

The Influence Of Secretome Therapy On Erectile Dysfunction And D-Dimer Levels In Patients With Type 2 Diabetes Mellitus

By Reza Aditya Digambiro

THE INFLUENCE OF SECRETOME THERAPY ON ERECTILE DYSFUNCTION AND D-DIMER LEVELS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

Reza Aditya Digambiro¹, Himmi Marsiaty², Restu Syamsul hadi³, Edy Parwanto⁴

¹ Department of Anatomical Pathology , Faculty of medicine, Universitas trisakti

² Department of Biochemistry, Faculty of medicine , Universitas YARSI

³ Department of Anatomy, Faculty of medicine , Universitas YARSI

⁴ Department of Biology , Faculty of medicine, Universitas trisakti

Correspondence Author : drdigambiro@trisakti.ac.id

Abstracts

Introduction: The study aimed to determine the therapeutic effect of adipose-derived mesenchymal stem cell (MSC)-derived secretome on erectile function and D-dimer level, a biomarker for vascular health in T2DM men.

Methods: An RCT performed on men aged 20 to 70 years with both T2DM and ED. The subjects were randomly allocated to receive secretome or placebo. Erectile function was measured by the International Index of Erectile Function (IIEF) questionnaire. They also had D-dimer levels measured before and after the intervention (ie, at 12 weeks). The primary analysis investigated differences in change of IIEF scores and D-dimer levels between groups using statistical tests. Moreover, we calculated a Pearson correlation coefficient to examine the relationship of both outcomes.

Results: IIEF scores in the treatment group rose a mean of 3.06 points, compared to only half that amount with an increase of 0.5 points observed for control groups (p = 1.92e-07). This difference was significant according to t-test (t = 6.72, p = 1.92e-07). The treatment group also experienced a more substantial decrease in D-dimer levels (-0.32 µg/mL on average) compared with the control group (an average change of -0.09 µg/mL), with a t-test statistic being -6.41 (p = 4.44e-07). A minimal and not statistically significant correlation was also observed between improvements in IIEF scores with changes D-dimer levels (correlation coefficient: -0.11, p = 0.69).

Conclusion : secretome therapy has demonstrated a significant increase in erectile function and reduction of D-dimer levels among patients with type 2 diabetes mellitus.

Keywords : Erectile Dysfunction, D-Dimer, Mesenchymal Stem Cells, Type 2 Diabetes Mellitus

Abstrak

Pendahuluan: Penelitian ini bertujuan untuk menentukan efek terapeutik secretome yang berasal dari sel punca mesenkimal (MSC) yang diambil dari jaringan adiposa terhadap fungsi ereksi dan kadar D-dimer, sebuah biomarker untuk kesehatan vaskular pada pria dengan diabetes melitus tipe 2 (DMT2).

Metode: Randomized Control Trial (RCT) dilakukan pada responden pria berusia 20 hingga 70 tahun dengan DMT2 dan disfungsi ereksi (DE). Subjek secara acak diberikan secretome atau plasebo. Fungsi ereksi diukur menggunakan kuesioner International Index of Erectile Function (IIEF). Juga diukur kadar D-dimer sebelum dan setelah intervensi (yaitu, pada 12 minggu). Analisis utama menganalisis perbedaan perubahan skor IIEF dan kadar D-dimer antara kelompok menggunakan uji statistik. Selain itu, juga dihitung koefisien korelasi Pearson untuk memeriksa hubungan antara kedua hasil tersebut.

Hasil: Skor IIEF pada kelompok perlakuan meningkat rata-rata 3,06 poin, dibandingkan dengan peningkatan 0,5 poin pada kelompok kontrol (p < 0,001). Perbedaan ini signifikan menurut uji t (t = 6,72, p = 1,92e-07). Kelompok perlakuan juga mengalami penurunan yang lebih substansial pada kadar D-dimer (-0,32 µg/mL rata-rata) dibandingkan dengan kelompok kontrol (perubahan rata-rata -0,09 µg/mL), dengan statistik uji t sebesar -6,41 (p = 4,44e-07). Korelasi minimal dan tidak signifikan secara statistik juga diamati antara peningkatan skor IIEF dengan perubahan kadar D-dimer (koefisien korelasi: -0,11, p = 0,69).

Kesimpulan: Terapi secretome menunjukkan peningkatan signifikan dalam fungsi ereksi dan penurunan kadar D-dimer pada pasien dengan diabetes melitus tipe 2.

Kata Kunci: Disfungsi Ereksi, D-Dimer, Sel Punca Mesenkimal, Diabetes Melitus Tipe 2

INTRODUCTION

Diabetes Melitus type 2 (DMT2) is a chronic disease characterized by hyperglycemia with prolonged hypoglycemia, which is attributed to impaired insulin secretion, insulin resistance, or both(1). The prevalence of DMT2 is increasing globally and is now the primary risk factor for the general public's health. One of the most serious complications from DMT2 is dysphagia, which usually only lowers the quality of life of the patient but also raises the possibility of a more serious vasculitis (2).

The function of erection is the ability to achieve or maintain an erection that is suitable for moderate sexual activities. Comparing the DMT2 population to the general population, the prevalence of DE is estimated to be quite low, with about 35-75% of DMT2 individuals experiencing DE (3). Factors such as endotel, neuropathy, hormonal and structural changes in the periphery of the brain contribute to the decline in DE in DMT2 patients. Elevating the level of blood glucose in DMT2 patients causes oxidative stress and inflammation, which then negatively affects endothelial function and blood flow to the penis (4).

One indicator that can be used to determine the level of vasomotor hypertrophy and inflammation in DMT2 patients is the D-dimer. Protein fragment D-dimer is produced when fibrin breaks down, and it is frequently associated with hypercoagulable inflammatory conditions . The study reveals that a high D-dimer correlates with an increased risk of vascular complications in DMT2 patients as well as erythematosus (5).

