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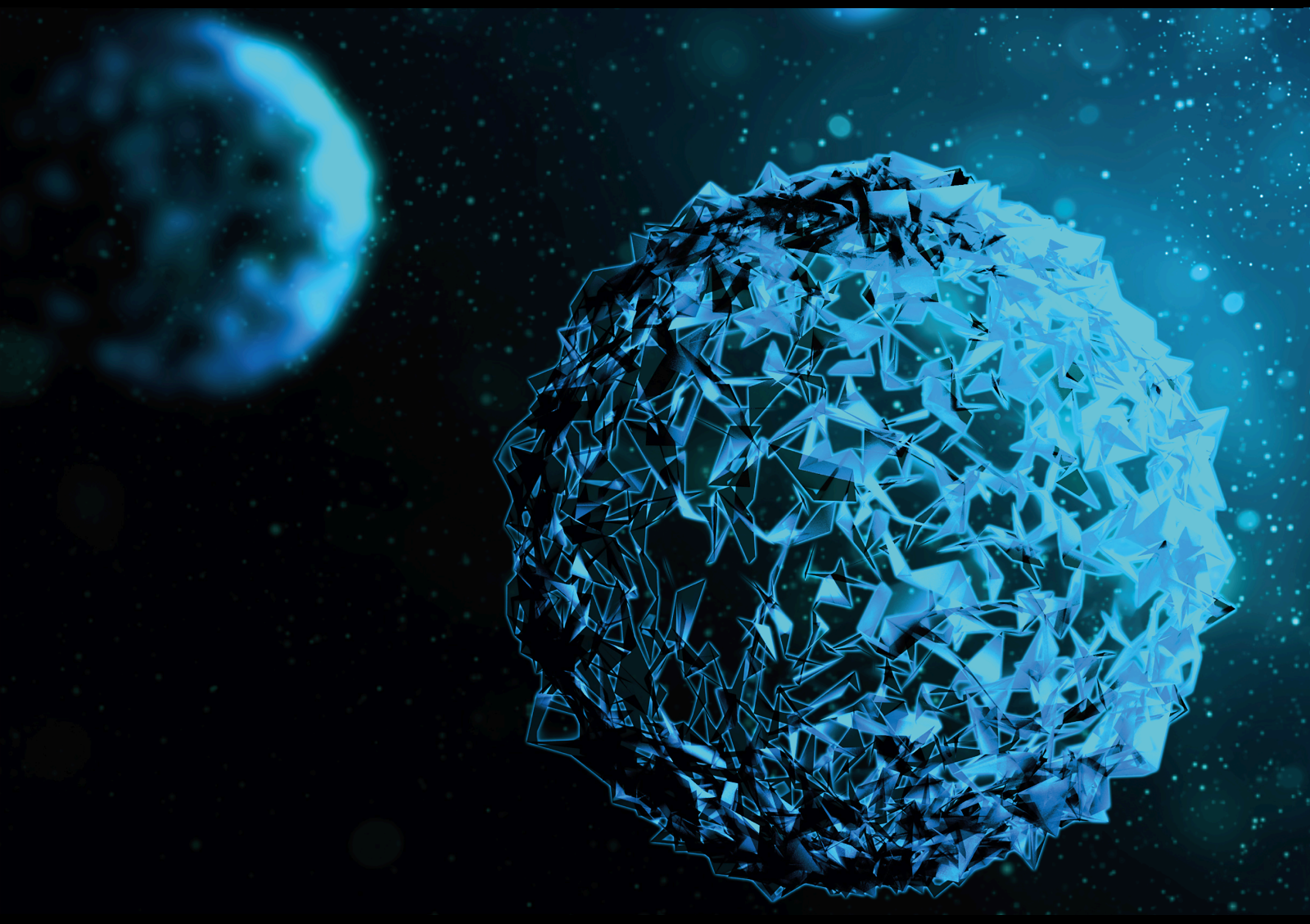

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Editorial Board

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Editorial

Integrated Role of Nonpharmacological Interventions for Rehabilitation of Individuals with Musculoskeletal Disorders

