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Effects of Moderate-Pressure Sport Massage on IL-6 and TNF-α Levels in Patients with Type 2 Diabetes Mellitus

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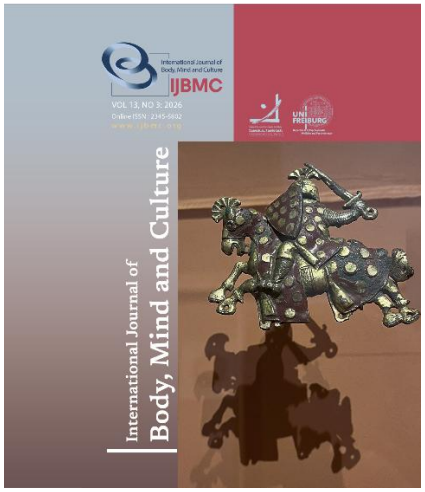

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ABSTRACT

Objective: Type 2 diabetes mellitus (T2DM) is characterized by chronic low-grade inflammation, reflected in elevated IL-6 and TNF-α levels. Type 2 diabetes mellitus (T2DM) is characterized by chronic low-grade inflammation, often reflected by elevated circulating interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Moderate-pressure sport massage has been suggested as a complementary approach for modulating inflammatory markers, although evidence in diabetic populations remains limited. This study evaluated changes in IL-6 and TNF-α following a four-week sport massage intervention in adults with T2DM.

Methods and Materials: A single-group pre–post quasi-experimental design was employed, with no non-massage control group. Twenty adults diagnosed with T2DM participated in the intervention. Participants were stratified by sex into male (n = 10) and female (n = 10) subgroups. All participants received moderate-pressure sport massage three times per week for four weeks. Serum IL-6 and TNF-α concentrations were assessed before and after the intervention using ELISA.

Findings: Sport massage was associated with reductions in IL-6 and TNF-α levels ($p < 0.05$). Although males showed larger mean decreases, this observation should be interpreted with caution given the small subgroup sizes and baseline differences, particularly in age and BMI.

Conclusion: In this short-term single-group study, moderate-pressure sport massage was associated with lower IL-6 and TNF-α levels in adults with T2DM. These preliminary findings highlight the need for controlled studies to determine the clinical relevance and reproducibility of these changes.

Keywords: Sport massage, type 2 diabetes mellitus, IL-6, TNF-α, pro-inflammatory.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the major global health challenges, with a continuously increasing prevalence and substantial impacts on mortality and quality of life (Yameny, 2024). More than 500 million individuals worldwide currently live with diabetes, and approximately 95% of these cases are type 2. Beyond impaired glucose metabolism, T2DM is characterized by chronic low-grade systemic inflammation that contributes to insulin resistance, endothelial dysfunction, and cardiovascular complications (Tsalamandris et al., 2019). Pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) play crucial roles in these pathological processes, and elevated concentrations of these biomarkers have been linked to disease severity and metabolic deterioration (Yılmaz et al., 2025). IL-6 and TNF-α, therefore, represent key inflammatory indicators and were selected as the primary outcomes of interest in this study.

With advances in mechanobiology, mechanical forces applied to soft tissues have been proposed to influence cellular activity and immune pathways via mechanotransduction (Suriyagandhi et al., 2025). Although mechanisms such as potential modulation of NF-κB signaling, enhancement of lymphatic flow, or promotion of anti-inflammatory mediators are frequently discussed, these explanations remain largely theoretical in the context of T2DM and have not yet been empirically demonstrated in diabetic populations. Evidence from non-diabetic samples suggests that massage therapy may influence inflammatory markers, including decreases in cytokine expression following exercise-induced muscle stress (Crane et al., 2012; Waters-Banker et al., 2014) and reductions in circulating IL-6 after Swedish massage among healthy adults (Stenbäck et al., 2024). Although limited, massage-related research in diabetic patients exists, including the review by Bayat et al. (2020), which describes potential benefits for vascular and metabolic outcomes; however, few studies have directly measured IL-6 or TNF-α responses in T2DM undergoing structured massage therapy.

