

# Wharton's Jelly Stem Cell Albumin-Based Scaffold Significantly Improves Erectile Function in Diabetic Patients: A Randomized Placebo-Controlled Trial

Ignacio Eduardo-Vega Tepos\*

Mexican Institute of Social Security, Mexico

**Corresponding Author:** Ignacio Eduardo-Vega Tepos, Mexican Institute of Social Security, Mexico.

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## Abstract

**Background:** Erectile dysfunction (ED) affects 322 million men globally, with diabetes being a key modifiable risk factor. Stem cell therapy offers regenerative potential but faces clinical translation challenges including poor cell retention and limited human trial data. Albumin-based cellular scaffolds may enhance therapeutic efficacy by improving stem cell delivery and microenvironment support.

**Objective:** To evaluate the safety and efficacy of intracavernosal Wharton's jelly-derived mesenchymal stem cells (MSCs) with an albumin scaffold in diabetic ED patients refractory to oral therapy.

**Methods:** A randomized, double-blind, placebo-controlled trial was conducted in two stages:

- Stage 1 (n=18): Patients received either placebo (saline), MSCs alone ( $125 \times 10^6$  cells), or MSCs + albumin scaffold. Injections targeted the left corpus cavernosum using a 29G needle, with penile clamping for 10 minutes.
- Stage 2 (n=7): Non-responders from Phase 1 (n=6) and one high-dose case ( $325 \times 10^6$  MSCs + scaffold) received combination therapy.

**Primary Outcomes:** International Index of Erectile Function-5 (IIEF-5) and penile Doppler parameters (peak systolic velocity, end-diastolic velocity) at 6 months. Histological analysis was performed in one patient requiring penile prosthesis.

## Results:

- **Stage 1:** The MSC + scaffold group showed significant IIEF-5 improvement ( $p^*=0.0259$ ) and enhanced cavernous blood flow ( $p^*=0.0107$ ). No significant changes occurred in placebo ( $p=0.356$ ) or MSC-alone groups ( $p=0.07$ ).
- **Stage 2:** 78% (5/6) of cross-over patients achieved significant IIEF-5 improvement ( $p^*=0.04$ ). Histology revealed localized neovascularization at injection sites.

**Safety:** No serious adverse events occurred.

**Conclusions:** Albumin-scaffolded MSC therapy significantly improves erectile function and hemodynamics in diabetic ED, while monotherapy lacks efficacy. Therapeutic benefits wane over time but are restored with re-administration. Localized angiogenesis at injection sites suggests multifocal delivery may optimize outcomes. These results support albumin scaffolds as a promising strategy for regenerative urology, warranting phase III trials to standardize protocols and assess long-term durability.

## Keywords

Erectile Dysfunction, Stem Cell Therapy, Albumin Scaffold, Diabetes Mellitus, Regenerative Urology, Intracavernosal Injection

## Introduction

Erectile dysfunction incidence has increased in recent years, with projections indicating 322 million men affected globally this year. While modifiable risk factors exist including obesity, metabolic syndrome, diabetes, and hypertension, age remains a primary determinant with prevalence rising from approximately 10% in men under 40 years to nearly 30% at age 50, exceeding 50% in men over 60 (1, 2). Age related erectile dysfunction involves increased cavernosal vasoconstriction due to heightened adrenergic tone, primarily from nitric oxide synthase-releasing neuron inactivation (3). This impairs nitric oxide release, reducing vasodilation while elevating reactive oxygen species that cause tissue damage (4, 5).

Erection requires integrated vascular, neurological, hormonal, and psychological functions with intact neural signaling, where parasympathetic nitric oxide release is essential for vasodilation (6, 7). Reduced nitric oxide levels induce structural penile changes that may be temporary (as in neuropraxia from cavernous nerve injury due to radiation, crush trauma, or surgical coagulation/stretching) or permanent (as in axonotmesis from ischemia) (8, 9). Cavernous body denervation promotes smooth muscle and collagen changes leading to fibrosis (10).

