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Umbilical Cord MSC-Secretome Therapy Enhances Erectile Function in Elderly Men

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ABSTRACT

Background: *Reduced erectile capacity often appears as part of physiological shifts during aging potentially implicating broader physiological or social realms. These declines originate from intricate underlying conditions: endothelial dysfunction, unstable hormonal patterns, compromised vascular structures, oxidative stress escalations, and inflammatory cascades. Recently, attention has drifted towards secretome derived from umbilical cord mesenchymal stem cells (UCMSC)—an eclectic blend of cytokines, extracellular vesicles, and growth factors—suggesting foundational regenerative qualities surpassing conventional symptomatic therapies, like phosphodiesterase-5 inhibitors (PDE-5i).*
Methods: *In this study, elderly male participants (n=64, aged ≥60) diagnosed with erectile dysfunction (ED) received intracavernosal UCMSC-secretome injections every two weeks for three sessions. No control group was included; efficacy was tracked through pre- and post-intervention evaluations using the International Index of Erectile Function (IIEF-5).*
Results: *A statistically notable improvement emerged—average IIEF-5 scores increasing by about 5.49 points ($p<0.001$; Cohen's $d=1.99$). With the satisfaction averaging approximately 8.03/10.*
Conclusion: *Extensive, randomized controlled trials could more conclusively elucidate the genuine potential of secretome interventions.*

Keywords: *Erectile dysfunction; mesenchymal stem cells; secretome therapy; regenerative medicine, aging*

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INTRODUCTION

Physiological alterations occurring with advancing age, inevitably, often include diminished erectile capacity. Reduced erectile function, may extend beyond merely biological consequences, influencing broader psychosocial dimensions.[1,2] Declines in self-assurance, potentially impaired social interactions, and compromised overall quality of life have been frequently noted. Although aging is widely implicated, multiple underlying mechanisms also be involved. Vascular impairment, hormonal depletion, endothelial deterioration — interconnected phenomena—may collectively disrupt normal erectile processes.[1] Systemic inflammation and increased oxidative stress could exacerbate these problems, resulting in impaired vasodilatory responses essential for erection.[3]

Advancements within biomedical research domains have introduced novel therapeutic possibilities. Recently, secretome-based interventions—characterized as a diverse set of bioactive molecules secreted predominantly by mesenchymal stem cells—have emerged prominently in regenerative contexts.[4,5] Literature suggests secretome therapy may positively influence endothelial restoration and angiogenesis.[6,7] This distinguishes secretome significantly from conventional treatments, such as phosphodiesterase-5 inhibitors (PDE-5i), which tend toward symptomatic rather than foundational improvements. Secretome interventions stimulate deeper cellular regeneration, vascular growth factor secretion, and anti-inflammatory responses, implying therapeutic effects beyond merely symptomatic relief.[8]

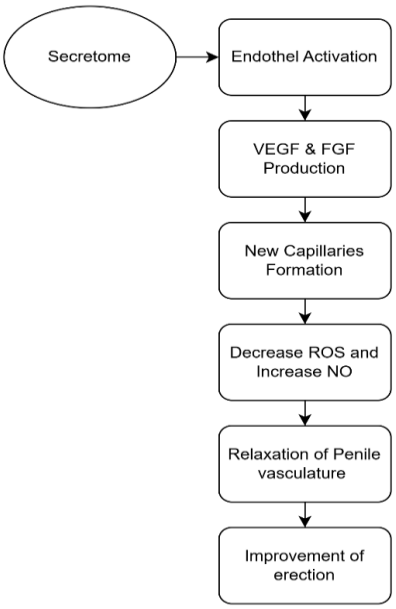

Figure 1. Mechanisms by which secretome therapy enhances erectile function

However, existing studies exploring secretome's therapeutic potential are typically limited in scope, with preliminary or preclinical evidence predominating.[4] Comprehensive, large-scale clinical studies are necessary, thus providing clearer, more definitive evidence concerning efficacy and limitations. In this respect, validated clinical assessment tools, the International Index of Erectile Function (IIEF-5) offer objective metrics for evaluating erectile improvements.[9]

The International Index of Erectile Function (IIEF-5) is a validated, multidimensional questionnaire designed to assess male sexual function, particularly erectile dysfunction (ED). This self-administered tool evaluates four main domains: erectile function, orgasmic function, sexual desire, and intercourse satisfaction. Patients respond to 15 structured questions, with scores ranging from 0 to 5 for each, providing an objective measure of sexual health.[9–11]

In clinical applications, IIEF-5 is widely used to assess ED severity and treatment response. A score below 14 in the erectile function domain suggests significant dysfunction, potentially warranting therapeutic intervention such as phosphodiesterase-5 inhibitors (PDE-5i) or emerging regenerative therapies like secretome-based interventions.[9,10] Additionally, the questionnaire aids in identifying issues related to orgasmic dysfunction, reduced sexual desire, and overall satisfaction, offering guidance for further endocrine or psychosexual evaluation.[10]