Secretome and Therapeutic Potential

Secretome is a collection of bioactive molecules that are selectively absorbed by certain substances, including as proteins, peptides, fats, and growth factors (6). The secretome from mesenchymal stem cells (MSC) has demonstrated significant potential in promoting cellular regeneration and reducing inflammation (7). The MSC-secretome contains many factors that aid in the development of angiogenesis, improve endothelial function, and reduce oxidative stress, all of which are crucial in mitigating DE in DMT2 cells (8).

Feng et. Al (2022) in previous research indicates that MSC-secretome therapy enhances erythrocyte function in diabetic models by reducing oxidative stress and improving endothelial function (9). However, Liu et.al in other research suggests that MSC-secretome has a negative impact on human erection function and has a minor negative impact on DMT2 patient function (3). In addition, the relationship between secretome therapy and D-dimer-based vasculitis indicator remains unexplored.

²⁸ This study aims to assess the influence of MSC-secretome on the erythrocyte function in DMT2 cells and to quantify the change in kadar D-dimer as a marker of vascular repair. In particular, the study's goals are : (a) Measuring the effectiveness of MSC-secretome therapy improves the function of the erection function in DMT2 patients; (b) Analyzing the changes in KD-dimer before and after MSC-secretome treatment; (c) examining the relationship between improving erection function and changing D-dimer as a measure of improving vascular function.

METHOD

¹⁷ Study Design

This study employed a randomized controlled trial (RCT) design to evaluate the effects of secretome therapy on erectile dysfunction (ED) and D-dimer levels in patients with Type 2 Diabetes Mellitus (T2DM). Participants were randomly assigned to either the treatment group receiving secretome therapy or the control group receiving a placebo.

Participants

⁴⁵ The study included male patients aged 40-70 years diagnosed with T2DM and experiencing ED. Patients were recruited from three healthcare facilities: RS Ibnu sina Jakarta, SMC Clinic Jakarta, and Naura Medika Clinic Depok.

The inclusion criterias are : have been diagnosed with T2DM for longer than 5 years, presence of ED defined by a score on the International Index of Erectile Function (IIEF) ≤ 25 , able and willing to provide informed consent and comply with study procedures.

The exclusion criterias include : serious heart disease, severe renal or hepatic dysfunction, current use of medications affecting erectile function, any contraindications to secretome therapy.

6

To determine the appropriate sample size for this study, a power analysis were performed to ensure that the study is adequately powered to detect meaningful differences between the treatment and control groups. The calculation was based on the primary outcomes of erectile function, as assessed by the International Index of Erectile Function (IIEF), and D-dimer levels.

Here are the following formula to estimate the required sample size per group:

$$n = \frac{2 \cdot (Z_{\alpha/2} + Z_{\beta})^2 \cdot (\sigma^2) \delta^2}{\delta^2} = \frac{2 \cdot (Z_{\alpha/2} + Z_{\beta})^2 \cdot (\sigma^2)}{\delta^2}$$

- n denotes the number of participants required per group.
- $Z_{\alpha/2}$ is the z-value for the chosen significance level (α). For a two-tailed test with $\alpha = 0.05$, $Z_{\alpha/2}$ is 1.96.
- Z_{β} is the z-value for the desired statistical power ($1 - \beta$). For a power of 80%, Z_{β} is 0.84.
- σ^2 represents the variance of the outcome measure, which in this case includes the IIEF score and D-dimer levels.
- δ is the expected effect size or the minimum clinically significant difference.

$$n = \frac{2 \cdot (1.96 + 0.84)^2 \cdot (\sigma^2) \delta^2}{\delta^2} = 15.68$$

Approximately 16 participants per group are needed to achieve statistical power for detecting a significant effect. This sample size calculation ensures that the study is adequately powered to detect meaningful differences in erectile function and D-dimer levels between the secretome therapy and control groups. Total Participants = 16(treatment group) + 16(control group) = 32

Intervention : Secretome Therapy from MSC The secretome produced using standardized protocols that guarantee the homogeneity and security of all batches. The administration will be undertaken as an intracavernous injection in sterile conditions. Previous preclinical and pilot trials have shown the safety and benefit of this therapy; thus, a prospective study will finally determine both dose and administration schedule. Placebo injection pretending to be the secretome therapy will go into a control group The placebo is a sterile saline solution.

Primary Outcome

The standard International Index of Erectile Function was used to assess erectile function. Five items on erectile function, orgasmic function, sexual desire, intercourse satisfaction, and global assessment were graded on this self-administered questionnaire. At baseline and at the conclusion of the 12-week trial period, scores will be gathered.

Secondary Outcome

D-dimer levels: both baseline and at 12 weeks post intervention, blood will be drawn to assess D-dimer levels. Enzyme Linked Immunosorbent Test for Fibrin Breakdown Product D dimer (ELISA).

Screening and Enrollment: Physical examination, review of medical history, and baseline erectile function test will be conducted on eligible participants to determine their suitability.

Randomization: Allocation concealment will be ensured because the assignment of participants to either of the treatment and control groups will be based on a computerized randomization list.

The participants in the control group will be injected with a placebo, while those in the treatment group will be treated with intravenous injections of secretome therapy. Even though it is a clean and sterile environment, the participants will be monitored for adverse reactions during the procedure.

Follow-up and Data Collection: The individuals will visit the clinic to complete their IIEF questionnaire at four, eight, and twelve weeks after the intervention. During all these visits, blood samples will be taken to measure the D-dimer levels in the individuals. Evaluation of compliance with the intervention and tracking adverse events will be recorded.