Stem cells offer therapeutic potential through unlimited proliferation, multi-differentiation capacity, perpetual self-renewal, and pro-angiogenic, anti-fibrotic, and anti-apoptotic properties (11). Stem cells are classified as totipotent (zygote/morula-derived, capable of forming fully differentiated organisms), pluripotent (derived from embryonic layers: ectoderm, mesoderm, endoderm), or multipotent (adult stem cells isolated from developed organs that differentiate within their germ layer) (12). Current applications and innovations include their use as drug delivery vehicles leveraging natural tumor-tropic migration, packaging anti-cancer agents to enhance tumor and metastasis accessibility while reducing systemic toxicity, and deployment in immuno-oncology, tissue repair, and hereditary diseases. Genetic editing applications include CCR5-modified hematopoietic stem cells for HIV blockade. Notably, microgravity research aboard the International Space Station demonstrates that 3D culture structures better mimic natural in vivo growth than terrestrial 2D methods, with stress-responsive secretome/proteome profiles under microgravity contrasting with Earth-based cellular senescence, where stem cells are depleted after limited replication cycles (13, 14).

Stem cell therapy is proposed for erectile dysfunction in chronic diseases like diabetes (15). Placental-derived cells—capable of differentiating into cavernous neurons, muscle, and endothelial cells—offer noninvasive access and clinical simplicity. Despite being allografts, placental stem cells express MHC-I but lack MHC-II and B7-1/B7-2 T-cell co-stimulatory molecules (16-18).

Their mechanisms of action primarily involve paracrine signaling through exosome secretion containing microRNAs, growth factors, cytokines, and chemokines that activate endogenous stem cells. These exosomes exert mitogenic and reparative effects by reducing scarring, apoptosis, and inflammation while promoting angiogenesis. They additionally downregulate fibrotic TGF- $\beta$ 1 while upregulating nNOS and eNOS expression. Collectively termed the secretome, these components include

growth factors such as VEGF and NGF (nerve growth factor) (19-23).

Clinical protocol development for erectile dysfunction faces multifactorial challenges. Wharton's jelly-derived mesenchymal stem cells show preclinical efficacy through secretory, immunomodulatory, and angiogenic capacities. However, human trials remain limited with fewer than 10 published studies by 2023, typically involving fewer than 20 patients per cohort. This scarcity stems from high operational costs where specialized infrastructure for viable cell isolation, characterization, and cryopreservation increases expenses by 40-60% compared to conventional pharmacotherapies; recruitment difficulties due to social stigma and etiological heterogeneity including diabetes and pelvic surgery; non-patentability as unmodified biological products lack novelty for patent protection, disincentivizing phase III private investment; and standardization gaps with no consensus on optimal dosing (e.g.,  $1 \times 10^6$  versus  $5 \times 10^6$  cells), administration routes (intracavernosal versus intravenous), or dosing intervals. Consequently, most studies are short-term phase I/II safety trials without comparative efficacy or mechanistic data (24).

A recent double-blind, randomized, placebo-controlled trial evaluated the inefficacy of isolated stem cells supports that severe erectile dysfunction requires combinatorial approaches using cells with bioactive scaffolds. Nevertheless, protocol heterogeneity in dosing and cell sources, along with absent predictive biomarkers, limits generalizability, warranting phase III multicenter trials with standardized scaffolds (25).