Another underexplored dimension involves the possibility of sex-related differences in inflammatory responses to massage therapy, which may contribute to a more nuanced understanding of individualized complementary treatments in diabetes management. [EDIT-6 — penguatan motivasi ilmiah] Although broader clinical endpoints such as HbA1c, insulin sensitivity, or endothelial function are important considerations in diabetes research, these outcomes were not assessed in the present study and are referenced only to contextualize the clinical relevance of inflammatory modulation. Therefore, the present study aimed to examine changes in IL-6 and TNF-α levels following a moderate-pressure sport massage intervention in adults with T2DM and to explore potential sex-related differences in these cytokine responses. By focusing specifically on cytokine-based outcomes, this investigation provides preliminary evidence that enriches the growing literature on complementary, non-pharmacological approaches for inflammation management in chronic metabolic disorders.

Methods and Materials

Study Design

This study employed a single-group pre–post design with sex-based subgroup analysis. It was conducted as an exploratory pilot study involving both male and female participants previously diagnosed with type 2 diabetes mellitus (T2DM). The absence of a control group limits causal inference, and sex-based comparisons were exploratory in nature and interpreted with caution. No a priori sample size calculation or power analysis was performed, and the sample size was determined based on feasibility and participant availability. Participants were recruited from a Community Health Center in Surabaya using purposive sampling based on predefined inclusion and exclusion criteria. Inclusion criteria were as follows: (1) a confirmed diagnosis of T2DM for at least one year, (2) age between 40 and 70 years, (3) stable blood glucose levels under regular medication, and (4) absence of open wounds, severe neuropathy, or cardiovascular complications that contraindicate massage therapy. Exclusion criteria included: (1) the presence of acute infection, (2) modification of insulin therapy regimen during the study period, and (3) participation in other exercise or rehabilitation programs during the intervention. All eligible individuals attending the clinic

during the recruitment period were informed about the study and invited to participate. Individuals who did not meet the predefined inclusion criteria, met any exclusion criteria, or declined participation were not enrolled. The final sample consisted of participants who fulfilled all eligibility criteria and completed the study.

Sport Massage Protocol

A moderate-pressure sport massage intervention was administered for four consecutive weeks, three times per week. All sessions were delivered by the same certified therapist following a standardized protocol, with a target duration of approximately 45 minutes per session. A limited duration range of 30–60 minutes was allowed only to accommodate individual tolerance and comfort, and all participants completed 12 sessions. The massage sequence consisted of effleurage, petrissage, friction, tapotement, and vibration, targeting the major muscle groups of the upper and lower extremities and the back. Massage pressure was standardized using participant-reported intensity ratings on a 0–10 Visual Analog Scale (VAS), with a target range of 5–7 corresponding to moderate, tolerable pressure. Participants were instructed to maintain their habitual diet and medication regimen without major changes throughout the study period.

Biochemical Examination

Venous blood samples (5 mL) were collected in the morning after an overnight fast (approximately 10 hours), both before (Pre) and after (Post) the four-week intervention. Serum was separated by centrifugation at 3,000 rpm for 15 minutes and analyzed immediately. Serum concentrations of interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were determined using a commercial enzyme-linked immunosorbent assay (ELISA) kit (BT-Lab, Bioassay Technology Laboratory, Inc., China) — Cat. No. E0090Hu for Human IL-6 and Cat. No. E0082Hu for Human TNF-α — following the manufacturer's instructions. Absorbance readings were obtained at 450 nm using a microplate reader (Bio-Rad, USA). The intra- and inter-assay coefficients of variation were maintained below 10%.