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Nonpharmacological interventions (NPI) include any treatment without drug treatment without medication such as physical activity and psychosocial interventions (speech-based therapies). These methods have a preventive or therapeutic action and aim to prevent, treat, or cure health problems. It takes the form of a product, method, and program or service whose content must be known by the user, and it is related to biological mechanisms and/or psychological processes. Among them, various technical procedures related to (i) physiotherapy (hand manipulations, electromagnetic radiations, and electrical and ultrasound sources), ((iii) assistive devices, (iv) psychotherapy and behavioral actions (habits in general and nutrition), (v) occupational therapy, (vi) speech and language therapy, and (vii) complementary and alternative medicine [1]. Moreover, physical exercises and vibratory therapy such as segmental and whole-body vibration exercises might be included among the NPI. In fact, various populations including the elderly with different clinical disorders have been submitted to these interventions.

It is important to highlight that nonpharmacological and pharmacological therapies are complementary on the management of the elderly with clinical conditions, often with multimorbidity. It is widely acknowledged that NPI, including surgery, can be effective and sometimes more effective than pharmacological therapy in the treatment of several common, chronic, and undesirable conditions [2, 3] Indeed, [4] consider that NPI in older people can be just as important as pharmacological therapies to treat chronic conditions. It is suggested that ageing populations would require more and more relief from chronic pain and disability and that the prevalence of musculoskeletal disorders (MSDs) will continue to rise [5, 6]. Moreover, MSDs consume a large amount of health and social resources and are a major cause of disability in both low- and high-income countries [7].

MSDs are undesirable multifactorial clinical conditions affecting different human body parts and are the leading cause of years lived with disability in the world affecting children, working age population, and elderly. Although not fatal, these conditions have a high prevalence and significant impact on daily living activities by limiting and restricting the participation of individuals affecting them and society. In addition, individuals with several diseases such as spinal cord injury, cerebral palsy, and stroke are more prone to develop MSDs. Otherwise, there is a widespread underuse of non-pharmacological therapies on the management of chronic diseases and associated clinical conditions of the elderly. Considering that the prevalence of these conditions is expected to increase in the coming years due to ageing, rising levels of obesity, and physical inactivity, there is a clear demand in research focusing on the rehabilitation of MSDs.

Putting together the previous rationale, the challenges and reflections in organizing this special issue, we thank the Hindawi publisher for the confidence. A special thanks to all authors that contributed in this special issue of the journal *Biomedical Research International* entitled "Integrated Role of Nonpharmacological Interventions for Rehabilitation of Individuals with Musculoskeletal Disorders." The authors tried to bring a useful issue involving the proper use of NPI for the rehabilitation of individuals having musculoskeletal disorders. They contributed by giving scientific evidence and disseminated the knowledge about the benefits and the plurality of NPI and the management of the MSDs. The aim was to provide a multidisciplinary discussion forum covering all rehabilitation professions regarding the integrated role of NPI in the aim to reduce the burden of individuals living with MSDs. The readers will find scientific information about the integrated role of NPI for MSDs in the elderly, sports, and special populations (e.g., pregnant women, cancer patients, and others) and strategies to avoid and manage musculoskeletal disorders in the workplace and prevention of MSDs across all lifespans and settings.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this editorial.

Mario Bernardo-Filho
Borja Sañudo
Adérito Seixas
Danúbia Sá-Caputo
Redha Taiar

References

[1] T. C. Hoffmann, C. Erueti, and P. P. Glasziou, "Poor description of non-pharmacological interventions: analysis of consecutive sample of randomised trials," *BMJ*, vol. 347, no. sep10 1, 2013.

[2] H. Naci and J. P. A. Ioannidis, "Comparative effectiveness of exercise and drug interventions on mortality outcomes: metaepidemiological study," *BMJ*, vol. 347, no. oct01 1, 2013.

[3] K. Rees, R. S. Taylor, and S. Ebrahim, "Exercise-based rehabilitation for heart failure," *The Cochrane Database of Systematic Reviews*, 2014.

[4] I. Abraha, A. Cruz-Jentoft, R. L. Soiza, D. O'Mahony, and A. Cherubini, "Evidence of and recommendations for non-pharmacological interventions for common geriatric conditions: the SENATOR-ONTOP systematic review protocol," *BMJ Open*, vol. 5, no. 1, p. e007488, 2015.

