSMCs interacts with SLC7A11, strengthening the glutamate-cysteine countertransport (Xc-) system and enhancing ferroptosis resistance, ultimately contributing to erectile function restoration. These results underscore the therapeutic potential of ADSCs in mitigating oxidative damage and improving vascular function in DMED [94].

Exosome-Mediated paracrine regulation in ADSC therapy

Exosomes, a type of small extracellular vesicle, play a significant role in paracrine regulation by delivering proteins, mRNAs, and microRNAs (miRNAs) that modulate intracellular signaling pathways [95, 96]. ADSC-derived exosomes act as natural gene-delivery vehicles, showing broad therapeutic effects in animal models of ED [68]. miRNAs are a class of endogenous 20–24-nt non-coding RNAs that negatively regulate gene expression post-transcriptionally, [97–99] and they have been implicated in erectile function [100]. For example, miR-93, miR-320, and miR-16 have been proposed as potential biomarkers for early detection of diabetic ED [101]. ADSCs were transfected with a CRISPR lentivirus carrying miR-423-5p or a negative control to assess the impact of miR-423-5p knockdown on endothelial function. ADSCs, miR-423-5p-modified ADSCs (miR-ADSCs), and negative control ADSCs (NC-miR-ADSCs) were co-cultured with human umbilical vein endothelial cells (HUVECs) under normal and high glucose conditions, and eNOS and VEGFa expression, cell proliferation, and apoptosis

were measured. HUVECs cultured with miR-ADSCs exhibited significantly higher eNOS and VEGFa protein levels, increased proliferation, and reduced apoptosis compared to ADSCs and NC-miR-ADSCs, particularly under high glucose conditions. Both ADSC and miR-ADSC groups showed improved erectile function compared to diabetic controls, with miR-ADSCs inducing a more pronounced recovery. Histological analysis confirmed that miR-ADSCs enhanced eNOS and VEGFa expression in penile tissues, reduced apoptosis, and preserved smooth muscle integrity, suggesting that miR-423-5p inhibition in ADSCs enhances their therapeutic efficacy for DMED by simultaneously upregulating the eNOS and VEGFa pathways [102].

An analysis of serum samples from 30 ED patients showed significantly lower levels of hsa-miR-301a-3p compared to healthy controls. Similarly, rats with ED induced by chronic intermittent hypoxia (CIH) exhibited reduced miR-301a-3p levels. To simulate CIH, ccSMCs were exposed to 14–15% oxygen for 5 min in each 60 min cycle over 24 h, then cultured for 24 h and co-cultured with miR-301a-3p-rich exosomes from ADSCs for 48 h. Post-CIH, ccSMCs showed reduced α–smooth muscle actin (α-SMA) levels. However, treatment with miR-301a-3p-enriched exosomes increased α-SMA levels more than standard exosome therapy [68].

Another study using an animal model of CIH addressed ED symptoms by injecting exosomes derived from ADSCs highly expressing circPIP5K1C (EXO-circ) into the rat corpus cavernosum. This mechanism involves promoting E3 ubiquitin-protein ligase (SMURF1) gene expression following miR-153-3p adsorption, facilitating protein-protein interactions and the ubiquitination-mediated destruction of 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3 (PFKFB3). This process inhibited glycolysis in spongiotic smooth muscle cells, ultimately restoring their function [103].

Additionally, let-7i was upregulated in rats with bilateral cavernous nerve crush injury (BCNI), although its specific role in ED remains unclear. Signal transducer and activator of transcription 3 (STAT3) is frequently implicated in both cancer progression and ED. Ge et al. [29] and Zheng et al. [104] proposed that Icariside II, a natural compound from *Herba Epimedii*, enhances proliferation and differentiation of ADSCs into Schwann cells in BCNI Sprague–Dawley rat models. This differentiation was evidenced by increased Schwann cell markers—NGF, neurotrophin-3 (NT-3), S100β, glial fibrillary acidic protein (GFAP), and p75—attributed to inhibition of let-7i and miR-34a. They further proposed that Icariside II acts via the Icariside II/let-7i/STAT3 and Icariside II/miR-34a/STAT3 axes, leading to upregulated STAT3 expression and preservation of erectile function more effectively than either treatment alone.

Xhu et al. [100] prepared ADSC-derived exosomes, as confirmed by CD63 and CD9 expression, which showed dose-dependent proangiogenic effects on human umbilical vein endothelial cells (HUVECs) in vitro, and improved erectile function while reducing corpus cavernosum fibrosis in vivo. These exosomes contained high levels of proangiogenic miRNAs (miR-126, miR-130a, miR-132 by activating the AKT/VEGF and ERK/VEGF signaling pathways) and antifibrotic miRNAs (miR-let-7b, miR-let-7c by inhibiting the TGF-β signaling). In another study, Li et al. [105] evaluated ADSC-Exo and BMSC-Exo ranging 30–100 nm in diameter, both positive for CD63, heat shock protein 70 (HSP70), and CD81. Western blot confirmed absence of calnexin, an ER marker, indicating high exosome purity. Treatment with these exosomes significantly mitigated pathological changes and enhanced erectile function in rats with BCNI.

ADSC and BMSC exosomes hold promise as therapeutic agents for post-radical prostatectomy ED. Western blot analysis from a different study indicated that ADSC-derived exosomes expressed exosomal markers like CD63 and CD81 but lacked calnexin, a protein located in the endoplasmic reticulum found in ADSC lysates [106]. Transmission electron microscopy revealed that ADSC-derived exosomes were cup-shaped or spherical, with a diameter of approximately 100 nm. Further validation demonstrated the presence of exosome markers CD63, CD81, CD31, and CD9 in ADSC-derived exosomes, confirming their identity as exosomes. Corin, an enzyme primarily localized in cardiac tissue, converts pro-atrial natriuretic peptide (pro-ANP) to active ANP, a signaling peptide that regulates blood pressure. These findings elucidate the therapeutic mechanism of ADSC exosomes in ED and underscore the beneficial role of corin [107].

Therapeutic efficiency of ADSCs in different models of ED

Therapeutic efficiency of ADSCs in diabetic ED

Streptozotocin (STZ) is administered intraperitoneally at 65 mg/kg in rats or mice to ablate pancreatic β-cells and induce hyperglycemia [108–110]. Ten weeks after diabetes onset, DMED is confirmed using an Apomorphine test. In this test, following a 10-minute habituation period in a dimly lit observation chamber, apomorphine is injected subcutaneously at 80 μg/kg, and the erectile response is recorded for 30 min. The criteria for penile erection include penile tumescence with a congested glans, repeated pelvic thrusts, full glans engorgement, and grooming of the distal penile shaft; animals not exhibiting these behaviors are classified as having DMED [111].

Chronic hyperglycemia resulting from diabetes leads to excessive production of reactive oxygen species (ROS) and oxidative stress. These conditions activate signaling pathways that reduce NADPH and NO levels, resulting in

endothelial dysfunction, impaired vasodilation, neuronal injury, and smooth muscle impairment—key contributors to DMED [112]. The phenotypic transition of ccSMCs from a contractile to a synthetic state plays a critical role in DMED pathogenesis [113]. Direct injection of mesenchymal stem cell–derived extracellular vesicles (MSC-EVs) into the corpus cavernosum has emerged as a potential therapeutic approach for DMED, with ongoing investigations into its mechanisms of action [112].

Colony formation assays revealed that ADSCs treated with LIPUS form significantly more colonies than untreated controls, indicating enhanced cell proliferation. Cell cycle analysis showed that LIPUS treatment decreases the proportion of cells in the G0/G1 and S phases while increasing the G2-phase population, suggesting that LIPUS facilitates cell cycle progression from S to G2. Furthermore, LIPUS stimulation promoted the secretion of pro-regenerative cytokines such as CXCL12, FGF2, and VEGF from ADSCs. ADSCs. Functionally, LIPUS-activated ADSCs modulate biological processes related to immune responses, inflammation, and angiogenesis. Mechanistically, LIPUS enhances cytokine activity, MAP kinase tyrosine/serine/threonine phosphatase activity, and interleukin-1 receptor binding. KEGG pathway analysis identified the activation of the TNF signaling pathway, NOD-like receptor signaling pathway, MAPK signaling pathway, and cytokine–cytokine receptor interactions, while pathways related to protein digestion, absorption, and lysine degradation were predicted to be downregulated. Collectively, these findings suggest that LIPUS promotes angiogenesis through MAPK pathway activation. The therapeutic efficacy of ADSCs in DMED is further augmented by LIPUS via activation of the Piezo–ERK–VEGF signaling axis. Thus, combining ADSC transplantation with LIPUS may offer a synergistic and promising therapeutic strategy for DMED [49].

The co-transplantation of ADSCs and endothelial progenitor cells (EPCs) into the corpus cavernosum of DMED rat models demonstrated a synergistic improvement in endothelial function, likely mediated by the paracrine release of VEGF and SDF-1 from ADSCs, which enhanced recruitment and proliferation of EPCs within the cavernosum [114].

Some reports indicate that diabetes may negatively impact the mesenchymal stem cell pool, suggesting that ADSCs from individuals with type 2 diabetes mellitus (T2DM) could exhibit reduced regenerative capacity. To address this, researchers directly compared ADSCs from age-matched diabetic Goto–Kakizaki rats (ASC_{GK}) and non-diabetic wild-type rats (ASC_{WT}) in terms of phenotype, proteome, and efficacy in a BCNI rat model of ED. Despite ASC_{GK} showing a slightly lower proliferation rate, quantitative proteomic analysis revealed nearly identical protein expression profiles between ASC_{GK} and ASC_{WT}. Following intracavernous injection, both ASC_{GK} and ASC_{WT} restored erectile function to a similar extent, with comparable increases in expression of endothelial-recovery genes in the corpus cavernosum. These findings indicate that T2DM does not limit the efficacy of autologous ADSC therapy for ED [115].

Natural compounds, including flavonoids such as icariin from *Epimedium koreanum* Nakai, exhibit significant antioxidative and anti-inflammatory properties. Chronic oxidative stress markedly impairs ADSC viability, and antioxidants can mitigate this damage. Icariin, a potent antioxidant flavonol glycoside, counters H_2O_2-induced cytotoxicity in ADSCs, substantially reducing the decline in cell viability caused by oxidative insult. Higher concentrations of icariin further enhanced ADSC survival under H_2O_2 challenge by ROS generation and inhibiting apoptotic cascades. This protective effect was evidenced by upregulation of anti-apoptotic proteins Bcl-2, phosphorylated STAT3 (p-STAT3), and phosphorylated Akt (p-Akt), alongside downregulation of pro-apoptotic markers caspase-3 and BAX. Moreover, icariin increased superoxide dismutase (SOD) activity and reduced lactate dehydrogenase (LDH) leakage in H_2O_2-treated ADSCs. Mechanistically, icariin's cytoprotection of ADSCs was mediated via STAT3 activation downstream of the PI3K/Akt signaling pathway [43].