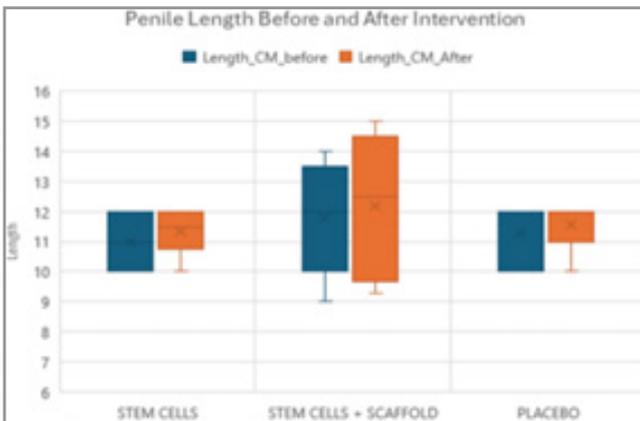
## Methodology

- Study Design:** A randomized, double-blind, placebo-controlled clinical trial was conducted in two sequential stages:
  - Stage 1:** Initial intervention comparing three parallel groups.
  - Stage 2:** Cross-over intervention for non-responders from Stage 1. Approval was obtained from the Ethics Committee of Corporativo de Hospitales SA de C.V., Mexico.
- Participants Inclusion Criteria:** Adult males with diabetes mellitus and erectile dysfunction refractory to oral pharmacotherapy (phosphodiesterase-5 inhibitors). Confirmed diagnosis via penile Doppler ultrasound. Sample Size:
  - Stage 1:** 18 patients randomized into three groups.
  - Stage 2:** 6 non-responders from Phase 1 + 1 additional case (total n=7).
- Interventions:** Stem Cell Source: Allogeneic mesenchymal stem cells (MSCs) derived from Wharton's jelly (placenta).
- Formulations:** Placebo: 3 mL saline solution.
- Stem Cell Monotherapy:** 1 mL MSCs ( $125 \times 10^6$  cells/mL) + 2 mL saline (total 3 mL). Combination Therapy: 1 mL MSCs + 2 mL albumin-based cellular scaffold (3 mL total). High-Dose Case:  $325 \times 10^6$  MSCs + albumin scaffold (administered separately).
- Administration Protocol:** Patients in supine position. Intracavernosal injection using insulin needle (29G) into the left lateral corpus cavernosum (base of penis). Penile base clamping for 10 minutes post-injection to retain therapy. Identical procedure for placebo group.

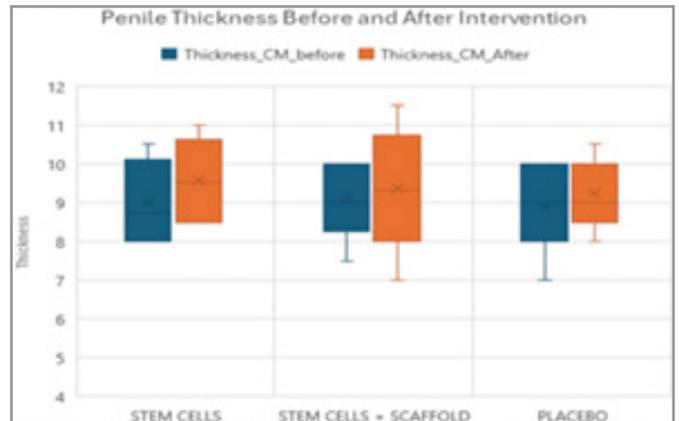


**Figure 1:** Intracavernous administration into the left corpus cavernosum

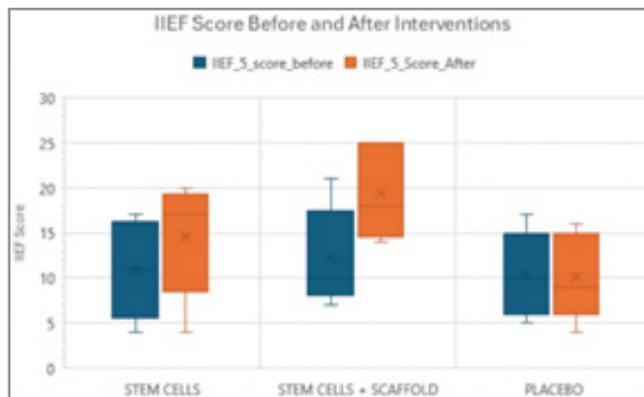
- **Follow-up:** Penile anthropometric measurements (length/circumference). Penile Doppler with alprostadil (10 mcg). IIEF-5 (baseline and 6 months). Adverse event monitoring.
- **Follow-up duration:** 14 months.