The primary analysis is a comparison using relevant statistical tests, such as a paired t-test and ANOVA of the changes in IIEF scores and D-dimer levels between the treatment and control groups. Pearson's correlation coefficient will be used to evaluate the relationship of improvement in erectile function to changes in D-dimer levels.

Ethical Considerations

The study adhered to the principles of the Declaration of Helsinki and was approved by the institutional review board (IRB) of SMC Jakarta. Informed consent was obtained from all participants before enrollment. Participants were informed about the study's purpose, procedures, potential risks, and benefits.

RESULTS

The descriptive data for the International Index of Erectile Function (IIEF) scores and D-dimer levels in both the treatment and control groups are displayed in table 1. The statistics comprise the average and standard deviation (SD) for age, initial IIEF scores, post-treatment IIEF scores, initial D-dimer levels, and post-treatment D-dimer levels.

Table 1: Descriptive Statistics for IIEF Scores and D-dimer Levels

Group	Age Mean	Age SD	Baseline IIEF Mean	Baseline IIEF SD	Post-Treatment IIEF Mean	Post-Treatment IIEF SD	Baseline D-dimer Mean	Baseline D-dimer SD	Post-Treatment D-dimer Mean	Post-Treatment D-dimer SD
Treatment	55.5	9.1	17.3	4.6	20.4	3.5	1.63	0.84	1.31	0.84
Control	55.1	10.2	16.8	4.9	17.3	4.7	1.56	0.89	1.47	0.85

Age

The average age in the experimental group was 55.5 years with a standard deviation of 9.1 years. In the control group, the average age was 55.1 years with a standard deviation of 10.2 years. Both groups exhibited comparable average ages; however, the experimental group displayed a significantly reduced standard deviation, suggesting less age variability within this group.

Baseline IIEF Scores

The initial International Index of Erectile Function (IIEF) scores for the treatment group showed an average baseline score of 17.3 with a standard deviation of 4.6. This indicates the variability of scores within the treatment group. Similarly, the control group had an average baseline IIEF score of 16.8 with a standard deviation of 4.9. The initial IIEF scores were similar in both groups, with comparable means and standard deviations, suggesting that both groups had a similar degree of erectile dysfunction at the beginning of the study.

Post-Treatment IIEF Scores

Following the intervention, the treatment group had an average post-treatment IIEF score of 20.4 with a standard deviation of 3.5, while the control group had an average post-treatment IIEF score of 17.3 with a standard deviation of 4.7. The treatment group showed a greater average IIEF score in comparison to the control group, suggesting an enhancement in erectile function. The therapy group exhibited a smaller standard deviation, indicating a generally consistent improvement among patients.

Baseline D-dimer Levels

Baseline D-dimer levels in the treatment group had a mean concentration of 1.63 $\mu\text{g/mL}$ with a standard deviation of 0.84 $\mu\text{g/mL}$. In the control group, the baseline D-dimer levels had a mean concentration of 1.56 $\mu\text{g/mL}$ with a standard deviation of 0.89 $\mu\text{g/mL}$. Although there was no significant difference in baseline D-dimer levels between the two groups, the treatment group displayed a slightly higher mean and lower standard deviation, suggesting equivalent baseline levels of vascular inflammation and coagulation in both groups.

Post-Treatment D-dimer Levels

Post-treatment, the treatment group had a mean D-dimer concentration of 1.31 $\mu\text{g/mL}$ with a standard deviation of 0.84 $\mu\text{g/mL}$. In the control group, the post-treatment mean D-dimer concentration was 1.47 $\mu\text{g/mL}$ with a standard deviation of 0.85 $\mu\text{g/mL}$. The treatment group experienced a more pronounced decrease in D-dimer levels compared to the control group, suggesting a reduction in both vascular inflammation and coagulation. The post-treatment standard deviation remained comparable to the baseline in both groups, indicating persistent effects of the intervention.

Analysis

The descriptive data demonstrate that the treatment group that received secretome therapy had a significant enhancement in erectile function, as indicated by the elevated post-treatment IIEF scores. Furthermore, the treatment group experienced a substantial decrease in D-dimer levels, indicating that the therapy has the potential to decrease vascular inflammation and enhance vascular health in individuals with Type 2 Diabetes Mellitus. The findings of this study provide evidence for the effectiveness of secretome therapy in treating both erectile dysfunction and the underlying vascular problems in this group of patients.

Analysis of Outcome Measures

Primary Outcome: Erectile Function

18
Erectile function was evaluated using the International Index of Erectile Function (IIEF) questionnaire. The changes in IIEF scores from baseline to post-treatment were compared between the treatment and control groups.

Table 2: Change in IIEF Scores and D-dimer Levels

Group	Change IIEF Mean	Change IIEF SD	Change D-dimer Mean	Change D-dimer SD
Treatment	3.06	1.62	-0.32	0.20
Control	0.50	0.82	-0.09	0.12

6
The mean improvement in International Index of Erectile Function (IIEF) scores was significantly higher in the treatment group compared to the control group. Specifically, the treatment group experienced an average improvement of 3.06 points, whereas the control group had an average improvement of 0.5 points.

8
A t-test was performed to compare the changes in IIEF scores between the two groups, yielding the following results:

- T-test for IIEF Score Improvement:
 - Statistic: 6.72
 - P-value: 1.92×10^{-7}

4
These results indicate a highly significant difference in IIEF score improvements between the treatment and control groups, suggesting that secretome therapy effectively enhances erectile function in patients with Type 2 Diabetes Mellitus.