Therapeutic efficiency of ADSCs in neurogenic ED

Therapeutic efficiency of ADSCs in neurogenic ED BCNI is the most commonly used model CNI, typically induced with a non-serrated hemostat at a location distal to the MPG. CNI may also be produced by nerve transection, electrical coagulation, or cryoinjury [79]. Researchers have differentiated ADSCs into neuron-like cells and transplanted them into rats with CNI. This intervention significantly increased maximal ICP and the ICP/MAP ratio, enhanced the number of myelinated axons and nNOS–positive fibers, and improved the smooth muscle–to–collagen ratio in the dorsal penile nerve [116]. To address oxidative stress in the corpus cavernosum following CNI, Chen et al. transfected ADSCs with Peroxiredoxin 2 (PRDX2), thereby augmenting their therapeutic potential. PRDX2-overexpressing ADSCs resisted H_2O_2-induced apoptosis and promoted proliferation and survival of both ADSCs and ccSMCs. In vivo, bilateral ICI of PRDX2-ADSCs in a BCNI model in Sprague–Dawley rats resulted in superior erectile function, reduced corporal fibrosis, increased smooth muscle content, and attenuated oxidative stress and ferroptosis within the corpus cavernosum [81].

Preclinical evidence indicates that ADSC self-aggregation prior to ICI may enhance cell retention within the corpus cavernosum, potentially improving the treatment of neurogenic ED [117]. In parallel, induced pluripotent stem cell–

derived mesenchymal stem cells (iMSCs) have emerged as a promising alternative for treating CNI–induced ED. In a rat model of CNI, animals receiving iMSC transplantation exhibited a significantly higher ICP/MAP ratio than those treated with ADSCs, indicating sustained functional improvement. iMSC therapy restored endothelial and smooth muscle integrity, as evidenced by normalized expression of von Willebrand factor (vWF), eNOS, α-SMA, and desmin, and by reduced histological markers of tissue damage. Moreover, iMSC treatment upregulated nNOS in the corpus cavernosum and S100β in MPG, correlating with improved neurogenic signaling. Anti-apoptotic effects were confirmed by decreased levels of pro-apoptotic proteins BAX and caspase-3, alongside increased expression of the survival factor Bcl-2. Notably, iMSCs exhibited minimal direct transdifferentiation; their primary mode of action appears to be paracrine modulation of the host microenvironment. These findings substantiate the potential of iMSC transplantation, via paracrine mechanisms, as a durable therapeutic strategy for CNI-related ED [118].

Preclinical investigations have revealed promising therapeutic outcomes using lipopolysaccharide-preconditioned allogeneic ADSCs (L-ADSCs) in models of CNI–induced ED. In these studies, low-dose lipopolysaccharide preconditioning enhanced ADSC viability, suppressed H_2O_2–induced caspase-3 activation, and promoted cell migration. Furthermore, the supernatant from L-ADSC cultures proved more effective than that from non-preconditioned ADSCs in reducing TGF-β1–mediated fibrosis in ccSMCs. In vivo, treatment with L-ADSCs led to improved erectile function, as demonstrated by increased expression of smooth muscle markers (α-SMA and desmin) and a concomitant reduction in penile fibrosis. Mechanistically, these effects appeared linked to an upregulation of HGF in the corpus cavernosum and myelin basic protein in the MPG [119]. In a distinct approach, researchers have investigated the transplantation of mitochondria isolated from ADSCs in a BCNI model. The isolated mitochondria (ADSCs-mito) exhibited high levels of cytochrome c oxidase subunit IV (COX IV), a marker indicative of mitochondrial integrity. Both in vitro and in vivo experiments demonstrated the efficient internalization of ADSCs-mito by ccSMCs. Importantly, mitochondrial transplantation was shown to protect ccSMCs from H_2O_2-induced cellular damage by restoring mitochondrial membrane potential, preventing ATP depletion, and reducing apoptosis. These results underscore the potential of ADSC-derived mitochondrial therapy as a novel strategy for the treatment of CNI-induced ED [30]. A comparative study further evaluated the efficacy of human umbilical cord blood–derived mesenchymal stem cells (CBMSCs) versus ADSCs in managing ED. Immunofluorescence staining revealed that both CBMSCs and ADSCs exhibited limited differentiation potential within the penile tissue; however, the conditioned medium (CM) from CBMSCs demonstrated a marked ability to ROS levels. The superior antioxidative stress effects of CBMSC-CM were attributed to its rich secretome profile, which included trophic factors such as NeuroD1, neuropilin-2, neurturin, nidogen-1, NrCAM, NT3, NT4, and VEGF as well as matrix metalloproteinases (MMP-1/3). These bioactive molecules collectively contributed to reduced oxidative stress, lowered apoptosis rates, enhanced cellular growth, and diminished fibrosis. Based on these findings, the authors concluded that CBMSCs may offer a more effective treatment modality for ED compared to ADSCs [120].

Therapeutic efficiency of ADSCs in other cases of ED Priapism, defined as a prolonged erection exceeding four hours without sexual stimulation, leads to severe hypoxia and acidosis within the corpora cavernosa, ultimately resulting in fibrosis, irreversible tissue damage, and permanent ED. In an experimental Wistar rat model of priapism, intracorporeal administration of ADSCs demonstrated a protective effect against fibrosis. Specifically, ADSC treatment significantly reduced TGF-β1 and collagen type I expression, key mediators of fibrotic remodeling. By attenuating fibrosis, ADSC therapy may hold promise as a regenerative approach to mitigating priapism-induced ED [121].

Modified ADSCs yield higher outcomes

Recent advancements in gene and stem cell therapies for ED have focused on enhancing ADSC-based approaches to improve efficacy. Strategies include adenoviral-mediated intracavernosal gene delivery targeting eNOS, calcitonin gene-related peptide, SOD, and the RhoA/Rho kinase pathway, alongside mesenchymal stem cell-based therapies aimed at addressing age- and diabetes-related ED [122]. Among these approaches, ICI of ADSCs genetically modified to overexpress inducible nitric oxide synthase (ADSCs-iNOS) has demonstrated significant therapeutic benefits for DMED. ADSCs-iNOS enhanced NO production, suppressed collagen I and IV deposition, and improved erectile function, as evidenced by an increased ICP/MAP ratio. Comparatively, ADSCs expressing enhanced green fluorescent protein (ADSCs-EGFP) also contributed to erectile function restoration but exhibited lower efficacy than ADSCs-iNOS [123]. Yang et al. [124] advanced this concept by engineering ADSCs to overexpress neurotrophic factors such as VEGF and glial cell line-derived neurotrophic factor (GDNF). These modified ADSCs prevented fibrosis in cavernosal tissues BCNI by downregulating the phosphorylated LIM kinase 2 (p-LIMK2)/phosphorylated cofilin (p-cofilin) pathway, which modulates actin cytoskeleton dynamics and stress responses. Suppression of this signaling pathway mitigated fibrosis in the corpus

cavernosum, underscoring the potential of ADSC-mediated neurotrophic enhancement in ED therapy [125]. Furthermore, reduction of apoptosis in ccSMCs has emerged as a crucial mechanism in optimizing erectile function recovery [126, 127]. In another notable study, Zhang et al. investigated the impact of myocardin overexpression in ADSCs on ED pathology. While myocardin downregulated the proliferative marker proliferating cell nuclear antigen (PCNA), it concurrently promoted ADSC differentiation into smooth muscle-like cells. This differentiation was marked by increased expression of α-SMA and calponin, alongside decreased levels of ADSC stemness markers SOX2 and OCT4. These findings suggest that myocardin-driven differentiation enhances ADSC therapeutic potential by facilitating their transition toward a contractile smooth muscle phenotype, thereby improving ED outcomes [127]. In a separate study, ADSCs were genetically modified using a CRISPR activation (CRISPRa) system to overexpress relaxin family peptide receptor 1 (RXFP1). Lentiviral transfection was employed for precise gene activation, and the engineered stem cells (RXFP1-ADSCs) were intracavernously injected into DMED rats. The findings demonstrated that RXFP1-ADSC transplantation significantly enhanced erectile function, outperforming both untreated DMED controls and conventional ADSC therapy. The maximum ICP/MAP ratio and total ICP exhibited marked improvement in RXFP1-ADSC-treated rats, underscoring their superior therapeutic efficacy. Histological and biochemical assessments confirmed that RXFP1-ADSCs effectively reduced oxidative stress, reflected by lower ROS and MDA levels, alongside increased SOD expression. Furthermore, ADSC transplantation mitigated apoptosis and fibrosis, as evidenced by decreased Bax/Bcl-2 ratios, caspase-3 activation, and collagen accumulation, while fostering the proliferation and functional restoration of endothelial and smooth muscle cells. These improvements were most pronounced in RXFP1-ADSC-treated rats, suggesting that RXFP1 enhances ADSC survival, paracrine activity, and regenerative potential. Collectively, this study establishes RXFP1 as a viable genetic target for optimizing stem cell-based interventions for DMED, providing a multi-faceted approach to counteract oxidative damage, apoptosis, fibrosis, and endothelial dysfunction [128]. In another investigation by Yang et al. [111]. ADSCs were genetically modified using a lentiviral vector encoding PDE5 siRNA to inhibit PDE5 expression (Lv-siPDE5-ADSCs). Genetic modification of ADSCs via PDE5 inhibition significantly increased IGF-1 and VEGF secretion in vitro compared to unmodified ADSCs. In diabetic rat models, ICI of Lv-siPDE5-ADSCs led to significantly improved erectile function compared to unmodified ADSC treatment, as indicated by increased ICP/MAP ratios at both one and two weeks post-treatment. Histological assessments showed that Lv-siPDE5-ADSC treatment resulted in higher smooth muscle content and improved cavernous tissue recovery, with significantly enhanced smooth muscle/collagen ratios compared to unmodified ADSCs. These findings suggest that PDE5 inhibition enhances ADSC-mediated paracrine activity, promoting erectile function recovery in DMED.