Analysis

Data analysis was performed using SPSS software version 26.0 (IBM Corp., Armonk, NY, USA). The Shapiro–Wilk test was used to assess data normality, and all data were expressed as mean ± standard deviation (SD). Within-group comparisons (pre- vs. post-intervention) were analyzed using paired sample t-tests, while between-group comparisons (male vs. female) were analyzed using independent samples t-tests. Effect size (Cohen's d) was calculated to determine the magnitude of the effect, interpreted as small (0.2–0.49), medium (0.5–0.79), or large (≥ 0.8). A p-value of less than 0.05 was considered statistically significant.

Ethical considerations

All participants provided written informed consent before enrollment. Ethical approval was obtained from the Research Ethics Committee, Community Service Institute (*Lembaga Pengabdian Kepada Masyarakat*, LPPM) of Universitas Negeri Surabaya (UNESA), in accordance with the principles of the Declaration of Helsinki (Ethical approval number: 0022/UN38.III.1/DL.01.02/2024).

Findings and Results

The analysis of baseline characteristics of the study participants showed that the male group (n = 10) had a higher mean age compared to the female group (69.83 ± 10.42 vs. 54.60 ± 11.89 years; p = 0.021). Male participants were also significantly taller than females (1.63 ± 0.07 m vs. 1.47 ± 0.06 m; p = 0.001). In addition, the male group had a lower body mass index (BMI) compared to the female group (23.49 ± 2.43 vs. 27.14 ± 2.27 kg/m^2; p = 0.014). No significant differences were observed between the two groups in terms of body weight, systolic and diastolic blood pressure, fasting blood glucose, uric acid, urea, total cholesterol, triglycerides, HDL, LDL, SGOT, or SGPT (p > 0.05) (Table 1). Therefore, significant differences between the sexes were found only in age, height, and body mass index.

Table 1

Baseline demographic, anthropometric, and medical characteristics of the study participants

Characteristic	Male (n=10)	Female (n=10)	p-value
Age (yrs)	69.83 ± 10.42*	54.60 ± 11.89	0.021
Height (m)	1.63 ± 0.07*	1.47 ± 0.06	0.001
Weight (kg)	62.17 ± 7.89	58.40 ± 6.39	0.348
Body Mass Index (kg/m²)	23.49 ± 2.43*	27.14 ± 2.27	0.014
SBP (mmHg)	148.50 ± 13.81	141.40 ± 13.96	0.343
DBP (mmHg)	88.00 ± 11.42	79.20 ± 8.32	0.138
Fasting Blood Glucose (mg/dL)	171.83 ± 79.76	180.20 ± 103.75	0.868
Uric Acid (mg/dL)	7.32 ± 2.43	6.25 ± 1.44	0.361
Urea (mg/dL)	36.83 ± 8.61	30.60 ± 6.17	0.113
Total Cholesterol (mg/dL)	235.50 ± 23.74	222.30 ± 23.73	0.305
Triglycerides (mg/dL)	179.00 ± 34.02	166.20 ± 29.37	0.462
HDL (mg/dL)	42.83 ± 5.15	45.60 ± 6.04	0.349
LDL (mg/dL)	136.00 ± 16.26	129.30 ± 16.94	0.449
SGOT (U/L)	35.33 ± 5.54	32.40 ± 4.58	0.303
SGPT (U/L)	38.00 ± 6.66	34.80 ± 5.12	0.297

Note: SGOT: Serum Glutamic Oxaloacetic Transaminase; SGPT: Serum Glutamic Pyruvic Transaminase; HDL: High-density lipoprotein; LDL: Low-density lipoprotein. (*) Significant in the male group (p < 0.05).