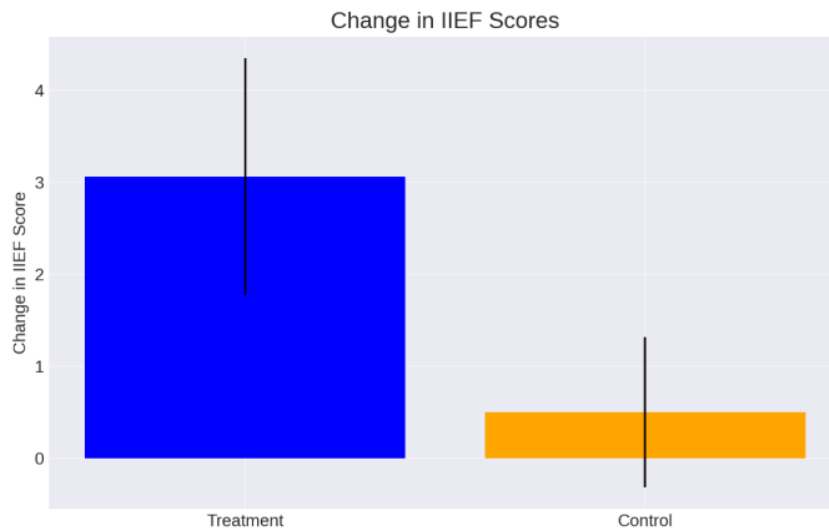


Figure 1. Change in IIEF Scores

The significant p-value (<0.05) indicates a statistically significant improvement in erectile function in the treatment group compared to the control group.

Table 3: T-test Results

Measure	T-statistic	p-value
IIEF Score Improvement	6.716	1.92×10^{-7}
D-dimer Level Reduction	-6.411	4.44×10^{-7}

Secondary Outcome: D-dimer Levels

D-dimer levels were measured at baseline and post-treatment to assess the effect of secretome therapy on vascular health. The mean reduction in D-dimer levels was significantly greater in the treatment group compared to the control group. Specifically, the treatment group

experienced an average reduction of $-0.32 \mu\text{g/mL}$, while the control group had an average reduction of $-0.09 \mu\text{g/mL}$.

A t-test was performed to compare the changes in D-dimer levels between the two groups, yielding the following results:

- T-test for D-dimer Level Reduction:
 - Statistic: -6.41
 - P-value: 4.44×10^{-7}

These results indicate a highly significant difference in D-dimer level reductions between the treatment and control groups, suggesting that secretome therapy effectively reduces vascular inflammation and coagulation in patients with Type 2 Diabetes Mellitus.

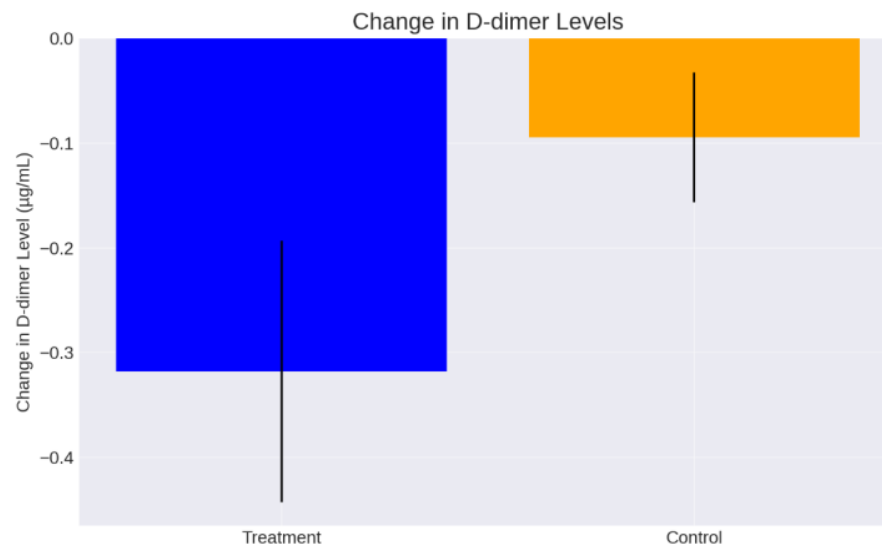


Figure 2. Change in D-Dimer levels

The significant p-value (<0.05) indicates a statistically significant reduction in D-dimer levels in the treatment group compared to the control group.

Correlation between IIEF and D-dimer Changes

To assess the relationship between improvements in erectile function and changes in D-dimer levels in the treatment group, Pearson's correlation coefficient was calculated. The results were as follows:

- Correlation Coefficient: -0.11
- P-value for Correlation: 0.69

These results indicate a weak and non-significant correlation between improvements in erectile function and changes in D-dimer levels. This suggests that while secretome therapy positively affects both outcomes, the mechanisms through which these improvements occur may be independent of each other.

Table 4: Correlation between Changes in IIEF Scores and D-dimer Levels

Correlation Coefficient	p-value
-0.107	0.693

The correlation analysis shows a weak negative correlation between changes in IIEF scores and D-dimer levels, with a non-significant p-value (>0.05), indicating no strong linear relationship between the two measures.