[5] A. Williams, S. J. Kamper, J. H. Wiggers et al., "Musculoskeletal conditions may increase the risk of chronic disease: a systematic review and meta-analysis of cohort studies," *BMC Medicine*, vol. 16, no. 1, p. 167, 2018.

[6] L. B. Connelly, A. Woolf, and P. Brooks, "Cost-effectiveness of interventions for musculoskeletal conditions," in *Disease Control Priorities in Developing Countries*, D. T. Jamison, J. G. Breman, A. R. Measham, G. Alleyne, M. Claeson, D. B. Evans, P. Jha, A. Mills, and P. Musgrove, Eds., World Bank, Washington (DC), 2nd edition edition, 2006, Chapter 51.

[7] R. Y. Barnes, J. Jelsma, and R. Parker, "Improvements in health-related quality of life and function in middle-aged women with chronic diseases of lifestyle after participating in a nonpharmacological intervention programme: a pragmatic randomised controlled trial," *African Journal of Disability*, vol. 8, 2019.

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Review Article

Whole-Body Vibration for Individuals with Reconstructed Anterior Cruciate Ligament: A Systematic Review

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Background. ACL ruptures are a prevalent condition, affecting daily living activities, associated with high financial burden. *Objective*. To assess the effect of whole-body vibration (WBV) in the rehabilitation of patients with reconstructed anterior cruciate ligament. *Methodology*. An electronic search in Pubmed, Scopus, Web of Science, and PEDro databases was conducted and randomized controlled trials (RCTs) in humans that analysed the effects of WBV in patients with ACL injury subjected to reconstruction surgery, published in English, Portuguese, Spanish, Italian, or French were included. Records were identified through database search and reference screening by two reviewers, which independently examined titles and abstracts and irrelevant studies were excluded based in eligibility criteria. Relevant full texts were analysed for eligibility, and all relevant studies were included in the systematic review. *Results*. Ten studies were included in the systematic review with a mean methodological quality score of 6. Results demonstrate positive effects of WBV in relevant outcomes such as knee function, electromyographic activity, balance, and muscle strength. *Conclusions*. WBV demonstrated a positive effect in strength, balance, electromyographic activity, and knee function.

1. Introduction

The knee is a complex joint that is mobile, flexible, strong, and resistant, responsible to support the body mass, that allows to be engaged in a wide range of movements and activities. Injuries in this joint and related structures greatly impair daily activities. The anterior cruciate ligament (ACL) is one of the cruciate ligaments responsible to stabilize the knee [1–3] during flexion and extension, in which the ACL and the posterior cruciate ligament act contributing to the prevention of excessive forward or backward movements of the tibia in relation to the femur, and providing rotational stability in the knee [4].

ACL rupture is a common sports-related injury that requires proper rehabilitation interventions aiming the complete recovery of the athlete [1, 5]. The annual incidence of ACL injuries is about 70 per 100,000 person-years and the costs to treat these patients arise to $7.6 billion when treated with reconstruction surgery [6, 7].

The causes of ACL sprains or ruptures are multifactorial, and this injury is the most prevalent sport injury in the knee [6, 8]. It is possible to consider that the impairment of the ACL occurs during activity/sports with sudden changes in the direction of movement, jumping and landing abnormally, rapid stopping, a stroke directly in the lateral side of the knee, or slowing down while running [1]. Symptoms of the ACL injuries include pain, tenderness along the joint line, and swelling, decreased or loss of range of motion, and difficulty to the ambulation [1]. The weakness of the knee extensor muscles has been described as one of the major concerns in the rehabilitation after ACL injury [9]. The mechanisms related to the loss of muscle strength due to ACL injuries

are not well understood [10], and depending on the severity of the injury, the individuals are referred to an orthopaedic physician to verify the treatment options, including surgery, or to a physiotherapist for rehabilitation interventions [1].

Surgical repair and reconstruction tend to be the option to athletes and individuals who are younger and more active. Moreover, surgical repair/reconstruction can be also an option for those with important instability of the knee [1]. An important factor contributing to weakness after ACL injury is a failure in voluntary activation of the knee extensors independently of structural damage to the muscle or motoneurons. It is suggested that abnormal afferent discharge from the knee may modify the excitability of reflex pathways within the spinal cord. In consequence, this would lead to a reduction of the excitability of the α-motoneuron of the knee extensors [11]. Different interventions, either open or closed kinetic chain exercises, have been proposed to deal with muscle weakness in individuals with deficient ACL [12, 13].