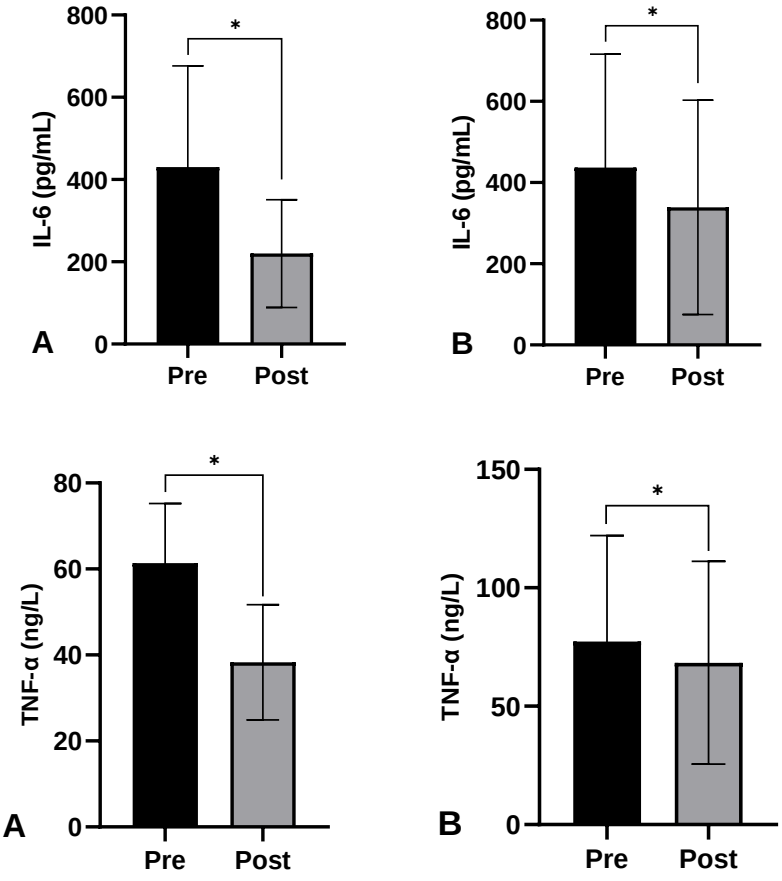

Figure 1

Comparison of IL-6 and TNF-α levels pre- and post-sport massage in type 2 diabetes mellitus patients in groups (A) male and (B) female. (*) indicates a significant difference at pretest (p < 0.05)

Based on Figure 1, sport massage in patients with type 2 diabetes mellitus significantly reduced pro-inflammatory cytokine levels in both sexes. In the male group, IL-6 and TNF-α levels decreased significantly after the intervention ($p < 0.05$), and a similar significant reduction was observed in the female group for both inflammatory markers. These results indicate that sport massage effectively attenuated the inflammatory response by reducing IL-6 and TNF-α concentrations in both male and female patients with type 2 diabetes mellitus.

Table 2

Comparison of changes in IL-6 and TNF-α levels pre-, post-, delta, and change after sport massage in type 2 diabetes mellitus patients based on gender

Parameters	Male (n=10)	Female (n=10)	p-value	95% CI	ES
Pre-IL-6 (pg/mL)	430.00 ± 246.42	437.00 ± 279.17	0.959	(-303.75) – (289.75)	0.026
Post-IL-6 (pg/mL)	220.00 ± 130.99	339.00 ± 264.29	0.251	(-369.21) – (131.21)	0.571
Δ-IL-6 (pg/mL)	-210.00 ± 127.44*	-98.00 ± 36.45	0.019	(-202.35) – (-21.65)	1.194
Change-IL-6 (%)	-49.42 ± 10.12*	-28.34 ± 16.12	0.006	(-36.89) – (-5.27)	1.565
Pre-TNF-α (ng/L)	61.34 ± 13.89	77.31 ± 44.72	0.316	(-56.73) – (24.79)	0.482
Post-TNF-α (ng/L)	38.31 ± 13.39	68.37 ± 42.82	0.063	(-69.11) – (8.99)	0.947
Δ-TNF-α (ng/L)	-23.03 ± 8.02*	-8.94 ± 6.27	0.005	(-21.78) – (-6.39)	1.957
Change-TNF-α (%)	-38.25 ± 15.19*	-14.90 ± 15.89	0.014	(-40.68) – (-6.02)	1.502

Note: (*) Indicates a significant difference in the female group ($p < 0.05$). Δ: Delta. ES: Effect size. 95% CI: 95% Confidence Interval of the Difference.