Nano-based ADSC therapy for ED

Stem cell-based treatments carry inherent risks, including the potential for carcinogenesis, which increases with the number of cells administered in vivo. To mitigate this risk while maintaining therapeutic efficacy, researchers have investigated nano-assisted stem cell delivery systems that enhance cell retention and therapeutic outcomes. Wu and colleagues [31] explored nanotechnology-assisted ADSCs, comparing conventional ADSCs with magnetically guided ADSCs (MagADSCs) in an ED model. MagADSCs, also termed NanoShuttle-bound ADSCs (NanoADSCs), were injected under an external magnetic field to enhance localization at the target site. Evaluations of mean ICP, ICP/MAP, and total ICP indicated that ADSCs improved erectile function compared to untreated ED animals. However, MagADSCs exhibited superior regenerative effects, promoting the restoration of smooth muscle, endothelial integrity, and neuronal function beyond that observed in the ADSC cohort. Further advancements involve the development of thermosensitive hydrogels for sustained ADSC-derived exosome delivery. Researchers engineered hydrogels incorporating polydopamine nanoparticles (PDNPs) and poly(ethylene glycol)-poly(ε-caprolactone-co-lactide) (PDNPs-PELA) using a straightforward in situ polymerization process for intratunical application. These hydrogels demonstrated a sol-gel transition at physiological temperature, ensuring precise and prolonged exosome release. The stability of PDNP dispersion within the gel system was further enhanced through templated polymerization using PELA block copolymer. Over a two-week period, encapsulated exosomes facilitated endothelial and neuronal repair, increased cavernous pressure, and improved erectile function in vivo. Additionally, the PDNPs within the thermosensitive hydrogel exhibited excellent photoacoustic properties, enabling real-time imaging-guided hydrogel delivery into the tunica albuginea, ensuring precise localization [129].

Despite promising outcomes, unbound ADSC-exosomes remain challenging to retain within injured tissues. To address this limitation, investigators developed an injectable thermosensitive hydroxyethyl chitosan/sodium β-glycerophosphate hydrogel (HG) encapsulating ADSC-exosomes (HG@Exo). This formulation exhibited excellent injectability, structural stability, and

responsiveness to body temperature. In vivo studies demonstrated enhanced exosome retention and sustained therapeutic release, resulting in significant improvements in erectile function in a BCNI rat model [130].

Researchers have demonstrated that a benzaldehyde-terminated poly(ethylene glycol)/glycol chitosan (CHO-PEG/GCS) hydrogel can serve as an effective carrier for stem cells, significantly extending cell retention in the corpus cavernosum. This hydrogel exhibits excellent injectability and self-healing properties and undergoes gelation under physiological conditions. Importantly, it encapsulated ADSCs without impairing their capacity to proliferate post-injection. In animal studies, labeled ADSCs encapsulated within the hydrogel displayed markedly greater fluorescence in the penile region 14 days after ICI compared to non-encapsulated cells. Moreover, the CHO-PEG/GCS hydrogel enhanced the therapeutic efficacy of ADSCs by mitigating diabetes mellitus–induced fibrosis and reducing apoptosis in both endothelial and smooth muscle cells. Twelve weeks post-operation, improved preservation of NeuN-positive neural fibers was observed. The synergistic interaction between the hydrogel and ADSCs contributed to elevated cGMP levels and improved erectile function. Consequently, the CHO-PEG/GCS hydrogel emerges as a novel and promising carrier for stem cell delivery in conditions that benefit from in situ gelation and prolonged cell retention [131]. In a complementary approach, researchers developed an erythropoietin (EPO)-loaded multifunctional hydrogel for cellular implantation in a BCNI-ED rat model. Fabricated from methacrylate gelatin (GelMA) to simulate the natural extracellular matrix, this hydrogel leverages its excellent biocompatibility to support cell viability. The incorporation of arginylglycylaspartic acid (RGD) motifs facilitated integrin-mediated cell adhesion, while catechol-catechol adducts fortified the hydrogel's adhesive properties and mechanical strength. These enhancements significantly improved ADSC retention and reduced cell death at the injury site. The sustained release of EPO further bolstered ADSC viability and paracrine activity, promoting increased Schwann cell migration and enhancing PC12 cell differentiation in vivo. In the BCNI model, the integrated stem cell–EPO–hydrogel strategy effectively alleviated ED. Enhanced neural regeneration was confirmed by increased Tuj1 expression alongside reduced GFAP levels in the MPG. Additionally, restored levels of eNOS, nNOS, and α-SMA in the penile tissue indicate effective penile rehabilitation through preservation of the vascular endothelium and inhibition of fibrosis following denervation [132]. The sponge-like architecture of the corpus cavernosum—with its abundant vasculature—renders ICI functionally similar to intravenous administration. This similarity raises the risk of cell escape, potentially undermining both the safety and therapeutic efficacy of the treatment, an issue that has not been comprehensively investigated. Xu et al. addressed this concern by comparing two ICI formulations: suspensions containing free ADSCs (FAs) and those containing size-specific ADSC-based spheroids (ASs). Their findings revealed that most free ADSCs failed to remain in the corpus cavernosum following injection due to their small size, which compromised the local concentration essential for therapeutic action. More critically, the escaped free cells were associated with widespread pulmonary embolism and even resulted in mortality in some rodent models. Evidence further suggested that the modest therapeutic improvements observed with free ADSCs might be attributable to spontaneous aggregation into larger clusters prior to injection, which then incidentally enhanced cell retention. In contrast, transplantation of preformed, size-specific ADSC spheroids substantially diminished both cellular loss and the incidence of pulmonary embolism. Moreover, therapeutic outcomes were significantly enhanced in the AS group compared to the FA group when the same total number of cells was administered. These observations indicate that using size-specific ADSC spheroids rather than single-cell suspensions represents a more prudent and effective strategy for achieving stable, localized cell retention, thereby optimizing the treatment of neurogenic ED and reducing associated risks in future clinical applications [133].

Stromal vascular fraction in ED treatment

SVF, a heterogeneous cell population isolated from adipose tissue, comprises various cell types including ADSCs, endothelial cells, hematopoietic cells, and pericytes [134]. Similar to ADSC therapy, numerous studies have demonstrated that SVF therapy can effectively improve erectile function. For example, intratunical injection of autologous adipose SVF significantly reduced collagen type III deposition in a model of chronic penile fibrosis, thereby alleviating fibrotic remodeling in the erectile tissue [135]. Further molecular analyses have elucidated the complex cellular responses within the SVF of patients with ED. Vishnubalaji and colleagues identified several dysregulated pathways based on gene expression profiles. Analysis of down-regulated genes in SVF revealed enrichment in signaling pathways such as MAPK, TGF-β, focal adhesion, adipogenesis, androgen receptor signaling, EGF-EGFR, actin cytoskeleton regulation, circadian clock regulation, IL-4 signaling, neural crest development, Wnt, and RANKL-RANK. Conversely, up-regulated genes were predominantly associated with inflammatory and immune responses, including notable markers like ZAP70. Additionally, critical angiogenic and fibrotic mediators such as VEGFA, PDGFRA, and JUN (involved in both the focal adhesion

kinase and TGF-β pathways), as well as IGF1 and LIF, were found to be down-regulated. These microarray findings, further validated by qRT-PCR, indicated substantial enrichment of pathways related to inflammatory responses, T-cell receptor signaling, immunoregulation, complement activation, and IL-7 signaling [50] (Table 2).

Using ADSCs as potential therapeutic agents in humans

The International Index of Erectile Function (IIEF) is a standardized, 15-question instrument designed to evaluate several dimensions of male sexual health, including erectile function, orgasmic function, sexual desire, intercourse satisfaction, and overall satisfaction. Total scores on the IIEF range from 0 to 75, making it the gold standard for assessing the effectiveness of treatments for ED. In addition, a condensed version known as the IIEF-5 or Sexual Health Inventory for Men (SHIM) focuses exclusively on erectile function, yielding scores from 5 to 25. The score interpretation is as follows: severe ED (5–7), moderate ED (8–11), mild to moderate ED (12–16), mild ED (17–21), and no ED (22–25) (22–25) [147].

In a 12-month phase I/IIa clinical trial, 31 patients experiencing decreased sexual activity underwent treatment with autologous ADSCs isolated via type I collagenase digestion. Each subject received an intravenous injection of ADSCs at a dose of 1 million cells per kilogram of body weight. Safety and efficacy were rigorously monitored through assessments of adverse events, hormonal levels (testosterone in men; anti-Müllerian hormone [AMH], estradiol [E2], and follicle-stimulating hormone [FSH] in women), and sexual function evaluations using the IIEF for men and the Female Sexual Function Index (FSFI) for women. Follow-ups were conducted at baseline and subsequently at 3, 6, and 12 months post-intervention. The study reported no severe adverse events. In the male cohort, improvements in testosterone levels were noted for up to six months following treatment, whereas the female participants showed no significant changes in AMH, FSH, or E2 levels. Importantly, overall sexual fulfillment improved post-transplantation in all participants. These findings indicate that autologous ADSC injections not only provide a favorable safety profile but also hold potential as an effective therapeutic option for reduced sexual activity, with particular benefits observed among males [148].

In one study, ten men with impaired erectile function—defined by an International Index of Erectile Function-Erectile Function (IIEF-EF) score below 17—underwent same-day ADSC transplantation using the myStem® X2 kit for cell harvest and injection. The primary endpoints were centered on safety and feasibility. Only one minor adverse event, characterized by a transient blue discoloration at the fat harvest site, was reported. Notably, significant improvements in IIEF-EF scores were observed at subsequent follow-ups (median increases from 5.5 at baseline to 10.5 at 1 month, 10.5 at 2 months, and 10 at 3 months), with three participants demonstrating clinically significant improvements. Although these preliminary outcomes are encouraging, the small sample size and study design necessitate further investigation to establish long-term safety and efficacy [149]. In another phase I clinical trial aimed at assessing the safety and effect of a one-time ICI of adipose-derived regenerative cells (ADRCs) in men with ED following radical prostatectomy, 17 patients who had not responded to conventional therapies were monitored over a six-month period post-treatment. Prior to administration, ADRCs were characterized for stem cell markers, viability, and differentiation capacity. The primary focus was on safety and tolerance—minor adverse events related to liposuction and the injection procedure were noted during the first month post-treatment, with no further complications reported. Importantly, eight of the 17 subjects regained sufficient erectile function to engage in sexual intercourse. The continence subgroup experienced an improvement in the Erection Hardness Score, which increased from 1 to 3, whereas no significant change was observed in incontinent individuals [150]. Complementing these findings, a 12-month evaluation of a single ICI of autologous ADRCs in post-prostatectomy ED patients reported no serious adverse events, although eight minor, transient liposuction-related events were recorded. In the continent subgroup, 8 out of 15 patients (53%) achieved erectile function adequate for intercourse at the 12-month follow-up. While the median IIEF-5 scores remained largely unchanged during the initial month, significant improvements were noted after six to seven months, with benefits maintained up to 12 months. It is noteworthy that no improvements were observed among incontinent patients or those presenting with preoperative ED [151].

