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

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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 40 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 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 ug/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 40 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.

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

Study Design

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

Participants

The study included male patients aged 40-70 years diagnosed with T2DM and experiencing ED. Patients were recruited from three healthcare facilities: RS Ibnusina 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) $\leq$ 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.

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=2·(Zα/2+Zβ)2·(σ2)δ2n = \frac{{2 \cdot (Z_{\alpha/2} + Z_{\beta})^2 \cdot (\sigma^2)}}{{\delta^2}}n=δ22·(Zα/2+Zβ)2·(σ2)

- nnn denotes the number of participants required per group.
- Zα/2Z_{\alpha/2}Zα/2 is the z-value for the chosen significance level (α\alphaα). For a two-tailed test with α=0.05\alpha = 0.05α=0.05, Zα/2Z_{\alpha/2}Zα/2 is 1.96.
- ZβZ_{\beta}Zβ is the z-value for the desired statistical power (1 - β\betaβ). For a power of 80%, ZβZ_{\beta}Zβ is 0.84.
- σ2\sigma^2σ2 represents the variance of the outcome measure, which in this case includes the IIEF score and D-dimer levels.
- δ\deltaδ is the expected effect size or the minimum clinically significant difference.

39225=15.68\frac{{392}}{{25}} = 15.6825392=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 asses 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 IIEF scores and D-dimer levels in both the treatment and control groups are display 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

Source, year : Neijenhuijs, et al (2019)

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 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 µg/mL with a standard deviation of 0.84

µg/mL. In the control group, the baseline D-dimer levels had a mean concentration of 1.56 µg/mL with a standard deviation of 0.89 µg/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 µg/mL with a standard deviation of 0.84 µg/mL. In the control group, the post-treatment mean D-dimer concentration was 1.47 µg/mL with a standard deviation of 0.85 µg/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 T2DM. 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

Erectile function was evaluated using the 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

Source, years : Neijenhuijs, et al (2019)

The mean improvement in 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.

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: $1.92\times10-71.92 \times 10^{-7}1.92\times10-7$

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 T2DM.

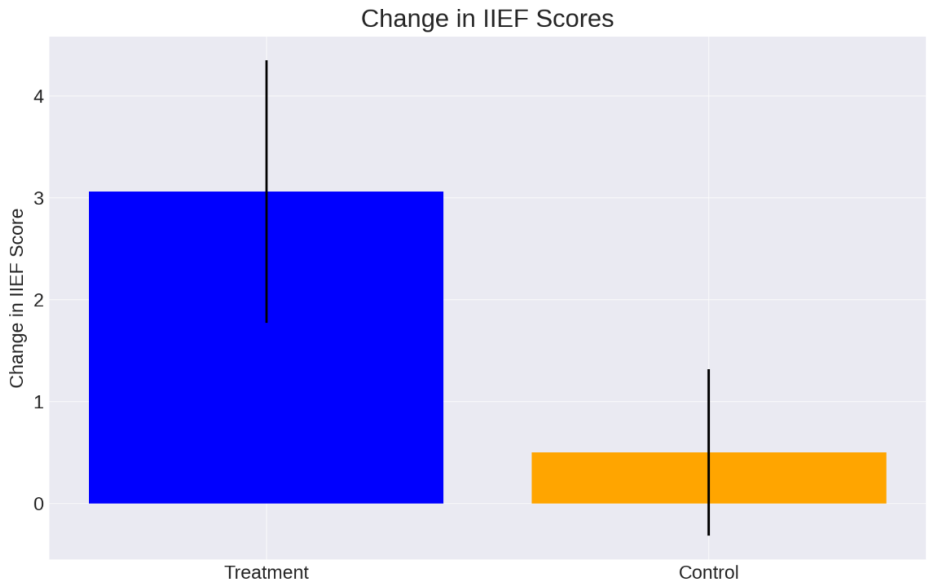

Figure 1. Change in IIEF Scores

Source, years : Source, year : Neijenhuijs, et al (2019)

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

Source, year : Neijenhuijs, et al (2019)

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 µg/mL, while the control group had an average reduction of -0.09 µg/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: 4.44×10−74.44 \times 10^{-7}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.