Based on the analysis in Table 2, sport massage therapy in patients with type 2 diabetes mellitus significantly decreased IL-6 and TNF-α levels, particularly in the male group. The ΔIL-6 value and percentage change in IL-6 were greater in males compared to females. Similarly, reductions in ΔTNF-α and percentage change in TNF-α were also more pronounced in males than in females. These results suggest that sport massage is more effective at reducing inflammatory responses (IL-6 and TNF-α) in male patients than in female patients with type 2 diabetes mellitus.

Discussion and Conclusion

This study demonstrated that moderate-pressure massage therapy administered over four weeks (a total of twelve sessions, each lasting 30–60 minutes) was associated with a significant pre–post reduction in the levels of pro-inflammatory cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in patients with type 2 diabetes mellitus (T2DM). These findings are consistent with the hypothesis that controlled mechanical stimulation through massage may be linked to changes in low-grade systemic inflammatory markers, which are considered key pathways contributing to insulin resistance and endothelial dysfunction in T2DM, though they do not directly demonstrate the underlying biological mechanisms. The present results are consistent with previous reports highlighting the involvement of IL-6 and TNF-α in impaired glucose regulation and increased vascular risk in T2DM (Li et al., 2023; Liu et al., 2016), reinforcing the relevance of these cytokines as inflammatory biomarkers in metabolic disease. Although reductions in inflammatory biomarkers observed in this study are directionally similar to responses reported following other non-pharmacological interventions, such as physical exercise Chen et al. (2020); Hejazi et al., 2023), direct comparability cannot be inferred due to differences in intervention modality, study design, and absence of a control group. Given that elevated IL-6 and TNF-α levels have been associated with adverse clinical outcomes in T2DM, the observed cytokine changes may warrant further investigation regarding potential implications for metabolic and vascular health; however, clinical endpoints such as insulin sensitivity or vascular function were not assessed in the present study and therefore cannot be concluded. In line with Stenbäck et al. (2024), who reported reductions in circulating IL-6 following a single Swedish massage session, the repeated exposure employed in this study may have contributed to more consistent short-term modulation of inflammatory markers. However, the cumulative or long-term physiological significance of this response remains to be established.

Inflammatory mechanisms involving IL-6 and TNF-α play crucial roles in insulin resistance and pancreatic β-cell dysfunction. As noted by Yılmaz et al. (2025), elevated pro-inflammatory cytokines disrupt insulin sensitivity through macrophage activation and nonspecific immune pathways. Indrawati et al. (2023) also reported that elevated IL-6 levels in T2DM are strongly associated with chronic oxidative stress, while Atmaja et al. (2023) found that IL-6 gene expression increases during the progression from prediabetes to overt diabetes due to systemic inflammation. Together, these studies provide important contextual evidence regarding the role of IL-6 and TNF-α as biomarkers of metabolic deterioration in T2DM. Within this context, the pre–post reductions in IL-6 and TNF-α observed in the present study are consistent with modulation of inflammatory markers reported in the literature. However, the current findings do not directly confirm the specific cellular or molecular mechanisms underlying these changes.