In one clinical investigation, six men with type 2 diabetes—whose ED persisted for over six months despite pharmacological treatment—received autologous ADSC transplantation without any adjunctive immunosuppressive therapy. The participants (mean age 63.7 years) were monitored over a six-month period using multiple metrics, including the IIEF-5, Sexual Encounter Profile diaries (SEP3), erection logs, blood glucose records, and medication dosages. Results indicated that four men restored morning erections within two months, and by day 95, all but one participant regained erectile function, with erections lasting over four months. Although ADSC therapy alone improved penile rigidity, it did not consistently support sufficient rigidity for penetration. However, when combined with a PDE5 inhibitor, three men achieved penetration and orgasm—a benefit sustained for over six months. Additionally, all patients

Table 2 Therapeutic effects of ADSCs in animal models of ED

Model of ED	Functional Outcomes or Targeted Effects	Detailed Cellular Mechanism(s)	Ref
Neurogenic	EF preservation Nerve repair Neuronal regeneration STAT3 Activation	ICI of ADSCs combined with intragastric administration of Icariside II increased ICP and the ICP/MAP ratio. This combination promoted the differentiation of ADSCs into Schwann cells through the Icariside II/let-7i/STAT3 and Icariside II/miR-34a/STAT3 pathways, thereby increasing the expression of Schwann cell markers NGF, NT-3, S100β, GFAP, and P75.	[29, 104]
	EF preservation Smooth muscle regeneration Anti-fibrosis/anti-apoptosis Anti-oxidative	ICI of ADSCs or ADSCs-derived mitochondria elevated the ICP/MAP ratio, smooth muscle content (α-SMA), and smooth muscle/collagen ratio. This treatment maintained ATP levels while reducing oxidative stress (increased SOD and decreased ROS/mitochondria derived active oxygen) and apoptosis (decreased cleaved-caspase 3).	[30]
	EF preservation Endothelial regeneration Smooth muscle regeneration Nerve regeneration Enhanced ADSC retention viamagnetic nanoparticles	ICI of ADSCs and magnetic field-assisted ADSCs (nano-ADSCs) increased mean ICP, ICP/MAP ratio, total ICP, β-III tubulin, α-SMA, PECAM-1, and CD31 levels.Nano-ADSCs were superior to ADSCs.	[31, 136]
	EF preservation Endothelial regeneration Smooth muscle recovery Nerve repair Anti-apoptosis	ICI of ADSCs enhanced the ratios of ICPmax/MAP and total ICP/MAP, restored the expression of vWF, eNOS, nNOS, desmin, and α-SMA. It also increased the smooth muscle-to-collagen ratio in penile tissue and inhibited apoptosis by reducing caspase-3 and BAX levels, while rescuing S100β and Bcl2 expression in the MPG.	[118]
	EF preservation Smooth muscle regeneration Anti-fibrosis Anti-ferroptosis Anti-apoptosis Anti-oxidative	ADSCs overexpressing Peroxiredoxin 2 (PRDX2-ADSCs) reduced apoptosis and oxidative stress while promoting ADSC growth in vitro when exposed to H_2O_2. PRDX2-ADSCs mitigated H_2O_2-induced oxidative stress in ccSMCs (maintains GSH, SOD levels and reduced ROS, MDA, and iron accumulation). ICI of ADSCs and PRDX2-ADSCs improved erectile function, as evidenced by increases in Total ICP/MAP and Max ICP/MAP. Both ADSCs and PRDX2-ADSCs enhanced smooth muscle (SM) content and the expression of SMA. Additionally, the ratio of SM to collagen increased, thereby preventing fibrosis of the corpus cavernosum, increasing cavernosal smooth muscle content, and preventing oxidative stress and RSL3-induced ferroptosis in the corpus cavernosum. PRDX2-ADSCs were superior to ADSCs, as they increased the expression of GPX4 and decreased the expression of ACSL4.	[81]
	EF preservation Smooth muscle regeneration Endothelial regeneration	Intratunical injection of ADSC-derived exosomes loaded in PDNPs-PELA hydrogel promoted the repair of endothelial cells and neurons, stimulated extracellular matrix remodeling, and contributed to improved blood flow and tissue repair.	[129]
	EF preservation Nerve regeneration Anti-fibrosis PI3K/Akt/p-eNOS activation	ICI of ADSCs increased ICP and ICP/MAP ratio, PEDF secretion, improved the number of nNOS-positive and S100-positive fibers in the penile dorsal nerve, increased the smooth muscle content, smooth muscle/collagen ratio, and ameliorated fibrosis in the corpus cavernosum.	[90]
	EF preservation Nerve repair Endothelial regeneration Smooth muscle regeneration Anti-fibrosis	ICI of ADSC-derived exosomes and ICI of BMSC-derived exosomes enhanced the ICP/MAP ratio, increased nNOS-positivity in penile dorsal nerve and MPG, facilitated endothelial cell regeneration (vWF), improved smooth muscle content (α-SMA), and elevated the smooth muscle/collagen ratio.	[105]
	EF preservation Nerve regeneration Smooth muscle preservation Angiogenesis promotion Anti-apoptosis	Human-ADSCs injected around the cavernous nerve combined with low-energy SWT increased the ICP/MAP ratio, nNOS positivity in the dorsal penile nerve, β-III tubulin in the cavernous nerve, smooth muscle content (α-SMA), eNOS/cGMP in the corpus cavernosum, and VEGF levels while decreasing apoptosis.	[137]
	EF preservation Nerve repair Endothelial regeneration Smooth muscle regeneration Anti-fibrosis p-LIMK2/p-cofilin inhibition	ADSCs co-expressing VEGF and GDNF increased ICP, ICP/MAP ratio, endothelium (RECA-1), nNOS, smooth muscle cell content, smooth muscle/collagen ratio, NF-H, and S100β, while decreased HIF-1α and fibrosis.	[124]

Table 2 (continued)

Model of ED	Functional Outcomes or Targeted Effects	Detailed Cellular Mechanism(s)	Ref
	EF preservation Endothelial regeneration Smooth muscle regeneration Anti-fibrosis NO/cGMP Activation TGFβ1/Smad2/3 & CTGF inhibition RhoA/ROCK inhibition	ADSCs overexpressing RXFP1 increased total ICP, ICP/MAP ratio, VEGF and bFGF secretion, α-SMA, smooth muscle: collagen ratio, SOD, Bcl2, while reduced Bax, Bad, caspase-3, cleaved caspase-3, TGFβ1, Smad 2/3, CTGF, collagen I/III, elastic fiber disruption, ROS, and NADPH oxidase activity	[128]
	EF preservation	ICI of free ADSCs (FAs) and ADSC-based spheroids (ASs) enhanced the ICP/MAP ratio and nNOS levels.	[133]
	EF preservation Nerve repair Smooth muscle regeneration	ICI of ADSCs and ADSCs expressing rBDNF increased the ICP/MAP ratio, nNOS-positive nerve fibers, and nNOS protein expression. Notably, ADSCs expressing rBDNF also elevated nNOS levels in dorsal penile nerve and improved the smooth muscle content/collagen ratio. Overall, ADSCs expressing rBDNF were superior to ADSCs alone.	[138]
	EF preservation Smooth muscle regeneration Nerve repair	ICI of ADSCs and CBMSCs increased ICPmax/MAP, nNOS levels, smooth muscle content (desmin), and the smooth muscle/collagen ratio. Notably, CBMSCs were superior to ADSCs.	[120]
	EF preservation Smooth muscle relaxation Anti-fibrosis	ICI of ADSCs co-expressing VEGF and Smad7 elevated the ICP/MAP ratio, nNOS, and α-SMA levels and improved the smooth muscle/collagen ratio while decreased TGF-β1 and RhoA/ROCK	[139]
	EF preservation Endothelial protection Nerve repair Smooth muscle regeneration Anti-fibrosis Anti-oxidant	tert-Butylhydroquinone (tBHQ)-ADSCs increased ADSC cell viability, ICP/MAP ratio, expression of S100β in the MPG, neurofilament growth length, and the smooth muscle/collagen ratio. Additionally, tBHQ-ADSCs suppressed oxidative stress (evidenced by increased SOD1) and fibrosis. Note that tBHQ acts as an Nrf2 activator, while ML385 is an Nrf2 inhibitor.	[140]
	EF preservation Nerve repair Endothelial regeneration Smooth muscle regeneration	ICI of ADSCs elevated the MICP/MAP ratio, nNOS levels, endothelium markers (eNOS, RECA-1, and vWF), and smooth muscle markers (α-SMA and desmin).	[141]
	EF preservation Nerve repair	Local transplantation of ADSCs into the injured spinal cord increased motor function scores, ICP/MAP ratio, and levels of nNOS, NGF, and c-FOS in the spinal cord.	[142]
Diabetic	EF preservation PI3K/Akt-STAT3 activation Endothelial regeneration Smooth muscle regeneration Anti-fibrosis Anti-apoptosis	ICI of ADSCs and ADSCs combined with icariin (administered via gastric route) improved ICP, maximum ICP/MAP ratio, endothelium content (vWF), and smooth muscle content (α-SMA), while reducing collagen deposition, ROS generation and apoptosis (Bax, caspase-3 downregulation, BCL2 upregulation). Notably, ADSCs combined with icariin were superior to ADSCs alone. Icariin potentiates ADSC survival under oxidative stress.	[43]
	EF preservation Angiogenesis promotion Paracrine enhancement	ICI of ADSCs and ICI of ADSCs combined with LIPUS treatment enhanced maximal ICP/MAP ratios and total ICP/MAP ratios, endothelium markers (eNOS and vWF), and cGMP levels in the corpus cavernosum. LIPUS triggered the ERK pathway in ADSCs, subsequently stimulating VEGF expression and secretion. The Piezo channel functions as an upstream activator of the ERK-VEGF pathway in the activation of ADSCs mediated by LIPUS. Notably, ICI of ADSCs + LIPUS was superior to ICI of ADSCs alone.	[49]
	EF preservation Smooth muscle regeneration Anti-fibrosis	ICI of ADSCs and ADSCs overexpressing myocardin increased △ICP/MAP ratio, improved CCSM cell function, and smooth muscle-to-collagen ratio.ADSC overexpressing myocardin were superior to ADSC as more effectively decreased cleaved caspase-3 and collagen I while increased α-SMA and calponin	[127]
	EF preservation Endothelial regeneration Smooth muscle preservation Anti-fibrosis	ICI of ADSCs and BMSCs increased total ICP and the ICP/MAP ratio, eNOS protein levels in penile tissue, revascularization of the corpus cavernosum, and improved the impairment of endothelial cells and smooth muscle cells. This treatment also decreased collagen content in the corpus cavernosum. Notably, ADSCs were superior to BMSCs.	[143]