**Graph 1.**



**Graph 2.**



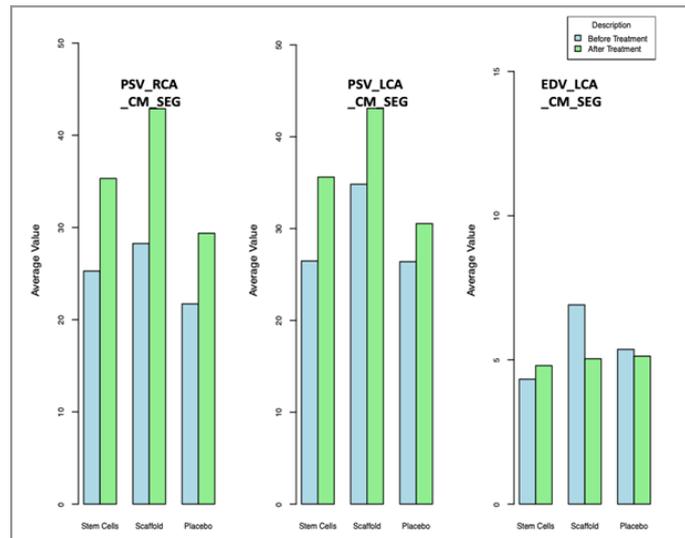
**Graph 3.**

## Results

Adverse Events were assessed, and no severe adverse effects or significant pain reported. One patient had a slight penile deviation and another had a history of prostate cancer with no adverse reactions. The IIEF-5 questionnaire (at baseline and at 6

months) and a penile color Doppler ultrasound were performed before treatment and at 6 months of treatment:

- Peak systolic velocity.
- End-diastolic velocity.



Graph 4.

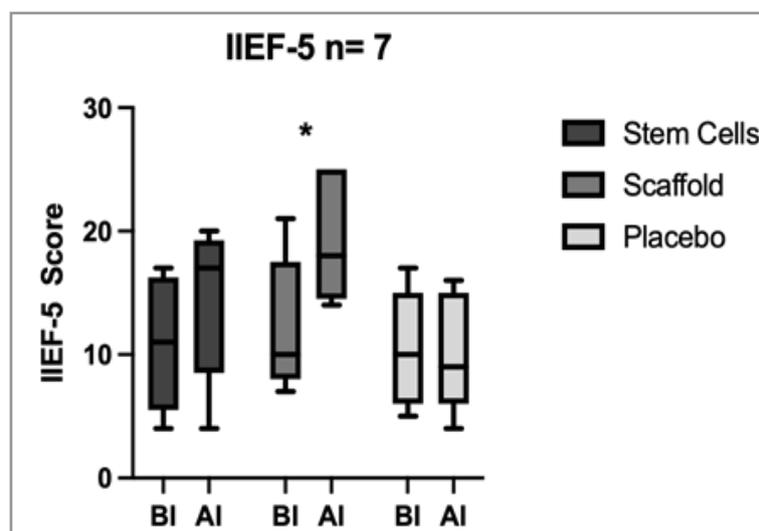
## Results at 6 months

**Stage 1: Stem Cells + Albumin Scaffold Group:** A statistically significant improvement in IIEF-5 scores (International Index of Erectile Function) was observed after the intervention ( $p = 0.0259$ ).

**Placebo Group:** No significant change in IIEF-5 scores ( $p = 0.356$ ). **Stem Cells Group:** non-significant improvement in IIEF-5 scores was observed ( $p = 0.07$ ). A significant increase in cavernous blood flow (penile Doppler) was observed in patients who received stem cells plus albumin scaffold. However, the Placebo Group and the Stem Cells Alone Group showed no significant improvements in IIEF-5 scores or hemodynamic parameters.