Mechanistically, the observed reductions in IL-6 and TNF-α following the massage intervention may be interpreted within the broader theoretical framework of mechanotransduction-mediated immunomodulation, as described in prior experimental and clinical studies. Repetitive mechanical pressure and shear forces applied to soft tissue during massage stimulate mechanosensitive receptors such as integrins and stretch-activated ion channels, which convert physical stimuli into intracellular biochemical signals (Shutova & Boehncke, 2022). Activation of these pathways is known to inhibit the transcription factor NF-κB, thereby suppressing the transcription of pro-inflammatory genes such as IL-6 and TNF-α, while simultaneously promoting anti-inflammatory mediators such as IL-10, as demonstrated primarily in experimental and non-diabetic models (Lowery et al., 2025); however, these molecular mediators were not directly assessed in the present study. White et al. (2020) demonstrated that post-exercise massage modulates immune mediators by influencing inflammatory signaling pathways, while improvements in blood and lymphatic circulation following moderate-pressure massage have been proposed to facilitate the clearance of inflammatory mediators and enhance tissue oxygenation. In the context of the current findings, these mechanisms should be regarded as biologically plausible explanations rather than demonstrated effects within the studied T2DM population.

The present study was grounded on the conceptual framework that increased tissue perfusion and reduced oxidative stress resulting from mechanical pressure could suppress pro-inflammatory cytokine expression. The findings, consistent with this hypothesis, strengthen the biological rationale that tissue mechanotransduction via massage may contribute to immune regulation in patients with T2DM. Empirical evidence also supports this mechanism; for example, Trisna-Windiani et al. (2015) found that massage stimulation decreased TNF-α and IL-6 levels in premature neonates. Bayat et al. (2020) confirmed that pressure intensity is a key determinant of physiological responses, while Lindgren et al. (2010) demonstrated that modulation of the autonomic nervous system activity contributes to immune balance and vascular homeostasis. Collectively, these findings align with the present study, indicating that moderate-pressure massage over four weeks exerts measurable immunomodulatory effects on inflammatory biomarkers in patients with T2DM. Overall, the data support the hypothesis that the mechanotransduction signaling pathway provides a biologically plausible mechanism for the anti-inflammatory effects of massage therapy in T2DM, rather than confirming direct metabolic or clinical effects.

The findings of this study are in agreement with previous reports demonstrating that physical therapies involving mechanical pressure can reduce pro-inflammatory cytokine levels. White et al. (2020) reported that post-exercise massage reduced inflammatory mediators such as TNF-α and enhanced tissue recovery capacity in healthy athletes. Similarly, Stenbäck et al. (2024) observed that a single Swedish massage session decreased circulating IL-6 and increased insulin-like growth factor-1 in healthy individuals. Comparable reductions were observed in the present study, but within a chronically metabolically compromised population, characterized by persistent low-grade inflammation and oxidative stress. These similarities reflect comparable directions of inflammatory change, rather than equivalence in magnitude or clinical impact across populations. This comparison suggests that the immunomodulatory effects of mechanical stimulation are not limited to

acute or healthy conditions but may also be observable in populations with metabolic disorders.

Moreover, the present findings complement those of Chen et al. (2020); Hejazi et al. (2023), who showed that regular physical activity, such as aerobic exercise, also decreases IL-6 and TNF-α levels in T2DM patients. Thus, massage can be viewed as a passive mechanical stimulation that elicits anti-inflammatory responses through partially overlapping biological pathways, while being more feasible for patients with limited mobility or high cardiometabolic risk. Importantly, massage should be considered a complementary or adjunctive approach rather than a substitute for established lifestyle or pharmacological interventions.

Clinically, these findings hold important implications for the development of biologically informed complementary therapies in T2DM management. The significant reductions in IL-6 and TNF-α suggest that massage therapy could serve as a non-pharmacological adjunct strategy for controlling chronic inflammation underlying insulin resistance. Li et al., (2023) emphasized that suppression of systemic inflammation can improve glucose regulation, and the current findings are consistent with this conceptual framework by demonstrating short-term reductions in inflammatory biomarkers, without directly assessing glycemic outcomes. Furthermore, mechanotransduction mechanisms—as described by Shutova & Boehncke (2022)—highlight potential signaling pathways that may underlie the observed biomarker changes, which could be explored in future biomechanically based rehabilitative approaches. In clinical practice, a four-week moderate-pressure massage protocol was found to be safe, standardized, and repeatable, making it a feasible intervention to be integrated into multidisciplinary T2DM care programs. With supportive physiological evidence from inflammatory biomarkers, this study supports the view that massage is not merely a relaxation therapy but a biologically active intervention with measurable short-term immunomodulatory effects, without establishing effects on metabolic outcomes.