Table 2 (continued)

Model of ED	Functional Outcomes or Targeted Effects	Detailed Cellular Mechanism(s)	Ref
	EF preservation Endothelial regeneration Smooth muscle regeneration	ICI of ADSCs expressing PDE5 inhibitor (Lv-siPDE5-ADSCs) increased ICP, ICP/MAP ratio, growth factors release (IGF-1 and VEGF), smooth muscle marker (desmin), and smooth muscle-to-collagen ratio.	[111]
	EF preservation Neuroprotection/nerve regeneration Anti-apoptosis Anti-inflammation Anti-oxidant NO/cGMP activation	ICI of ADSCs and ADSCs overexpressing PEDF increased ICP, ICP/MAP ratio, nNOS expression, cGMP levels, NGF, and BDNF. Additionally, they reduced TNF-α, IL-6, IL-1β, NOX1/4 (oxidative stress), TLR4, cleaved caspase 3, and cleaved PARP (apoptosis) in penile tissue. Notably, ADSCs overexpressing PEDF were superior to ADSCs alone.	[91]
	EF preservation Endothelial regeneration Angiogenesis promotion Anti-fibrosis	ICI of ADSC-derived exosomes increased the ICP/MAP ratio and endothelium content (vWF) while suppressing collagen deposition in the corpus cavernosum through the actions of three proangiogenic miRNAs (miR-126, miR-130a, miR-132) and antifibrotic miRNA family members (miR-let7b and miR-let7c).	[100]
	EF preservation Endothelial regeneration Smooth muscle regeneration Nerve repair Anti-apoptosis	ICI of ADSCs and ADSC-derived exosomes elevated the ICP/MAP ratio, endothelium (CD31 positive) and smooth muscle cells (α-SMA) in corpus cavernosum tissue, smooth muscle content/collagen ratio, and Bcl-2 levels, while reducing apoptosis and cleaved caspase-3.	[106]
	EF preservation Endothelial regeneration Smooth muscle regeneration Nerve repair Anti-fibrosis Anti-inflammation NO/cGMP activation	ICI of ADSC-derived exosomes increased ICP, angiogenesis, cGMP levels, ANP, BNP, and nNOS, while reducing TNF-α, IL-6, and IL-1β, possibly mediated through corin.	[107]
	EF preservation Endothelial regeneration Smooth muscle regeneration Nerve repair	ICI of ADSCs and ADSCs combined with Endothelial Progenitor Cells increased ICP, ICP/MAP ratio, endothelium (CD31), eNOS, cGMP, serum NO, VEGF, SDF-1, nNOS in penile dorsal nerve, and smooth muscle content/collagen ratio. The combinational treatment was superior to ADSCs alone.	[114]
	EF preservation Smooth muscle regeneration Anti-fibrosis NO/cGMP activation TGF-β1/Smad inhibition	ICI of ADSCs-overexpressing iNOS increased the ICP/MAP ratio, NO, and cGMP while decreased TGF-β1/Smad and collagen I/IV.	[123]
	EF preservation Endothelial regeneration Smooth muscle regeneration	ICI of ADSCs and SPIONs-labeled ADSCs increased the ICP/MAP ratio, smooth muscle content (α-SMA), endothelium (vWF), and VEGF expression in the corpus cavernosum. Notably, SPIONs-labeled ADSCs were superior to ADSCs alone.	[144]
	EF preservation Endothelial regeneration Smooth muscle restoration Nerve repair	ICI of ADSCs and ADSC-based microtissues (MTs) increased ICP and the ICP/MAP ratio, as well as endothelium content (vWF positive), smooth muscle cell content of the corpus cavernosum (α-SMA positive), VEGF, NGF, TSG-6, nNOS-positive neurons in the major pelvic ganglia, and nNOS expression in the dorsal penile nerve. Notably, ADSC-based microtissues were superior to ADSCs alone.	[92]
	EF preservation Endothelial regeneration Smooth muscle protection Nerve repair	ICI of ADSCs and ADSCs + insulin increased ICP, ICP/MAP ratio, smooth muscle content (α-SMA), endothelium (vWF), VEGF, and nNOS levels while decreasing the apoptotic index. Notably, ADSCs + insulin were superior to ADSCs alone.	[145]

Table 2 (continued)

Model of ED	Functional Outcomes or Targeted Effects	Detailed Cellular Mechanism(s)	Ref
Hypoxic	EF preservation Smooth muscle regeneration Autophagy promotion	ICI of ADSC-derived exosomes enriched with miR-301a-3p mimic significantly increased the ratio of ICP/real-time carotid arterial pressure, promoted smooth muscle content (α-SMA), and enhanced eNOS expression. CIH exposure stimulated iNOS expression, which was subsequently reduced by miR-301a-3p-enriched exosomes. Additionally, protein levels of PTEN and TLR4 in the rat dorsal nerve of penile tissue were reduced by ADSC-derived exosomes overexpressing miR-301a-3p. HIF-1α expression was enhanced by miR-301a-3p.	[68]
	Anti-apoptosis PTEN and TLR4 inhibition	miR-301a-3p-enriched exosomes from ADSCs inhibited CIH-induced apoptosis and upregulated CIH-induced autophagy. This was evidenced by increased LC3I/II and nuclear p65 levels, while inhibiting p62 expression, ultimately inducing autophagy and suppressing apoptosis in CCSMCs.	
Aging	EF preservation Endothelial regeneration Smooth muscle cell protection & proliferation Anti-oxidant	ICI of ADSCs elevated the ICP/MAP ratio and increased the contents of IGF-1, bFGF, and VEGF in penile tissue. This treatment also enhanced cavernous smooth muscle cells (α-SMA positive) and endothelial cells (vWF positive), while reducing oxidative stress (indicated by elevated SOD and reduced MDA levels).	[85]
Tobacco	EF preservation Endothelial restoration Smooth muscle regeneration Anti-oxidant Anti-apoptosis	ICI of ADSCs increased mean ICP, the ICP/MAP ratio, serum NO, nNOS, endothelial integrity (RECA-1 positivity), smooth muscle content/collagen ratio, and improved total antioxidant capacity of plasma. Additionally, it decreased apoptosis and 8-OHdG/creatinine levels (indicating reduced oxidative stress).	[146]

ACSL4 Acyl-CoA Synthetase Long Chain Family Member 4, *ADSC* Adipose-Derived Stem Cell, Akt Protein kinase B (part of PI3K/Akt pathway), *ANP* Atrial Natriuretic Peptide, *ASs* ADSC-based spheroids, *ATP* Adenosine Triphosphate, *BAX* Bcl-2 Associated X protein, *Bcl2* B-cell lymphoma 2, *BDNF* Brain-Derived Neurotrophic Factor, *bFGF* basic Fibroblast Growth Factor, *BMSC* Bone Marrow-derived Stem Cell, *BNP* Brain Natriuretic Peptide, *CBMSC* Cord Blood Mesenchymal Stem Cell, *CCSMCs* Corpus Cavernosum Smooth Muscle Cells, *cGMP* cyclic Guanosine Monophosphate, *CIH* Chronic Intermittent Hypoxia, *EF* Erectile Function, *eNOS* endothelial Nitric Oxide Synthase, *ERK* Extracellular signal-Regulated Kinase, *FAs* Free ADSCs, GFAP Glial Fibrillary Acidic Protein, *GDNF* Glial cell line-Derived Neurotrophic Factor, *GPX4* Glutathione Peroxidase 4, *GSH* Glutathione, H_2O_2 Hydrogen Peroxide, *HIF-1α* Hypoxia-Inducible Factor 1-alpha, *ICP* Intracavernosal Pressure, *IGF-1* Insulin-like Growth Factor 1, *IL* Interleukin, i*NOS* inducible Nitric Oxide Synthase, LC3I/II Microtubule-associated protein 1 , A/1B-light chain 3 I/II; LIPUS: Low-Intensity Pulsed Ultrasound; Lv-siPDE5-ADSCs: Adipose-Derived Stem Cells expressing PDE5 inhibitor (via lentiviral vector for small interfering RNA against PDE5); MAP: Mean Arterial Pressure; MDA: Malondialdehyde; MICP: Maximal Intracavernosal Pressure; miR: microRNA; MPG: Major Pelvic Ganglion; MTs: Microtissues; NF-H: Neurofilament-H; NGF: Nerve Growth Factor; nNOS: neuronal Nitric Oxide Synthase; NO: Nitric Oxide; NOX1/4: NADPH Oxidase 1/4; Nrf2: Nuclear factor erythroid 2-related factor 2; NT-3: Neurotrophin-3; PARP: Poly(ADP-ribose) Polymerase; PDGF: Platelet-Derived Growth Factor; PDNPs-PELA: Polydopamine Nanoparticles - Poly(ethylene glycol)-poly(ε-caprolactone-co-lactide) hydrogel; PDE5: Phosphodiesterase type 5; PEDF: Pigment Epithelium-Derived Factor; PECAM-1: Platelet Endothelial Cell Adhesion Molecule-1 (also CD31); PI3K/Akt: Phosphoinositide 3-kinase/Protein kinase B; PRDX2: Peroxiredoxin 2; PTEN: Phosphatase and Tensin homolog; rBDNF: recombinant Brain-Derived Neurotrophic Factor; RECA-1: Rat Endothelial Cell Antigen-1; RhoA/ROCK: Ras homolog family member A/Rho-associated protein kinase; ROS: Reactive Oxygen Species; RSL3: A specific ferroptosis inducer; RXFP1: Relaxin Family Peptide Receptor 1; S100β: S100 calcium-binding protein B; SDF-1: Stromal cell-Derived Factor 1; SM: Smooth Muscle; SOD: Superoxide Dismutase; STAT3: Signal Transducer and Activator of Transcription 3; SWT: Shockwave Therapy; tBHQ: tert-Butylhydroquinone; TGF-β1: Transforming Growth Factor-beta 1; TLR4: Toll-Like Receptor 4; TNF-α: Tumor Necrosis Factor-alpha; TSG-6: TNF-stimulated gene 6 protein; VEGF: Vascular Endothelial Growth Factor; vWF: von Willebrand Factor; α-SMA: alpha-Smooth Muscle Actin; △ICP: Change in Intracavernosal Pressure