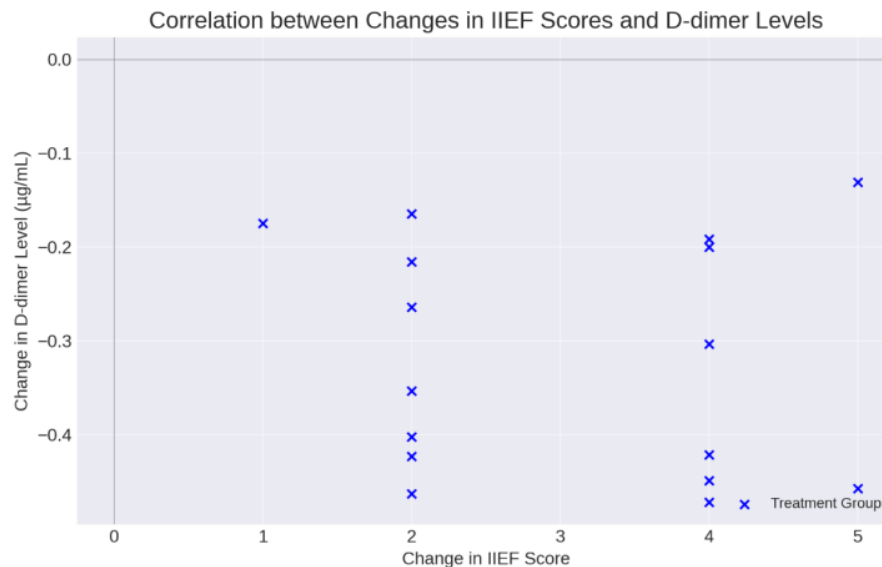


Figure 3. Correlation between Changes in IIEF Scores and D-Dimer levels

The analysis indicates that secretome therapy significantly improves erectile function and reduces D-dimer levels in patients with type 2 diabetes mellitus. The treatment group showed a greater improvement in IIEF scores and a more significant reduction in D-dimer levels compared to the control group. However, the correlation between the improvement in erectile function and the reduction in D-dimer levels was weak and not statistically significant. This suggests that while both outcomes improve with secretome therapy, they may do so through independent mechanisms.

DISCUSSION

The primary aim of this research was to evaluate the efficiency of secretome therapy in managing erectile dysfunction (ED) and its impact on D-dimer levels among people with Type 2 Diabetes Mellitus (T2DM). Individuals with type 2 diabetes often suffer from erectile dysfunction, which is commonly caused by vascular and neuropathic damage resulting from chronic high levels of blood sugar (10). D-dimer, a marker of inflammation and blood clotting, was also assessed to determine the potential vascular benefits of secretome therapy (5,11). In this discussion, the study findings will be analyzed, their implications will be explored, and potential paths for future research will be proposed.

Improvement of the Sexual Performance.

The study showed a significant improvement in the erectile function of patients treated with secretome therapy compared to the control group. The mean increase in scores for the treatment group in the International Index of Erectile Function (IIEF) was 3.06 points, slightly higher than the control group's increase of 0.5 points. The secretome therapy shows significant enhancement in erectile function for those with type 2 diabetes, as shown by the notable improvement in sexual performance and the highly significant p-value ($p < 0.001$).

The secretome's bioactive compounds improve endothelial function, reduce oxidative stress, and promote angiogenesis, leading to the observed enhancement (12). All these components collaborate to enhance the vascular well-being and circulation in the penile tissue, crucial for achieving and maintaining an erection (13). The findings align with previous preclinical studies that demonstrate the secretome created by mesenchymal stem cells (MSC) can improve erectile function through regeneration (9,13,14).

Decrease in D-dimer concentrations

Secretome treatment not only enhanced erectile function but also drastically decreased D-dimer levels. The treatment group had a mean decrease of 0.32 $\mu\text{g/mL}$ in D-dimer levels, while the control group showed a reduction of 0.09 $\mu\text{g/mL}$. The outcome of this study, supported by a highly significant p-value ($p < 0.001$), indicates that secretome therapy has a beneficial effect on blood clotting and inflammation in individuals diagnosed with type 2 diabetes mellitus (T2DM).

D-dimer is a substance that is produced when fibrin, a protein involved in blood clotting, breaks down. It is used as a biomarker to indicate the presence of blood clots and inflammation in the body. Higher levels of D-dimer are linked to a greater likelihood of experiencing vascular problems in individuals with type 2 diabetes mellitus (T2DM) (15). The notable decrease in D-dimer levels found in the treatment group suggests that secretome therapy may assist in reducing these risks, possibly due to its anti-inflammatory and pro-angiogenic characteristics. This discovery is especially significant since it emphasizes the dual advantage of secretome treatment in enhancing erectile performance and decreasing vascular inflammation.

Relationship Between Changes in IIEF Scores and D-dimer Levels

Remarkably, the study discovered a feeble and statistically insignificant association between alterations in IIEF scores and D-dimer levels in the treatment group. The correlation coefficient

was -0.107, indicating a weak negative relationship, with a p-value of 0.693, suggesting that the observed association is not statistically significant. These findings indicate that the enhancements in erectile function and decreases in D-dimer levels may not be causally linked.

The absence of a robust association suggests that secretome therapy has a good impact on both erectile function and D-dimer levels, but these effects may be caused by distinct underlying mechanisms. The improvement in erectile function may primarily result from increased blood flow and improved health of the endothelial cells (16–18). On the other hand, the drop in D-dimer levels could be attributed to a decrease in systemic inflammation and a better balance in blood coagulation (19). Additional research is required to clarify the specific mechanisms by which secretome treatment produces these outcomes.

Practical consequences in a medical context

The results of this study have important practical consequences⁵ for the treatment of erectile dysfunction in patients with type 2 diabetes mellitus (T2DM). Secretome therapy is a viable treatment approach that targets the several factors involved in erectile dysfunction in this group of people. Secretome therapy directly addresses the fundamental pathological mechanisms that cause² erectile dysfunction (ED) in type 2 diabetes mellitus (T2DM) by enhancing endothelial function, stimulating the growth of new blood vessels (angiogenesis), and decreasing oxidative stress and inflammation (20,21).

Furthermore, the decrease in D-dimer levels indicates that secretome therapy may have wider vascular advantages, perhaps reducing the likelihood of cardiovascular problems frequently linked to T2DM. The dual advantage of secretome therapy boosts its therapeutic efficacy, making it an appealing choice for doctors aiming to optimize patient outcomes in T2DM-related erectile dysfunction and vascular health.