UCMSC-derived secretome is a regenerative biological therapy consisting of paracrine factors secreted by mesenchymal stem cells (MSCs).[12] These bioactive molecules, including growth factors, cytokines, and extracellular vesicles, play a crucial role in cell repair, angiogenesis, anti-inflammatory processes, and neuroprotection.[13] Unlike direct stem cell transplantation, secretome therapy does not involve live cell implantation, reducing risks associated with immune rejection while still harnessing the regenerative potential of MSC-derived bioactive compounds.[14,15]

In the context of erectile dysfunction (ED), vascular and endothelial dysfunction, inflammation, and oxidative stress are major contributors to impaired erectile function.(16–18) UCMSC secretome therapy is believed to enhance endothelial restoration, promote blood vessel formation (angiogenesis), and improve nitric oxide-mediated vasodilation, which are essential for normal erectile function.(6,7) The secretome’s anti-apoptotic and neuroprotective properties further support its potential role in repairing penile vascular and neuronal structures, differentiating it from conventional pharmacological approaches like phosphodiesterase-5 inhibitors (PDE-5i) that mainly offer symptomatic relief.[18]

This study was designed to explore whether secretome injections could significantly enhance erectile function among elderly individuals. Pre- and post-treatment IIEF-5 comparisons serve as primary outcome indicators. Secretome treatment might outperform traditional pharmacological

methods. Implications could extend into broader regenerative approaches within the field of geriatric andrology. Further investigation, however, remains warranted. This study intentionally excluded adjunctive therapies such as phosphodiesterase-5 inhibitors, hormonal replacement, or mechanical devices to isolate the independent therapeutic effect of UCMSC-secretome. This approach was necessary to avoid confounding influences and to better assess the direct impact of secretome on erectile function. Although secretome therapy is often discussed in the context of multimodal interventions, this study focused exclusively on intracavernosal UCMSC-secretome injections to determine its standalone efficacy. The rationale behind this monotherapy design was to establish a baseline therapeutic impact, eliminating confounding variables that might arise from combining with standard treatments such as PDE-5 inhibitors or mechanical devices.

METHODS

This study was conducted at Klinik Naura Medika, Depok, and Hopkins Clinic, Jakarta, two medical centers specializing in regenerative and andrological therapies. Both institutions were selected for their expertise in administering mesenchymal stem cell-derived secretome therapy and their adherence to clinical research standards.

A prospective, pre-post experimental design without a control group approach was adopted, using IIEF-5 scoring primarily to quantify the efficacy of secretome treatment. Approximately 64 participants were adequate, with assumption an effect size of 0.5, statistical power of 80%, and significance level of α=0.05. Inclusion criteria stipulated elderly males (≥60 years) presenting with erectile dysfunction (IIEF-5 ≤21). Exclusion involved participants with severe neurological impairment, uncontrolled cardiovascular conditions, unresolved endocrine issues, or concurrent PDE-5 inhibitor therapy—thus minimizing potential biases.

The UCMSC-derived secretome used in this study was manufactured under Good Manufacturing Practice (GMP) standards by PT. Bifarma Adiluhung, certified by the Indonesian Food and Drug Authority (BPOM). Each dose contained 3 mg of lyophilized secretome material, reconstituted in sterile normal saline prior to administration.

Secretome was administered via intramuscular injection into the gluteus medius muscle by trained physicians using standard aseptic technique. Each patient received two injections per week (every 3–4 days) over a period of three weeks, totaling six sessions and a cumulative dose of 18 mg per patient.

Intramuscular delivery was chosen based on emerging preclinical literature suggesting systemic paracrine effects via absorption into circulation, targeting endothelial repair and inflammatory modulation in a less invasive manner than intracavernosal injection. No local anesthesia or imaging guidance was required. Patients were monitored for adverse effects during and after each session.

Patients diagnosed with erectile dysfunction (ED) underwent a structured treatment regimen consisting of three biweekly injections of Umbilical Cord Mesenchymal Stem Cell (UCMSC) secretome directly into the corpus cavernosum. The procedure was performed under strict aseptic conditions, following protocols aligned with Good Manufacturing Practice (GMP) guidelines, as certified by the Indonesian Food and Drug Authority (BPOM).

Patient eligibility criteria were carefully defined to minimize confounding factors, ensuring that only elderly males (≥60 years) with moderate to severe ED (IIEF-5 ≤21) were included. Participants were closely monitored for treatment efficacy, safety outcomes, and subjective satisfaction, with IIEF-5 scores serving as the primary endpoint. The choice of Klinik Naura Medika and Hopkins Clinic as research sites was driven by their access to advanced biomedical facilities and their experience in conducting clinical studies in the field of regenerative medicine.