In addition, modern pharmacological strategies such as SGLT2 inhibitors have also been shown to reduce IL-6 and TNF-α levels through systemic anti-inflammatory mechanisms (Zhang et al., 2024). This suggests that suppression of inflammatory pathways represents a therapeutic target across modalities—whether through pharmacological or physical interventions. Accordingly, the anti-inflammatory effects of massage may involve overlapping inflammatory pathways with pharmacological therapies, but cannot be considered physiologically or clinically equivalent in efficacy, particularly given the exploratory nature of the present study. Globally, Bayat et al. (2020) emphasized that massage therapy is a safe complementary approach in individuals with diabetes, with potential benefits related to physiological well-being and inflammation modulation. Integrating this therapy into diabetes management may support inflammation control as part of a multimodal care strategy, without adding to patients' pharmacological burden.

Despite these promising results, several limitations should be acknowledged when interpreting the findings. First, the intervention duration was relatively short (four weeks), so long-term effects on inflammatory regulation and glycemic control remain uncertain. Second, the sample size was limited, and individual factors such as age, physical activity level, and dietary patterns may have influenced inflammatory responses to massage. Additionally, this study did not assess secondary metabolic parameters such as HbA1c, insulin levels, or HOMA-IR, which could provide a more comprehensive understanding of the relationship between inflammation improvement and metabolic control. Future studies employing randomized controlled trial (RCT) designs with longer intervention durations and molecular signaling assessments (e.g., NF-κB, IL-10, TGF-β) are needed to elucidate the underlying biological mechanisms. Combining massage therapy with light physical exercise or nutritional interventions could further enhance anti-inflammatory effects and should be explored in future clinical research.

This study provides empirical evidence that moderate-pressure massage therapy administered over four weeks significantly reduces IL-6 and TNF-α levels in patients with type 2 diabetes mellitus. The findings suggest that mechanical stimulation through tissue mechanotransduction may play a role in attenuating chronic systemic inflammation that contributes to insulin resistance. With demonstrated immunomodulatory effects and a simple, practical therapeutic protocol, massage therapy holds potential

for integration as a non-pharmacological complementary intervention in holistic T2DM management. These findings contribute preliminary support to the mechanical immunomodulation concept and generate hypotheses for future biomechanically driven rehabilitative approaches to control chronic metabolic inflammation. Consequently, this study provides a preliminary scientific rationale, rather than conclusive evidence, for the further investigation of safe and sustainable complementary therapy models and their potential implications for patient-centered outcomes, including quality of life, in larger and better-controlled studies.

Overall, this study demonstrated that sport massage was associated with reductions in the pro-inflammatory cytokines IL-6 and TNF-α in patients with type 2 diabetes mellitus. Although greater reductions were observed in male participants than in females, these sex-related differences should be interpreted cautiously, as they may be influenced by potential confounding factors such as age, body mass index, baseline inflammatory levels, and regression to the mean. Therefore, sport massage may represent a complementary therapeutic approach for attenuating inflammatory responses in individuals with type 2 diabetes mellitus; however, further controlled studies are warranted to clarify the extent and mechanisms of any sex-specific effects.

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Declaration of Interest

The authors of this article declared no conflict of interest.

Ethical Considerations

The study protocol adhered to the principles outlined in the Helsinki Declaration, which provides guidelines for ethical research involving human participants. Ethical considerations in this study were that participation was entirely optional.

Transparency of Data

In accordance with the principles of transparency and open research, we declare that all data and materials used in this study are available upon request.

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Authors' Contributions

All authors equally contribute to this study.

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