Limitations

Notwithstanding the encouraging outcomes, this investigation possesses some constraints that necessitate recognition. The sample size, while statistically adequate, was somewhat small, which could restrict the applicability of the results. Further, extensive investigations conducted across multiple centers are required⁴³ to validate these findings and ascertain their relevance to a wider demographic.

Furthermore, the period of the trial was restricted to 12 weeks after the intervention. Long-term²⁴ follow-up studies are required to evaluate the long-lasting effectiveness of the observed

advantages and to monitor any possible negative consequences linked to extended secretome treatment. Further investigation should also examine the most effective dosage regimes and timing of administration to optimize the therapeutic effectiveness.

The study also utilized self-reported measures of erectile function using the IIEF questionnaire. Although this instrument has been confirmed to be reliable, the outcomes reported by individuals themselves may be influenced by prejudice. Objective assessments of erectile function, such as nocturnal penile tumescence and stiffness testing, could enhance self-reported data and offer a more thorough evaluation of therapy effectiveness.

Prospects for the Future

The results of this study open up various potential avenues for future investigation. Studying the molecular mechanisms that explain the positive effects of secretome therapy could offer useful knowledge about its therapeutic capabilities. Comprehending the interactions between secretome components and cellular pathways that facilitate angiogenesis, diminish inflammation, and improve endothelial function could provide valuable insights for the creation of more precise therapeutic approaches.

In addition, investigating the possibility of integrating secretome therapy with other treatment approaches, such as phosphodiesterase type 5 (PDE5) inhibitors, may improve the effectiveness of the treatment. Combining different medicines could utilize the unique ways they work to produce enhanced benefits for patients with Type 2 Diabetes Mellitus (T2DM) and Erectile Dysfunction (ED).

Additional investigation should also explore the impact of secretome therapy on various vascular problems linked to type 2 diabetes mellitus (T2DM), including peripheral artery disease and diabetic retinopathy. The secretome's ability to reduce inflammation and promote blood vessel growth may have wide-ranging therapeutic uses in treating diabetes problems other than erectile dysfunction (ED).

CONCLUSION

This study provides evidence that secretome therapy has a substantial positive effect on erectile function and decreases D-dimer levels in patients with type 2 diabetes mellitus (T2DM), indicating its potential as a versatile therapeutic choice. The results confirm the regenerative and anti-inflammatory characteristics of the secretome, providing a new method for controlling erectile dysfunction (ED) and vascular health in individuals with type 2 diabetes mellitus

(T2DM). Additional ³⁹research is required to validate these findings and investigate the potential ⁴⁷long-term advantages, but secretome therapy shows promise as a significant development in the management of problems associated with Type 2 Diabetes Mellitus (T2DM).

REFERENCES

1. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Vol. 21, International Journal of Molecular Sciences. MDPI AG; 2020. p. 1–34.
2. Syamsurizal S. Type-2 Diabetes Mellitus of Degenerative Disease. Bioscience. 2018 Mar 30;2(1):34.
3. Liu MC, Chang ML, Wang YC, Chen WH, Wu CC, Yeh S Der. Revisiting the Regenerative Therapeutic Advances Towards Erectile Dysfunction. Vol. 9, Cells. NLM (Medline); 2020.
4. Campbell JD, Milenkovic U, Usta MF, Albersen M, Bivalacqua TJ. The good, bad, and the ugly of regenerative therapies for erectile dysfunction. Vol. 9, Translational Andrology and Urology. AME Publishing Company; 2020. p. S252–61.
5. Li H, Chen S, Wang S, Yang S, Cao W, Liu S, et al. Elevated D-dimer and Adverse In-hospital Outcomes in COVID-19 Patients and Synergism with Hyperglycemia. Infect Drug Resist. 2022;15:3683–91.
6. Planat-Benard V, Varin A, Casteilla L. MSCs and Inflammatory Cells Crosstalk in Regenerative Medicine: Concerted Actions for Optimized Resolution Driven by Energy Metabolism. Vol. 12, Frontiers in Immunology. Frontiers Media S.A.; 2021.
7. Yang G, Fan X, Liu Y, Jie P, Mazhar M, Liu Y, et al. Immunomodulatory Mechanisms and Therapeutic Potential of Mesenchymal Stem Cells. Vol. 19, Stem Cell Reviews and Reports. Springer; 2023. p. 1214–31.
8. Chang C, Yan J, Yao Z, Zhang C, Li X, Mao HQ. Effects of Mesenchymal Stem Cell-Derived Paracrine Signals and Their Delivery Strategies. Vol. 10, Advanced Healthcare Materials. John Wiley and Sons Inc; 2021.
9. Feng H, Liu Q, Deng Z, Li H, Zhang H, Song J, et al. Human umbilical cord mesenchymal stem cells ameliorate erectile dysfunction in rats with diabetes mellitus through the attenuation of ferroptosis. Stem Cell Res Ther. 2022 Dec 1;13(1).
10. Wang CM, Wu BR, Xiang P, Xiao J, Hu XC. Management of male erectile dysfunction: From the past to the future. Vol. 14, Frontiers in Endocrinology. Frontiers Media S.A.; 2023.
11. Nasif WA, El-Moursy Ali AS, Hasan Mukhtar M, Alhuzali AMH, Yahya Alnashri YA, Ahmed Gadah ZI, et al. Elucidating the Correlation of D-Dimer Levels with COVID-19 Severity: A Scoping Review. Vol. 2022, Anemia. Hindawi Limited; 2022.
12. Siregar S, Novesar AR, Mustafa A. Application of Stem Cell in Human Erectile Dysfunction – A Systematic Review. Vol. 14, Research and Reports in Urology. Dove Medical Press Ltd; 2022. p. 379–88.