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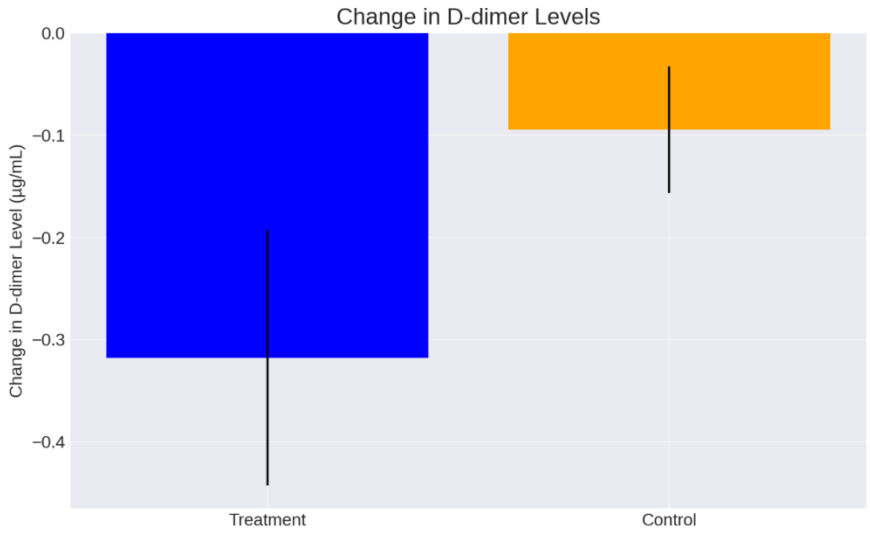

Figure 2. Change in D-Dimer levels

Source, year : Neijenhuijs, et al (2019)

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

Source, year : Neijenhuijs, et al (2019)

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.

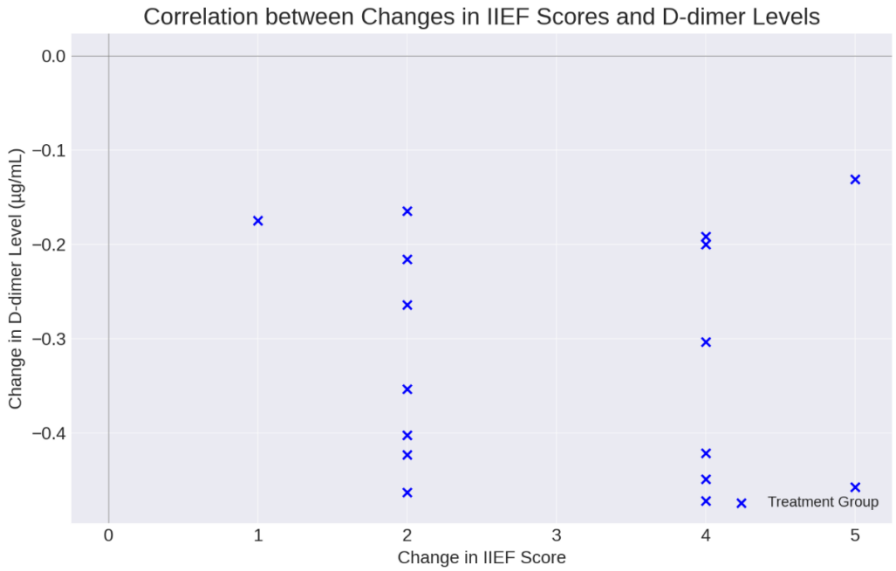

Figure 3. Correlation between Changes in IIEF Scores and D-Dimer levels

Source, year : Neijenhuijs, et al (2019)

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 ED and its impact on D-dimer levels among people with 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 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 µg/mL in D-dimer levels, while the control group showed a reduction of 0.09 µg/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 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 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 consequences for the treatment of erectile dysfunction in patients with 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 cause ED in 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 ED 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 required 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-term 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 T2DM and ED.

Additional investigation should also explore the impact of secretome therapy on various vascular problems linked to 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 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 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 ED and vascular health in individuals with T2DM. Additional research is required to validate

these findings and investigate the potential long-term advantages, but secretome therapy shows promise as a significant development in the management of problems associated with T2DM.

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