except one reported an increased sexual desire. Interestingly, improvements in glycemic control were also noted, with reduced blood glucose levels within two weeks post-treatment and consequent decreases in medication dosages, along with improvements in HbA1c. No adverse effects were attributed to the stem cell therapy, although most patients felt that the efficacy was enhanced when combined with PDE5 inhibitors. Only one patient expressed confidence in stem cell therapy's effect on ED without a PDE5 inhibitor [152]. A separate phase I, single-center pilot study evaluated the safety and efficacy of ADSCs in patients with organic ED attributed to conditions such as diabetes, hypertension, hypercholesterolemia, and Peyronie's disease. Exclusion criteria eliminated patients with psychogenic, neurologic, or hormonal ED, as well as those with penile injuries unrelated to Peyronie's disease or a history of cancer. Over six months, most patients exhibited improved IIEF-5 scores. Hemodynamic assessments demonstrated improvement in peak systolic velocity (PSV) in all subjects—indicating enhanced endothelial function—although changes in end diastolic velocity (EDV) were less consistent. Clinically, some patients were able to transition from requiring ICI to either oral PDE5 inhibitor therapy or even unassisted erections. The treatment was well-tolerated, with only minor transient pain during injections reported. Furthermore, the combined use of ADSCs with platelet lysate plasma (PLP) appeared promising, suggesting that this combination might offer enhanced regenerative benefits while maintaining a favorable short-term safety profile. Nonetheless, longer-term studies are required to establish enduring efficacy and safety [153]. Another pilot study explored the therapeutic potential of combining ADSCs with platelet lysate (PL) for the treatment of ED.

With a three-month follow-up, both treatment groups—one receiving ADSCs combined with PL, and another receiving PL alone—demonstrated improved erectile function as measured by increases in IIEF-5 scores. These preliminary findings suggest that both combination therapy and PL monotherapy may serve as effective, minimally invasive treatments for ED with minimal short-term risks [154] (Table 3).

Challenges and limitations in ADSC therapy: future directions and prospects

The transition of stem cell therapy discoveries to clinical practice has been hindered by inadequate standardization and absence of comprehensive guidelines. Variations in cell origins, cultivation conditions, and obtainment methods obstruct the effective translation of research findings to clinical applications. The primary functions of ADSCs — adhesion, proliferation, and viability — are influenced by factors such as platelet lysate-coated culture plates and adipose tissue harvesting techniques. Moreover, the variability in ADSCs' properties is affected by the anatomical location of fat, patient age, gender, and BMI. Additionally, the origin and isolation methods of allogeneic grafts contribute to cellular and molecular variability. There are significant safety concerns regarding graft infections with latent viruses. The major issue with fat grafting and other biological substances is the inconsistency of experimental and clinical results, attributable to poor standardization, varied harvesting methods, and the lack of objective assessment protocols. Thus, comprehensive standardization of adipose tissue harvesting, donor health conditions, storage procedures, and ADSCs' properties is crucial for achieving predictable treatment outcomes. [156] However, in terms of ED, no major adverse events were noted during or after the treatment period, which implies that the therapeutic option was safe [157].

Safety concerns and severe side effects: lack of universal guidelines for biological product assessment

ADSC therapy has proven to be effective and efficient, offering significant promise in the field of regenerative medicine. It has shown positive benefit-risk profiles in addressing wound defects, bone regeneration, and treating autoimmune and neurodegenerative diseases. However, some severe side effects, such as blindness in SVF-treated patients with macular degeneration, challenge the justification of this cell therapy. Therefore, ensuring patient safety and security is crucial for the widespread adoption and market introduction of stem cell-based therapies. At present, there are no universal guidelines for assessing biological products, especially those used for "non-homologous use" [158]. For instance, their physiological degradation in diabetic conditions limits their effectiveness of the therapeutic potential in autologous transplants. Results confirm that type 2 diabetes detrimentally affects ASCs' essential functions of stemness, including viability, proliferation, mitochondrial dynamics, oxidative stress defenses, and secretion capabilities. Moreover, metabolic disorders appear to impair glucose regulation and insulin sensitivity through the downregulation of important mRNA and miRNA involved in glucose and lipid metabolism. Therefore, it is crucial to pharmacologically enhance ASCs from diabetic patients ex vivo before any clinical applications. Significant variations were noted in the expression of miRNAs involved in cell proliferation (miR-16-5p, miR-146a-5p, and miR-145-5p) and those regulating glucose homeostasis and insulin sensitivity (miR-24-3p, miR-140-3p, miR-17-5p, SIRT1, HIF-1α, LIN28, FOXO1, and TGFβ). Additionally, ASC_{T2D} exhibited reduced secretion of VEGF, adiponectin, and CXCL-12, but increased production of leptin [159].

Risk of malignant transformation and immunological issues

ICI of ADSCs shows promising therapeutic potential for ED. However, preclinical studies have highlighted several critical safety concerns, particularly regarding cell retention, biodistribution, and oncogenic risk.

One of the primary challenges arises from the highly vascular, porous architecture of the corpus cavernosum, which can facilitate the unintended systemic dissemination of transplanted cells. Xu et al. [133] demonstrated that free ADSCs (FAs), when injected via ICI, are frequently not retained at the target site. Instead, they migrate into the systemic circulation, where they can induce adverse events such as pulmonary embolism. This loss of local cell concentration compromises tissue regeneration and reduces therapeutic efficacy. To address this issue, the use of ADSC-based spheroids (ASs) has been proposed. These size-controlled, three-dimensional aggregates demonstrate enhanced retention in the corpus cavernosum due to their cohesive structure, which limits premature cell escape. The application of ASs has been shown to reduce the risk of embolic complications while improving treatment consistency and safety in preclinical settings.

Beyond mechanical and circulatory concerns, tumorigenic and immunomodulatory risks must also be considered. ADSCs possess a high proliferative capacity, raising concerns about potential malignant transformation. Several studies have reported that mesenchymal stem cells (MSCs), including ADSCs, may promote tumor growth either directly through transformation or indirectly by modulating the tumor microenvironment. For example, via the SDF-1/CXCR4 signaling axis, ADSCs can enhance the proliferation, migration, and invasion of gastric cancer cells [160]. Additionally, adipokines secreted by

Table 3 Human studies of ADSCs in improving ED

Type of Study	Participants	Follow-up Duration	Safety Data	Efficacy Endpoints & Outcomes	Long-term Safety Notes
Open-label, single-arm Phase I Clinical Trial [150] NCT02240823	17 post-radical prostatectomy ED (11 continent, 6 incontinent)	6 months	No serious adverse events; minor events included transient redness/swelling at injection sites, scrotal hematoma (resolved within 14 days), and brief abdominal pain post-liposuction.	8 of 17 men recovered erectile function; continent men showed statistically significant IIEF-5 improvement (median score increased from 7 to 17 at 6 months); incontinent men did not regain erectile function (no significant change in IIEF-5 or EHS).	No reported data on immune rejection or tumorigenicity beyond 6 months.
Open-label, single-arm Phase I Clinical Trial [151] NCT02240823	21 post-radical prostatectomy ED (15 continent, 6 incontinent)	12 months	No serious adverse events; 8 reversible minor events related to liposuction, including redness, swelling at injection sites, scrotal hematoma (resolved within 14 days), and transient.	8 of 15 continent men recovered erectile function sufficient for intercourse; median IIEF-5 score increased from 6 (baseline) to 8 at 12 months; improvement seen only in continent men, while incontinent men showed no recovery.	No reported data on immune rejection or tumorigenicity beyond 12 months.
Pilot study, prospective case series [149]	10 patients with organic ED (mixed vascular etiologies)	6 months (IIEF assessments at baseline, 1, 2, and 3 months post-treatment)	No serious adverse events; one case of minor blue discoloration at the fat harvest site (resolved in a few days).	Statistically significant increase in IIEF-EF scores; median score improved from 5.5 (baseline) to 10.5 (1 month), 10.5 (2 months), and 10 (3 months); 3/10 patients achieved improvement equal to or greater than the minimal clinically important difference (MCID); transient increase in overall satisfaction at 2 months.	No reported data on immune rejection, tumorigenicity, or long-term adverse effects beyond 6 months.
Clinical Trial [155] IRCT20190624043991N11	14	3 months	No severe adverse effects reported; three patients experienced minor ecchymosis on the penis.	Significant improvement in IIEF scores (pre-treatment mean: 41.85 ± 8.56; post-treatment mean: 63.78 ± 4.87); EHS also increased (pre-treatment mean: 2.64 ± 0.49; post-treatment mean: 3.35 ± 0.63).	No reported data on immune rejection or tumorigenicity.
Pilot case series [152]	6 Type-2 diabetic ED	6–12 months	No adverse events reported; no immunosuppression used.	4/6 recovered morning erections within 2 months, maintained for over 4 months; 3/6 achieved penetration + orgasm with PDE5 inhibitor, maintained for 6–9 months; IIEF-5, SEP-3, erection diaries all showed overall improvement; blood glucose levels improved, reducing medication dosage.	No reported data on immune rejection or tumorigenicity.