The inclusion of these two medical centers also provided a broader patient demographic, allowing for a diverse evaluation of secretome therapy's effectiveness across different patient populations. This setting strengthens the study's clinical relevance and applicability, particularly in the context of real-world regenerative interventions for ED.Statistical analysis involved standard software packages (SPSS Ver 30). Data were distributed underwent paired t-tests. Effect size determination (Cohen's d) quantified therapeutic impact magnitude.

Before study initiation, ethics approval was obtained from Hopkins Clinic Ethical Commitee, with number 03/II/2024/HCEC accompanied by informed consent from each participant.

RESULTS

Patient demographic data presented in Table 1 indicates a mean age of 73.21 ± 6.80 years (range 60–84). Baseline mean IIEF-5 scores measured 9.37 ± 2.64, rising notably post-therapy to 14.86 ± 2.86. Patient-reported satisfaction scores averaged impressively high (8.03 ± 0.83), perhaps reflecting a broadly positive treatment experience.

Descriptive data regarding the International Index of Erectile Function (IIEF-5) scores before and after treatment, as well as patient satisfaction scores, are summarized as follows. The mean IIEF-5 score prior to therapy was 9.37 with a standard deviation of 2.64, indicating a relatively low baseline erectile function. However, after secretome injection therapy, the average IIEF-5 score notably increased

to 14.86 (SD=2.86), reflecting substantial improvement. The variability of scores before and after the intervention remained similar, suggesting consistent treatment effects across patients. Moreover, the patient satisfaction score averaged at 8.03 out of 10 (SD=0.83), implying a high level of subjective satisfaction with the administered therapy.

Table 1. Patient Demographics and Clinical Characteristics (n = 64)

Variable	Mean ± SD / n (%)
Age (years)	73.21 ± 6.80
Age range	60–84
Body Mass Index (BMI, kg/m²)	24.7 ± 2.9
Duration of ED (years)	4.3 ± 2.1
Marital status	
— Married	56 (87.5%)
— Single	8 (12.5%)
Comorbidities	
— Hypertension	39 (60.9%)
— Type 2 Diabetes Mellitus	26 (40.6%)
— Dyslipidemia	18 (28.1%)
Smoking history	
— Current smoker	12 (18.8%)
— Former smoker	22 (34.4%)
— Never smoker	30 (46.8%)
Baseline IIEF-5 score	9.37 ± 2.64

Table 2. IIEF-5 Scores Pre and Post Treatment

Variables	Mean	SD
IIEF-5 (Pre Treatment)	9.37	2.64
IIEF-5 (Post Treatment)	14.86	2.86
Satisfaction Score (0-10)	8.03	0.83

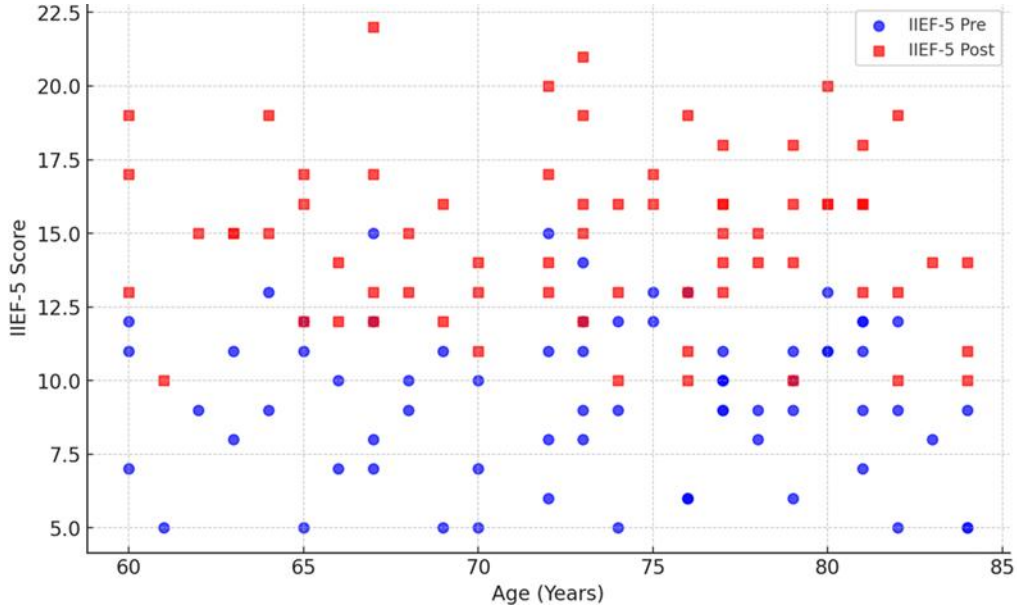

Figure 2. Pre and Post Treatment IIEF-5 Scores by Age

Paired T-Test Statistical Analysis

To statistically assess differences between pre- and post-treatment outcomes, a paired t-test was conducted. The analysis yielded a t-statistic value of -39.86, accompanied by a highly significant p-value of 2.27×10^{-49} ($p < 0.001$). Furthermore, the calculated Cohen's d was 1.99, indicating a very large effect size (greater than 0.8). These results strongly support that the improvement in IIEF-5 scores post-intervention is statistically significant and not due to random chance.