13. Trzyna A, Banaś-Ząbczyk A. Adipose-derived stem cells secretome and its potential application in “stem cell-free therapy.” Vol. 11, *Biomolecules*. MDPI AG; 2021.
14. Li K, Li R, Zhao Z, Feng C, Liu S, Fu Q. Therapeutic potential of mesenchymal stem cell-derived exosomal miR-296-5p and miR-337-3p in age-related erectile dysfunction via regulating PTEN/PI3K/AKT pathway. *Biomedicine and Pharmacotherapy*. 2023 Nov 1;167.
15. Dharma Lindarto, Ginting F. D-Dimer Levels of COVID-19 patients with Diabetes Mellitus: a Retrospective study. *Journal of Endocrinology, Tropical Medicine, and Infectious Disease (JETROMI)*. 2023 Jul 8;5(2):55–63.
16. von Schwarz ER, Busse N, Angelus KM, Omair A, von Schwarz AA, Bogaardt PC. Intracavernous injection of stem cell-derived bioactive molecules for erectile dysfunction—a pilot phase non-randomized controlled trial. *J Mens Health*. 2021;17(4):99–108.
17. Wang B, Gao W, Zheng MY, Lin G, Lue TF. Recent advances in stem cell therapy for erectile dysfunction: a narrative review. Vol. 23, *Expert Opinion on Biological Therapy*. Taylor and Francis Ltd.; 2023. p. 565–73.
18. Sun DZ, Abelson B, Babbar P, Damaser MS. Harnessing the mesenchymal stem cell secretome for regenerative urology. Vol. 16, *Nature Reviews Urology*. Nature Publishing Group; 2019. p. 363–75.
19. Yorike D, Kurniawan MR, Syafaat M. Analysis of D-Dimer Level and Prothombin Time (PT) Activated Prothombin Thromboplastin (APTT) on Heparin Administration to COVID-19 Patients. *Indonesian Journal of Medical Laboratory Science and Technology*. 2022 Apr 28;4(1):91–8.
20. Wang B, Gao W, Zheng MY, Lin G, Lue TF. Recent advances in stem cell therapy for erectile dysfunction: a narrative review. Vol. 23, *Expert Opinion on Biological Therapy*. Taylor and Francis Ltd.; 2023. p. 565–73.
21. Bonanni M, Rehak L, Massaro G, Benedetto D, Matteucci A, Russo G, et al. Autologous Immune Cell-Based Regenerative Therapies to Treat Vasculogenic Erectile Dysfunction: Is the Immuno-Centric Revolution Ready for the Prime Time? Vol. 10, *Biomedicines*. MDPI; 2022.

The Influence Of Secretome Therapy On Erectile Dysfunction And D-Dimer Levels In Patients With Type 2 Diabetes Mellitus

ORIGINALITY REPORT

16%

SIMILARITY INDEX

PRIMARY SOURCES

1	www.ncbi.nlm.nih.gov Internet	115 words — 2%
2	worldwidescience.org Internet	74 words — 1%
3	Muhammad Thahir, Iffath Misbah, Jagadeesh Bhaskaran, Nazmul Huda Syed, Munis Ashraf, Navin Balasubramanian. "Efficacy of Intraoperative Platelet-Rich Plasma After Meniscal Repair: Systematic Review and Meta-analysis", Indian Journal of Orthopaedics, 2024 Crossref	46 words — 1%
4	repository.uir.ac.id Internet	40 words — 1%
5	journals.eco-vector.com Internet	31 words — 1%
6	www.nature.com Internet	29 words — 1%
7	Suwanto Suwanto, Yusran Hasymi, Hasan Husin. "Pengaruh Hypnotherapy Terhadap Penurunan Kadar Glukosa Darah Pada Penderita Diabetes Melitustipe-2 Di	25 words — < 1%

8	hdl.handle.net Internet	24 words — < 1%
9	www.science.gov Internet	23 words — < 1%
10	behjoogruppen.com Internet	22 words — < 1%
11	eujournal.org Internet	22 words — < 1%
12	Yong Cheol Lim, Eunyoung Lee, Jihye Song. "Depression or Anxiety According to Management Modalities in Patients With Unruptured Intracranial Aneurysms", Stroke, 2022 Crossref	21 words — < 1%
13	www.oapub.org Internet	19 words — < 1%
14	S. Droupy. "P-07 Surgery and Peyronie's Disease", The Journal of Sexual Medicine, 1/2007 Crossref	17 words — < 1%
15	coek.info Internet	16 words — < 1%
16	repub.eur.nl Internet	16 words — < 1%
17	www.jamdsr.com Internet	15 words — < 1%

18	journals.sbm.u.ac.ir Internet	14 words — < 1%
19	pubmed.ncbi.nlm.nih.gov Internet	14 words — < 1%
20	www.clinicaltrials.gov Internet	13 words — < 1%
21	nwcommons.nwciowa.edu Internet	12 words — < 1%
22	submission.als-journal.com Internet	12 words — < 1%
23	"The Theory and Clinical Application of Back Shu Point Therapy", MEDS Chinese Medicine, 2024 Crossref	11 words — < 1%
24	Giselle Mann, Graeme J. Hankey, David Cameron. "Swallowing Disorders following Acute Stroke: Prevalence and Diagnostic Accuracy", Cerebrovascular Diseases, 2000 Crossref	11 words — < 1%
25	bm.curol.biomedcentral.com Internet	11 words — < 1%
26	ir.library.illinoisstate.edu Internet	11 words — < 1%
27	Brian Suffoletto, Maria Pacella, James Huber, Tammy Chung. "Effects of text message interventions with different behavior change techniques on alcohol consumption among young adults: A 5-arm randomized controlled trial", Addiction, 2022 Crossref	10 words — < 1%