Table 3 (continued)

Type of Study	Participants	Follow-up Duration	Safety Data	Efficacy Endpoints & Outcomes	Long-term Safety Notes
Phase I study [153]	5 organic ED received ADSCs and platelet lysate plasma	6 months (evaluations at 1 st, 3rd, 6th, and 12th months post-treatment)	No side effects observed; minor injection-related discomfort resolved within minutes.	IIEF-5 scores improved in all but one patient; PSV increased across all patients, EDV showed more variability.	No reported data on immune rejection or tumorigenicity beyond 6 months; CT scans performed pre-treatment and at 12 months to monitor potential changes.
Phase I study [154]	8 organic ED (Group A: Received ADSC + Platelet Lysate, $n=5$; and Group B: Received Platelet Lysate, $n=3$)	3 months	No serious adverse events; minor injection-related discomfort reported but within tolerable limits.	Statistically significant improvement in IIEF-5 scores post-treatment (at 1 and 3 months); penile triplex showed improved PSV and increased morning erections in most patients; patients in group A transitioned from requiring ICI to oral PDE5 inhibitors, while some achieved unassisted erections.	No reported data on immune rejection or tumorigenicity; CT scans conducted pre-treatment and at 12 months to monitor potential changes.

ADSC Adipose-Derived Stem Cell, *CT* Computed Tomography, *ED* Erectile Dysfunction, *EDV* End Diastolic Velocity, *EHS* Erection Hardness Score, *ICI* Intracavernosal Injection, *IIEF* International Index of Erectile Function, *IIEF-EF* International Index of Erectile Function-Erectile Function score, *MCID* Minimal Clinically Important Difference, *NCT* National Clinical Trial, *PDE5* Phosphodiesterase type 5, *PSV* Peak Systolic Velocity, *SEP-3* Sexual Encounter Profile (question 3)

ADSCs in animal models have been implicated in angiogenesis, a critical step in tumor expansion. Notably, the migration of ADSC from white adipose tissue to tumors has been observed, suggesting that ASC-derived trophic factors may modulate the tumor microenvironment in a paracrine manner rather than an endocrine one. ADSCs have been observed to migrate from adipose tissue to tumor sites, where their trophic factors may exert paracrine effects that support tumor progression. These stromal cells can also integrate into the tumor microenvironment, contributing to neovascularization and stromal remodeling [161, 162].

Indeed, MSCs hold promise for therapeutic use as immunomodulatory and regenerative agents. However, the immunogenicity and survival of MSCs post-infusion remain unclear, with evidence indicating that both allogeneic and autologous MSCs rapidly disappear after infusion. This phenomenon may be linked to their susceptibility to lysis by natural killer (NK) cells, potentially due to culture-induced stress. Immunosuppressive drugs such as tacrolimus, rapamycin, and sotrastaurin have not been effective in preventing the lysis of allogeneic and autologous ADSCs by activated NK cells. Therefore, alternative strategies for controlling the lysis of ADSCs should be explored, as this could determine the therapeutic efficacy of ADSC treatments [163]. Given the present obstacles in achieving a clinically useful volume for ADSC-based tissue engineering, the surgical applications that ASC might meet are still relatively few [164].

Economic and socioeconomic factors (stem cell tourism)

There is increasing evidence pointing out the risks associated with unregulated stem cell therapies such as stem cell tourism. Stem cell tourism can have serious financial and socioeconomic effects, potentially leaving patients in poverty. The cost for stem cell treatment is estimated to range from US$10,000 to US$60,000, not including travel expenses. Patients bear the full financial burden, and follow-up care is seldom provided once they leave the treatment facilities. This situation has significant economic impacts on their native healthcare systems, especially if patients require follow-up care for complications and infections from treatments received abroad. The financial strain affects not only the patients but also public health programs, insurance companies, and hospitals. This presents challenges for publicly funded healthcare systems like in Canada, where follow-up care tends to be complicated and expensive. Moreover, medical tourism poses global public health security risks due to the potential introduction of multidrug-resistant bacteria from countries with lower levels of antimicrobial stewardship [165]. While stem cell therapy is advancing worldwide, patients sometimes have unfounded expectations about its efficacy. In some cases, stem cell treatments are given without proper medical indications, resulting in dangerous outcomes. Factors such as high costs, poor quality, extended waiting periods, legal restrictions, exclusion from clinical trials, and lack of access to unapproved treatments contribute to the rise of stem cell tourism. The USA, China, India, Thailand, and Mexico are prominent leaders in this field [156].

Age-related decline and potential interventions in ADSC therapy

Growing evidence suggests that the proliferation and differentiation potential of ADSCs diminishes with advancing age, higher body mass index, diabetes mellitus, metabolic syndrome, or exposure to radiotherapy [166]. ADSCs from older donors exhibit signs of senescence, including elevated levels of p21 and p53, and increased senescence-associated β-galactosidase (SA-β-gal) activity. This includes the secretion of inflammatory factors, referred to as the senescence-associated secretory phenotype (SASP). Aging and obesity compromise mitochondrial efficiency and lysosomal integrity, leading to heightened oxidative stress and cellular dysfunction. Similarly, changes in DNA methylation patterns, such as increased 5-hydroxymethylcytosine (5hmC), are observed in ADSCs from older and obese donors, which significantly impair their tissue repair capabilities. These cells demonstrate reduced proliferative and migratory abilities, diminished multilineage differentiation potential, increased senescent characteristics, and a proinflammatory secretome due to aging [166]. The application of senolytic agents such as fisetin, dasatinib, and quercetin shows promise in selectively removing senescent cells and maintaining the regenerative capacity of the remaining ADSCs [166]. Cultivating ADSCs in low oxygen conditions has been shown to decrease senescence and enhance their differentiation and repair capabilities [167]. Thymosin beta-4 (Tβ4) also enhanced the viability of adipose tissue in autologous fat grafting (AFG) by encouraging the proliferation of ADSCs and decreasing cell death. It serves as a critical positive regulator of angiogenesis associated with ADSCs. Furthermore, Tβ4 could be responsible for the phenotypic modulation of ADSCs by regulating the Hippo signaling pathway [168]. Vitamin C has shown potential in counteracting senescence by down-regulating p21 expression and modulating the cell cycle in ADSCs [169]. Silencing DUXAP10 can enhance stem cell proliferation and migration, halt cell senescence, and reduce the secretion of proinflammatory cytokines. It also improved the rejuvenation and functional restoration of aged ADSCs through the miR-214-3p/RASSF5 axis, providing new insights into the mechanisms of age-related ASC dysfunction. DUXAP10 and miR-214-3p are identified as potential targets for revitalizing aged stem cells [170]. Considering alternative strategies like cell banking or using allogeneic cell sources might be more appropriate for developing future ADSC-based therapies for elderly patients [171].

Future perspectives: ADSC exosomes, cell-free therapies, and cytokine therapy

Given the predominant role of paracrine signaling in ADSC therapy, cell-free approaches represent a promising avenue. ADSC-derived extracellular vesicles, particularly exosomes, encapsulate many of the bioactive molecules found in their parent cells while circumventing the risks associated with live cell transplantation. Indeed, in a diabetic rat model of ED, intracavernous administration of ADSC-derived exosomes produced effects comparable to ADSC transplantation. The treatment increased the smooth muscle-to-collagen ratio, restored endothelial and smooth muscle markers (CD31, α-SMA), upregulated the anti-apoptotic protein Bcl-2, and attenuated caspase-3–mediated apoptosis. These findings suggest that exosomes may effectively rescue cavernous tissue in the absence of cellular engraftment [106].

Beyond biological efficacy, cell-free strategies confer substantial logistical advantages. Secretome-based products, including exosomes and soluble factors, can be biobanked, sterilized, and subjected to rigorous quality control more efficiently than living cells. Numerous studies have demonstrated that the ADSC secretome (including exosomes and soluble factors) exerts potent immunomodulatory, pro-angiogenic, and neurotrophic effects [83]. Compared to whole-cell therapy, exosome-based interventions may face fewer regulatory obstacles and carry no risk of ectopic tissue formation. Nonetheless, several challenges must be addressed before exosome-based therapies can be clinically translated. These include the scalable production of therapeutic-grade exosomes, the precise determination of optimal dosing, and the standardization of batch consistency. To enhance retention and bioavailability, advanced delivery systems are under development. Recent work explored an injectable thermo-sensitive hydrogel to encapsulate ADSC-derived exosomes. This composite—a hydroxyethyl chitosan/β-glycerophosphate gel—enabled controlled exosome release at the site of injury. In a rat model of CNI, this strategy significantly improved erectile function compared to exosomes alone. More broadly, hydrogels have been shown to extend the retention of transplanted MSCs or exosomes within the corpora, facilitating the sustained release of pro-angiogenic and reparative factors [172]. Future research will prioritize the standardization of exosome-based therapies by establishing potency assays and ensuring safety, particularly given that exosomal cargo may vary with donor cell health. Additionally, novel delivery technologies—such as targeted nanoparticles carrying exosomes—could enable precise localization within penile tissues, maximizing therapeutic efficacy. If these hurdles are successfully overcome, ADSC-derived exosomes and conditioned media could emerge as scalable, cell-free interventions for ED, offering a viable alternative to direct cell transplantation.

The concept of cytokine therapy for ED was first introduced in a 2019 Chinese review, which classified cytokines into four functional categories: angiogenic (e.g.,

VEGF, IGF-1), neurotrophic (e.g., BDNF, NGF), smooth muscle protective, and inflammation-modulating (e.g., IL-1RA). While preclinical studies in rat models have demonstrated improvements in erectile function, these cytokine-based interventions remain untested in large animals or human trials [173]. Preclinical research has shown that intracavernous delivery of VEGF can restore endothelial function and nerve integrity in diabetic or nerve injury rat models [174]. Another promising approach, PRP—which contains a mixture of growth factors, including PDGF and CXCL5—was evaluated in a randomized, double-blind, placebo-controlled trial involving 61 men. While PRP was deemed safe, it failed to outperform placebo on the IIEF at six months [175]. Moreover, although a phase I trial assessed intracavernosal delivery of a smooth muscle-specific gene vector (hSlo plasmid), no clinical study has investigated the efficacy of a cytokine-only therapeutic strategy in ED patients [176]. Despite promising preclinical data, cytokine therapy is not yet available in clinical practice due to several unresolved challenges. The existing body of evidence is largely limited to small-animal studies, characterized by heterogeneous delivery methods and a lack of standardized dosing or long-term safety data. Additionally, regulatory hurdles surrounding biologics, inconsistencies in cytokine preparations (recombinant proteins vs. cell-derived secretomes), and the absence of large, well-controlled randomized trials continue to impede clinical translation. Until robust phase II/III clinical trials establish optimal cytokine combinations, dosing regimens, and safety profiles, cytokine-based treatments for ED will remain an experimental concept rather than a clinical reality.