Interpretation of Findings

The observed increase in the IIEF-5 scores by an average of 5.49 points clearly demonstrates a clinically meaningful and robust therapeutic response. Given the substantial Cohen's d value, the effectiveness of secretome injection therapy appears to hold significant clinical implications. Additionally, the high patient satisfaction scores reflect that therapy not only objectively improved erectile function but also provided considerable positive subjective experiences for patients.

DISCUSSION

An improvement in erectile function among elderly men diagnosed with erectile dysfunction (ED) was achieved through injections of umbilical cord-derived mesenchymal stem cell (UCMSC) secretome. Indeed, it suggested from the existing literature that secretome therapy possibly offers

foundational therapeutic benefits beyond symptomatic relief commonly observed with conventional treatments like phosphodiesterase-5 inhibitors (PDE-5i). (18,19) Endothelial repair, enhanced angiogenesis, and improved vasodilation mediated by increased nitric oxide (NO) levels contribute significantly to these observed benefits.[7,17]

Vascular dysfunction, systemic inflammation, and heightened oxidative stress frequently accompany ED, especially in aging and diabetic cohorts, according to prior studies.[1,20] Endothelial impairment and hormonal disturbances compound these issues.[12,19] Interestingly, secretome derived from MSCs reportedly mitigates such pathologies differently compared to PDE-5 inhibitors, primarily symptomatic treatments.[17,19]

Moreover, when examined closely, the data aligns well with preclinical evidence showing increased cavernous blood flow and restoration of erectile function in diabetic animal models treated with secretome.[6,17] Anti-inflammatory and antifibrotic properties of secretome, based on preliminary observations, contribute to reversing chronic pathological changes associated with ED.[2,5]

The clinical significance of the observed 5.49-point average increase in IIEF-5 scores surpasses the minimal clinically important difference (MCID), often cited as approximately 4 points.[10] Patient-reported satisfaction, averaging 8.03 out of 10, further suggests subjective therapeutic benefits possibly extending beyond purely physiological improvements.

The present study observed a 5.49-point increase in IIEF-5 scores following intramuscular UCMSC-secretome injection, surpassing the minimal clinically important difference (MCID) of approximately 4 points. This magnitude of improvement aligns with previous preclinical and clinical observations. For instance, Hasannuri et al. (2024) reported increased VEGF expression and enhanced wound healing in diabetic rat models treated with hypoxic MSC-secretome gel, indicating pro-angiogenic properties comparable to our findings in erectile tissue vascularization.[6] Similarly, Ormazabal et al. (2022) demonstrated that MSC-endothelial cell secretome significantly improved vascular repair and perfusion in a type-2 diabetes mouse model, reinforcing the regenerative capacity of secretome in endothelial dysfunction—one of the key mechanisms underlying ED.[7]

While our approach utilized systemic intramuscular injection, previous studies, such as those reviewed by He & von Schwarz (2021), mostly investigated intracavernosal stem cell delivery and noted mixed clinical responses due to variability in cell viability and immune compatibility[12]. In contrast, secretome-based therapy, as suggested by Trigo et al. (2024), offers a cell-free alternative with more consistent pharmacological behavior and reduced immunogenicity.[4]

Furthermore, our results parallel the findings of Digambiro et al. (2024), who applied secretome therapy in diabetic patients with ED and reported improvements in both erectile function and biomarkers

like D-Dimer.[20] Although their protocol may have differed in administration method and population, the congruent outcomes support the biological plausibility of secretome's effects across metabolic and age-related ED etiologies.

Nevertheless, limitations must be noted—small sample size, lack of a placebo-controlled group, and absence of long-term follow-up data. Further comprehensive randomized controlled trials are therefore required, hypothetically, to confirm secretome therapy's effectiveness and define optimal patient profiles.

CONCLUSION

Findings suggest secretome injections could effectively enhance erectile function among elderly men diagnosed with erectile dysfunction. Beyond physiological effects, patient satisfaction reports seemingly confirm therapeutic success. Larger, rigorously designed randomized controlled trials may therefore be recommended. Such further studies might substantiate and expand upon these encouraging preliminary results.

Conflicts of Interest

There is no conflict of interest.

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