**Stage 2 of the study (N=6):** After confirming the effectiveness of stem cells with an albumin cellular scaffold, 6 patients from the initial placebo and stem cells alone groups who did not respond to the initial treatment and voluntarily continued into the study's second stage were included. Only IIEF-5 analysis was possible; Doppler ultrasound could not be performed due to a severe nationwide shortage of alprostadil that made the medication unobtainable. All received mesenchymal stem cells derived from placenta + albumin scaffold.

**Results at 6 months post-treatment:** 78% (5/6 patients) Significant improvement in IIEF-5. Responses comparable to those observed in the initial combined group (Stage 1).

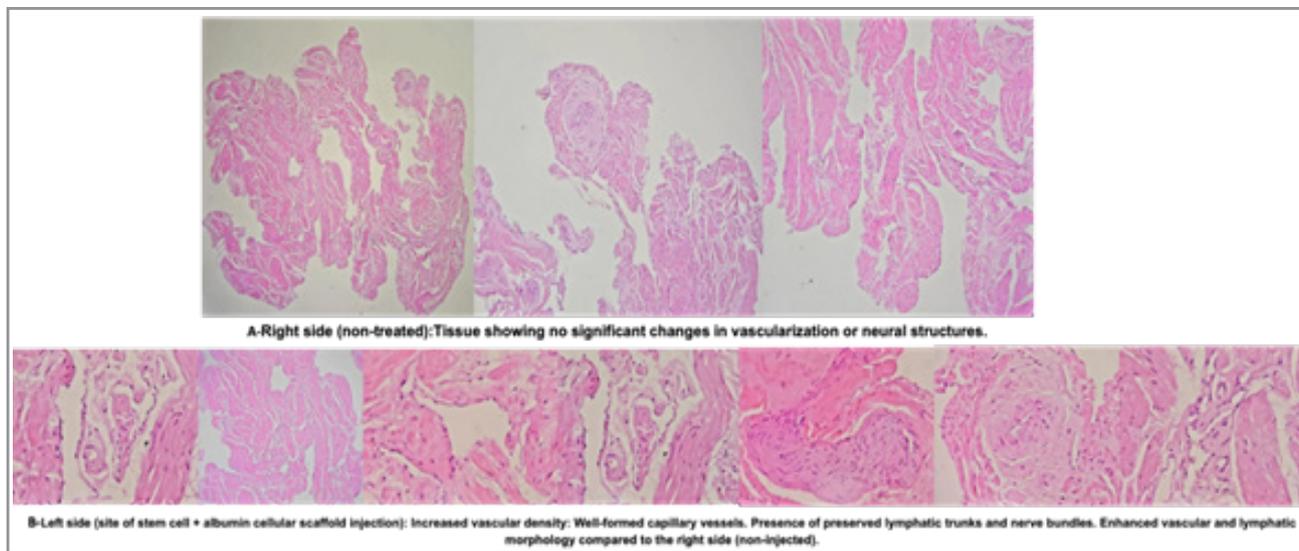


Graph 5: BI-Before Treatment. AI-After Treatment

And an Additional Case (n=1) was included with an increased number of stem cells.

- **Intervention:** The patient was treated with 325 million placenta-derived stem cells + albumin scaffold (intracavernosal injection).

- **6-Month Follow-up:** After the 8 months, a progressive reduction in the therapeutic effect was observed: Deterioration in IIEF-5 score and erectile function following an initial improvement.
- **Patient decision:** Penile prosthesis implantation. A cavernous body biopsy was performed prior to implantation.