Conclusion

ADSC-based therapy offers a novel, minimally invasive approach to treating ED, with particular benefits observed in neurogenic and diabetic models. Despite these advancements, several challenges remain. First, the longstanding safety and efficacy of ADSC therapy in people need further validation through rigorous clinical trials. Additionally, ADSCs face potential issues such as inconsistent cell retention in target tissues and varying therapeutic outcomes due to donor variability. However, opportunities to enhance ADSC therapy include the development of gene-modified ADSCs to overexpress angiogenic or neurogenic factors, the use of exosome-based therapies, and combining ADSCs with other regenerative techniques like low-intensity shockwave therapy. Future research should focus on optimizing ADSC delivery, understanding mechanisms of ADSC differentiation, and exploring personalized therapeutic approaches tailored to individual patient profiles. The integration of nanotechnology for improved ADSC retention and function also holds considerable promise in addressing ED more effectively.

Abbreviations

5hmC	5-hydroxymethylcytosine
8-OHdG	8-hydroxy-2′-deoxyguanosine
ABCG2	ATP Binding Cassette Subfamily G Member 2
ADRCs	Adipose-derived Regenerative Cells
ADSC	Adipose-Derived Stem Cell
AFG	Autologous Fat Grafting
Akt	Protein kinase B
AMH	Anti-Müllerian Hormone
ANP	Atrial Natriuretic Peptide
ASC	Adipose Stem Cell (often used interchangeably with ADSC)
ASs	Adipose-Derived Stem Cell-based Spheroids
ATP	Adenosine Triphosphate
BAX	Bcl-2 Associated X protein
Bcl-2	B-cell lymphoma 2
BCNI	Bilateral Cavernous Nerve Crush Injury
BDNF	Brain-Derived Neurotrophic Factor
bFGF	basic Fibroblast Growth Factor (also FGF-2)
BMI	Body Mass Index
BMSC	Bone Marrow-derived Mesenchymal Stem Cell
BNP	Brain Natriuretic Peptide
CBMSCs	Human Umbilical Cord Blood-derived Mesenchymal Stem Cells
CCSM	Corpus Cavernosum Smooth Muscle
CCSMCs	Corpus Cavernosum Smooth Muscle Cells
CD	Cluster of Differentiation
cGMP	cyclic Guanosine Monophosphate
CIH	Chronic Intermittent Hypoxia
CM	Conditioned Medium
CNI	Cavernous Nerve Injury
CNs	Cavernous Nerves
COX IV	Cytochrome c Oxidase subunit IV
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeats
CT	Computed Tomography
CXCL12	C-X-C Motif Chemokine Ligand 12 (also SDF-1)
CXCL5	C-X-C Motif Chemokine Ligand 5
CXCR4	C-X-C Motif Chemokine Receptor 4
ΔICP	Change in Intracavernosal Pressure
DM	Diabetes Mellitus
DMED	Diabetes-related Erectile Dysfunction
DUXAP10	Double Homeobox A Pseudogene 10
E2	Estradiol
ED	Erectile Dysfunction
EDV	End Diastolic Velocity
EF	Erectile Function
EGF-EGFR	Epidermal Growth Factor - Epidermal Growth Factor Receptor
EHS	Erection Hardness Score
ELISA	Enzyme-Linked Immunosorbent Assay
eNOS	endothelial Nitric Oxide Synthase
EPO	Erythropoietin
ER	Endoplasmic Reticulum
ERK	Extracellular Signal-Regulated Kinase
FAs	Free Adipose-Derived Stem Cells
FGF	Fibroblast Growth Factor
FGF-2	Fibroblast Growth Factor 2 (also bFGF)
FOXO1	Forkhead Box O1
FSH	Follicle-Stimulating Hormone
FSFI	Female Sexual Function Index
GDNF	Glial Cell Line-Derived Neurotrophic Factor
GelMA	Methacrylate Gelatin
GFAP	Glial Fibrillary Acidic Protein
GPX4	Glutathione Peroxidase 4
GSH	Glutathione
GTP	Guanosine Triphosphate
H_2O_2	Hydrogen Peroxide

hADSCs	Human Adipose-Derived Stem Cells
HbA1c	Hemoglobin A1c/Glycated Hemoglobin
HGF	Hepatocyte Growth Factor
HIF-1α	Hypoxia-Inducible Factor 1-alpha
HLA	Human Leukocyte Antigen
hSlo	human large conductance calcium-activated potassium channel gene
HSP70	Heat Shock Protein 70
HUVECs	Human Umbilical Vein Endothelial Cells
ICI	Intra-cavernosal injection
ICP	Intracavernosal Pressure
IGF-1	Insulin-like Growth Factor 1
IIEF	International Index of Erectile Function
IIEF-EF	International Index of Erectile Function-Erectile Function score
IL-10	Interleukin-10
IL-1RA	Interleukin-1 Receptor Antagonist
IL-1β	Interleukin-1beta
IL-4	Interleukin-4
IL-6	Interleukin-6
iMSC	induced pluripotent stem cell-derived mesenchymal stem cell
iNOS	inducible Nitric Oxide Synthase
KEGG	Kyoto Encyclopedia of Genes and Genomes
L-ADSCs	Lipopolysaccharide-preconditioned allogeneic Adipose-Derived Stem Cells
LC3I/II	Microtubule-associated protein 1 A/1B-light chain 3 I/II
LDH	Lactate Dehydrogenase
LIF	Leukemia Inhibitory Factor
LIN28	Lin-28 Homolog A/B
LIPUS	Low-Intensity Pulsed Ultrasound
MAP	Mean Arterial Pressure
MAPK	Mitogen-Activated Protein Kinase (also MAP kinase)
MCID	Minimal Clinically Important Difference
MDA	Malondialdehyde
MICP	Maximal Intracavernosal Pressure
miRNAs	microRNAs
MMP-1/3	Matrix Metalloproteinase-1/3
MPG	Major Pelvic Ganglion
mRNA	messenger Ribonucleic Acid
MSC	Mesenchymal Stem Cell
MSC-EVs	Mesenchymal Stem Cell-derived Extracellular Vesicles
MTs	Microtissues
NF-H	Neurofilament-H
NGF	Nerve Growth Factor
NK cells	Natural Killer cells
nNOS	neuronal Nitric Oxide Synthase
NO	Nitric Oxide
NOD	Nucleotide-Oligomerization Domain
NOS	Nitric Oxide Synthase
NOX1/4	NADPH Oxidase 1/4
Nrf2	Nuclear factor erythroid 2-related factor 2
NrCAM	Neuronal Cell Adhesion Molecule
NT-3/4	Neurotrophin-3/4
OCT4	Octamer-binding transcription factor 4
p-cofilin	phosphorylated cofilin
p-eNOS	phosphorylated endothelial Nitric Oxide Synthase
p-LIMK2	phosphorylated LIM kinase 2
PARP	Poly(ADP-ribose) Polymerase
PCNA	Proliferating Cell Nuclear Antigen
PDE5	Phosphodiesterase type 5
PDGF	Platelet-Derived Growth Factor
PDGFR	Platelet-Derived Growth Factor Receptor
PDGFRA	Platelet-Derived Growth Factor Receptor Alpha
PDNPs	Polydopamine Nanoparticles
PDNPs-PELA	Polydopamine Nanoparticles - Poly(ethylene glycol)-poly(ε-caprolactone-co-lactide) hydrogel
PEDF	Pigment Epithelium-Derived Factor
PECAM-1	Platelet Endothelial Cell Adhesion Molecule-1 (also CD31)
PELA	Poly(ethylene glycol)-poly(ε-caprolactone-co-lactide)
PFKFB3	6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3
PI3K/Akt	Phosphoinositide 3-kinase/Protein kinase B
PKG	Protein Kinase G (cGMP-dependent protein kinase)
PL	Platelet Lysate
PLP	Platelet Lysate Plasma
PPI	Periprostatic Implantation
PRDX2	Peroxiredoxin 2
PRDX2-ADSCs	Adipose-Derived Stem Cells overexpressing Peroxiredoxin 2
pro-ANP	pro-Atrial Natriuretic Peptide
PRP	Platelet-Rich Plasma
PSV	Peak Systolic Velocity
PTEN	Phosphatase and Tensin homolog
RANKL-RANK	Receptor Activator of Nuclear factor Kappa-B Ligand - Receptor Activator of Nuclear factor Kappa-B
RASSF5	Ras Association Domain Family Member 5
rBDNF	recombinant Brain-Derived Neurotrophic Factor
RECA-1	Rat Endothelial Cell Antigen-1
RGD	Arginylglycylaspartic acid
RhoA/Rho kinase	Ras homolog family member A/Rho-associated protein kinase
RNA-seq	RNA sequencing
ROCK	Rho-associated coiled-coil containing protein kinase (part of RhoA/Rho kinase pathway)
ROS	Reactive Oxygen Species
RXFP1	Relaxin Family Peptide Receptor 1
S100β	S100 calcium-binding protein B
SA-β-gal	Senescence-Associated β-galactosidase
SASP	Senescence-Associated Secretory Phenotype
SCs	Schwann Cells
SDF-1	Stromal Cell-Derived Factor 1 (also CXCL12)
SEP3	Sexual Encounter Profile (question 3)
sGC	soluble Guanylate Cyclase
SHIM	Sexual Health Inventory for Men (also IIEF-5)
siRNA	small interfering RNA
SIRT1	Sirtuin 1
SMA	Smooth Muscle Actin
SMURF1	Smad Ubiquitin Regulatory Factor 1
SOD	Superoxide Dismutase
SOX2	SRY-Box Transcription Factor 2
SSEA-1	Stage-Specific Embryonic Antigen-1
STAT3	Signal Transducer and Activator of Transcription 3
STZ	Streptozotocin
SVF	Stromal Vascular Fraction
SWT	Shockwave Therapy
T2DM	Type 2 Diabetes Mellitus
Tβ4	Thymosin beta-4
tBHQ	tert-Butylhydroquinone
TGF-β	Transforming Growth Factor-beta
TLR4	Toll-Like Receptor 4
TNF-α	Tumor Necrosis Factor-alpha
TSG-6	TNF-stimulated gene 6
US$	United States Dollar
VEGF	Vascular Endothelial Growth Factor
vWF	von Willebrand Factor
ZAP70	Zeta-chain Associated Protein kinase 70
α-SMA	alpha-Smooth Muscle Actin

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AG, FS, MMH, MV, and ZM wrote the article and prepared the tables/figures; FS and SG designed and revised the article. All the authors studied and approved the final manuscript. The authors declare that all data were generated in-house and that no paper mill was used.

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