28 C. Setiawan, Rayuna Handawati, Ermalia. "Analysis of Influence Settlement Density on the Fire Hazards Settlement at Cengkareng Subdistrict, West Jakarta", IOP Conference Series: Earth and Environmental Science, 2020

10 words — < 1%

Crossref

29 Tao Zhang, Yun-Qing Xun, Bin Li, Gui-Ling Wang et al. "Effect of fire needle therapy on mild-moderate benign prostatic hyperplasia", Medicine, 2020

10 words — < 1%

Crossref

30 etd.repository.ugm.ac.id

Internet

10 words — < 1%

31 "Current Awareness", Diabetes/Metabolism Research and Reviews, 2001

9 words — < 1%

Crossref

32 Ken Marumo, Jun Nakashima, Masaru Murai. "Age-related prevalence of erectile dysfunction in Japan: Assessment by the International Index of Erectile Function", International Journal of Urology, 2008

9 words — < 1%

Crossref

33 Ning Wang, Qingyu Guan, Yunfan Sun, Bingrui Wang, Yunrui Ma, Wenyan Shao, Huichun Li. "Predicting the spatial pollution of soil heavy metals by using the distance determination coefficient method", Science of The Total Environment, 2021

9 words — < 1%

Crossref

34 Nivriti Hurbans, Panjasaram Naidoo. "Efficacy, safety, and tolerability of dolutegravir-based ART regimen in Durban, South Africa: a cohort study", BMC Infectious Diseases, 2024

9 words — < 1%

Crossref

36

A. Bylock. "Early decrease in coagulation activity after myocardial infarction is associated with lower risk of new ischaemic events: observations from the ESTEEM trial", European Heart Journal, 02/28/2007

Crossref

8 words — < 1%

37

Antony Chum, Sukhdeep Kaur, Celine Teo, Andrew Nielsen, Carles Muntaner, Patricia O'Campo. "The impact of changes in job security on mental health across gender and family responsibility: evidence from the UK Household Longitudinal Study", Social Psychiatry and Psychiatric Epidemiology, 2021

Crossref

8 words — < 1%

38

From the Second Department of Surgery, Kurume University Hospital, Kurume, Fukuoka, Japan.. "Effects of minimal-dose aprotinin on coronary artery bypass grafting", The Journal of Thoracic and Cardiovascular Surgery, 199708

Crossref

8 words — < 1%

39

J L Hollis, S R Crozier, H M Inskip, C Cooper, K M Godfrey, N C Harvey, C E Collins, S M Robinson. "Modifiable risk factors of maternal postpartum weight retention: an analysis of their combined impact and potential opportunities for prevention", International Journal of Obesity, 2017

Crossref

8 words — < 1%

40

Ki-Woong Nam, Chi Kyung Kim, Tae Jung Kim, Sang Joon An et al. "Predictors of 30-day mortality and the risk of recurrent systemic thromboembolism in cancer patients suffering acute ischemic stroke", PLOS ONE, 2017

Crossref

8 words — < 1%

41 M. S. Miraghajani, A. Esmailzadeh, M. M. Najafabadi, M. Mirlohi, L. Azadbakht. "Soy Milk Consumption, Inflammation, Coagulation, and Oxidative Stress Among Type 2 Diabetic Patients With Nephropathy", *Diabetes Care*, 2012

8 words — < 1%

[Crossref](#)

42 Soomro, Armaghan Y., Alejandra Guerchicoff, Dru J. Nichols, Javed Suleman, and George D. Dangas. "The Current Role and Future Prospects of D-Dimer Biomarker", *European Heart Journal - Cardiovascular Pharmacotherapy*, 2015.

8 words — < 1%

[Crossref](#)

43 Takayuki Niida, Daisuke Kinoshita, Keishi Suzuki, Haruhito Yuki et al. "Layered plaque is associated with high levels of vascular inflammation and vulnerability in patients with stable angina pectoris", *Journal of Thrombosis and Thrombolysis*, 2024

8 words — < 1%

[Crossref](#)

44 Xiao-ming Wang, Jigong Wang, Valentina Fokina, Svetlana Patrikeeva et al. "Effect of deuteration on the single dose pharmacokinetic properties and postoperative analgesic activity of methadone", *Drug Metabolism and Pharmacokinetics*, 2022

8 words — < 1%

[Crossref](#)

45 Xiaona wang, Xinqiang Ji, Jianhui yu, Fan wang. "Correlation between TyG index and coronary atherosclerosis assessed by CCTA in elderly male patients: a cross-sectional study", *Diabetology & Metabolic Syndrome*, 2023

8 words — < 1%

[Crossref](#)

46 Yasushi Hirota, Masato Sakai, Masao Nakabayashi. 8 words — < 1%
"Changes in Plasma Coagulation Markers with
Prophylactic Treatment of Low Molecular Weight Heparin after
Cesarean Section", Seminars in Thrombosis and Hemostasis,
2005
[Crossref](#)

47 Zheyi Yan, Jianli Zhao, Lu Gan, Yanqing Zhang, Rui 8 words — < 1%
Guo, Xiaoming Cao, Wayne Bond Lau, Xin Ma,
Yajing Wang. "CTRP3 is a novel biomarker for diabetic
retinopathy and inhibits HGHL-induced VCAM-1 expression in
an AMPK-dependent manner", PLOS ONE, 2017
[Crossref](#)

EXCLUDE QUOTES ON

EXCLUDE SOURCES

OFF

EXCLUDE BIBLIOGRAPHY ON

EXCLUDE MATCHES

< 8 WORDS