**Figure 2:** Biopsy of both Corpora Cavernosa

Stage 2 of the treatment: Stem cells with an albumin scaffold continue to demonstrate statistically significant effectiveness ( $p=0.04$ ). Notably, one patient with erectile dysfunction secondary to pancreatectomy for a pancreatic abscess showed a moderate response, suggesting potential involvement of other pathways in erectile dysfunction, such as hormonal factors. Additionally, the cavernous body biopsy finding—where improvement was localized solely to the injection site in the biopsied patient—is highly significant. This observation leads us to reconsider using a more uniform distribution across multiple injection sites in the cavernous bodies for future treatments, which could potentially yield more effective results.

### Discussion

Cellular scaffolds can play a significant role in tissue formation and healing by attracting circulating cells to adhere to their surface, stimulating proliferation and extracellular matrix secretion. Meanwhile, the scaffold biomaterial's slow degradation creates space for new tissue formation (26). Consequently, scaffold-based materials can mimic an extracellular matrix, showing greater promise in tissue engineering as they provide a functional environment for appropriate cell-cell interactions, stabilize forming tissues, and serve as reservoirs for nutrients and growth factors (27). In vivo, albumin-based scaffolds proved biodegradable (approximately 50% degradation after 3 weeks) and induced a mild inflammatory response. Multiple cell types have been successfully cultured in vitro on albumin structures, indicating that the scaffold promotes cellular adhesion and proliferation. Further research includes a 3D cardiac patch fabricated from albumin fibers (28).

Mesenchymal stem cells seeded onto scaffolds exhibited enhanced proliferation and differentiation (29). This is attributed to albumin coatings improving biological and immunological compatibility, tissue formation, corrosion resistance, and conferring antibacterial and anticoagulant properties to materials (30). Albumin is a potent cellular adhesive in structures like human bone allografts and was among the first proteins used as a coating to prevent surface-induced platelet activation (31, 32).

Therefore, albumin-based cellular scaffolds represent an innovative strategy to optimize stem cell therapy efficacy. Their mechanism relies on modifying the physicochemical properties of the support material through surface coating with a protein layer, resulting in increased hydrophilicity. Albumin's hydrophilic domains reduce the water-surface contact angle, converting hydrophobic materials (e.g., synthetic polymers) into biocompatible surfaces. This hydrophilicity promotes directed cellular adhesion—stem cell integrins interact with albumin, potentially enhancing post-transplant cell survival. Additionally, the albumin layer prevents adverse biological responses by acting as a barrier that blocks nonspecific adsorption of plasma proteins (e.g., fibrinogen) and platelet activation, thereby mitigating acute inflammatory responses.

In applications such as cavernous tissue (erectile dysfunction) or myocardial regeneration, this scaffolding addresses key limitations of free stem cells. It prevents cell washout by retaining cells at the implantation site within its 3D matrix, contrasting with conventional injections. Furthermore, it provides protection against mechanical stress by cushioning shear forces during intracavernosal or intracardiac administration (33).

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Inhibition of cellular adhesion: Reducing adherent platelet numbers and their surface activation (34, 35).

Multiple *in vitro* and *in vivo* studies demonstrate that despite anti-adhesive properties on plastic surfaces, albumin coating promotes mammalian cell growth and tissue formation (36). Albumin-coated grafts implanted *in vivo* in bone defects showed improved graft integration (37). While recruiting cells like mesenchymal stem cells to the defect region favors tissue formation, the question arises whether inflammatory cells are also attracted by the albumin layer (38). Consequently, Mijiritsky et al. investigated monocyte-stem cell interactions in co-cultures on albumin-coated bone grafts and bovine xenograft granules. Key observations included monocytes degrading uncoated bovine bone granules, while albumin coating protected grafts from degradation. The albumin-coated group also showed significantly reduced reactive oxygen species (ROS) and reactive nitrogen species (RNS) levels. Furthermore, mitochondrial energy metabolism gene expression suggested albumin coating alleviates gene expression under both inflamed and non-inflamed conditions, resulting in fewer differentially expressed genes versus cells seeded on uncoated xenografts. Cytokine analysis revealed elevated levels of tissue-repair cytokines and anti-inflammatory cytokines PGE-2 and IL-10 in stem cell-monocyte cultures on albumin-coated grafts compared to uncoated xenografts. This study indicates albumin, beyond its aforementioned properties, may possess immunomodulatory functions crucial for tissue healing and regeneration (39).

Beyond extensive publications on albumin-coated bone allografts, bone is not the sole regenerative medicine tissue combined with albumin. For example, absorbable polyfilament sutures coated with fibronectin, poly-L-lysine, and albumin were seeded with mesenchymal stem cells. After 48 hours, albumin-coated sutures had the highest cell count *in vitro*. Following implantation into the triceps surae muscle, cells detached from the albumin-coated surface and migrated toward injured tissue, demonstrating albumin-coated biomaterials' potential for soft tissue regeneration (40).

Albumin, a globular protein, is significant due to its biocompatibility, biodegradability, non-immunogenicity, non-toxicity, water solubility, cost-effectiveness, and tumor-detection capability (41). Its binding property is among its most important clinical functions, enabling interactions with fatty acids, bilirubin, metal ions, and drugs like penicillins, sulfonamides, indole compounds, benzodiazepines, etc. (42).

It could be considered the most universal protein in biomedical and therapeutic fields—a well-characterized, readily accessible protein with low production costs and excellent regenerative effects. In its native form, albumin serves as a passivating protein for inert materials via its antithrombotic, anti-inflammatory, and antibacterial properties. Conversely, structural modifications or combinations with other biomaterials enhance cellular binding, tissue formation, and healing. We believe patients can benefit from incorporating albumin-based biomaterials and therapies into regenerative medicine strategies, achieving superior clinical outcomes with minimal side effects. This represents an ongoing advancement, as albumin could be utilized in novel regenerative medicine products, leveraging the extensive scientific evidence

supporting its regenerative properties and exceptional biocompatibility. As regenerative medicine matures and innovations transition from bench to bedside, the humble albumin protein gains increasing recognition (43).

## Conclusion

Despite emerging interest in stem cell therapy for erectile dysfunction treatment, clinical evidence in humans remains highly limited. To date, published studies are scarce and characterized by small sample sizes, with fewer than 130 patients total included in clinical trials evaluating this intervention. These studies have primarily focused on safety and feasibility parameters, such as treatment tolerance, absence of serious adverse effects, and technical feasibility of cell administration.

However, participant scarcity and the lack of robust control groups represent critical methodological limitations, as they preclude definitive conclusions regarding therapeutic efficacy. Furthermore, most studies lack long-term follow-up, hindering assessment of treatment effect durability. This gap is particularly relevant given that erectile dysfunction is frequently associated with chronic conditions (e.g., diabetes or cardiovascular diseases), where persistence of clinical improvement is a determining factor. While preliminary results are promising, stem cell therapy for this indication remains exploratory. Larger clinical trials with expanded cohorts, randomized designs, and standardized endpoints (such as validated erectile function or quality-of-life scales) are required to confirm translational potential and mitigate biases associated with small samples.

Results from our placebo-controlled study suggest that although stem cell monotherapy shows no statistically significant efficacy, its effectiveness improves when combined with a cellular scaffold. However, a progressive decline in therapeutic effects over time was observed, whereas a second application maintained benefits. Critical unknowns persist, including optimal dosing and mechanisms underlying efficacy loss—potentially linked to unsustainable stem cell retention or progression of diabetes mellitus. These findings highlight the need for further research to optimize this therapeutic strategy.

We evaluated a novel hypothesis by incorporating a cellular scaffold to potentially enhance stem cell effectiveness, while also analyzing durability and the need for repeated dosing. Our data support the adjuvant role of cellular scaffolds in improving stem cell retention and functionality.

The progressive efficacy loss may relate to unsustainable cellular microenvironments or active diabetes mellitus pathogenesis—factors requiring further investigation. This study underscores the critical importance of placebo-controlled designs for validating emerging interventions.

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