A type exercise that can be used to an effective management of individuals with ACL injuries comprises the use of mechanical vibration generated in a vibrating platform (VP) that is transmitted to an individual standing over the VP. This modality is called whole-body vibration (WBV) [14–16].

The interest in the clinical application of WBV exercise is increasing, and it is believed that WBV can improve strength in the lower limb muscles [17, 18]. The authors demonstrated that the enhanced muscle contraction during WBV would be evoked via the stretch reflex pathway [12, 13]. Indeed, acute changes in motor output have been related to the increased sensitivity of muscle spindles [17, 19]. The neuromuscular response to WBV would depend on the type, frequency, peak-to-peak displacement, peak acceleration, and duration of the intervention with mechanical vibration as well as on the adopted body position on the VP [20]. The frequency of the mechanical stimulus has received increased attention [21, 22]. Cardinale and Lim [21] described a rise in neuromuscular activation of the vastus lateralis (VL) muscle when frequency increased up to 30 Hz, which was followed by a decrease in activation as WBV frequency increased. Marín et al. [23] reported that the magnitude of the WBV effect was higher with the amplitude of 4 mm in comparison to 2 mm for the VL and gastrocnemius medialis muscles. This neuromuscular activation can be of interest in individuals with ACL injuries and previous research has evidenced beneficial effects in strength, balance, and electromyographic activity (e.g., [15]); however, no systematic analysis of the existing literature about this topic has been conducted.

Considering this rationale, the aim of this systematic review is to assess the effect of WBV in the rehabilitation of patients with reconstructed anterior cruciate ligament (RACL).

2. Methods

The review was reported based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [24].

2.1. Eligibility Criteria. We considered randomized controlled trials (RCTs) in humans that analysed the effects of WBV in patients with ACL injury subjected to reconstruction surgery, if the effects of WBV could be isolated from concomitant interventions, if focusing on the effects of WBV in muscle strength, balance, postural stability, proprioception, electromyographic activity, and functionality, and if published in English, Portuguese, Spanish, Italian, or French. No publication date restrictions were defined.

2.2. Operational Definitions. WBV was defined as an exercise intervention consisting of the application of sinusoidal vibration to individuals using specialized vibrating platforms. These platforms deliver vibration to the whole body using two different systems, uniform movements of the platform up and down and side alternating displacements on the left and right side of a fulcrum [25].

2.3. Search Strategy. We conducted an electronic search in Pubmed, Scopus, Web of Science, and PEDro databases using the following search string ((“whole-body vibration” OR “whole body vibration”) AND (“anterior cruciate ligament” OR ACL)). Secondary searches were conducted on the reference lists and citation tracking of included studies to identify other possible relevant studies. The keywords used in the search were defined based on the PICO strategy, focusing on patients with RACL (Participants) receiving WBV intervention (Intervention) without restrictions regarding comparisons (Comparison), allowing comparisons to placebo, usual care or no intervention. All reported outcomes (Outcomes) were allowed if considered relevant to the studied population.

2.4. Study Selection and Data Extraction. All references were exported to a data management software (EndNote X9), and duplicates were removed. The review was conducted following four steps. Records were identified through database search and reference screening (Identification) and two reviewers (AS, MB-F) independently examined titles and abstracts and irrelevant studies were excluded based in eligibility criteria (Screening). Relevant full texts were analysed for eligibility (Eligibility), and all relevant studies were included in the systematic review. The disagreement was resolved by a third reviewer (DS-C).

The same researchers were responsible for data extraction from the included studies. Data regarding study information (author and year), study design and time of follow-up, subjects (sample size), demographics (age, sex, Body Mass Index), type of graft, intervention protocols, WBV intervention, outcomes, and results were extracted.

2.5. Methodological Quality and Risk of Bias. Two reviewers (AS, BS) used the PEDro scale [26, 27] to assess the methodological quality and the Cochrane Collaboration’s tool to assess the risk of bias of the included studies [28].

3. Results

A total of 59 studies were identified through a database search and, after the removal of duplicates, 27 studies were

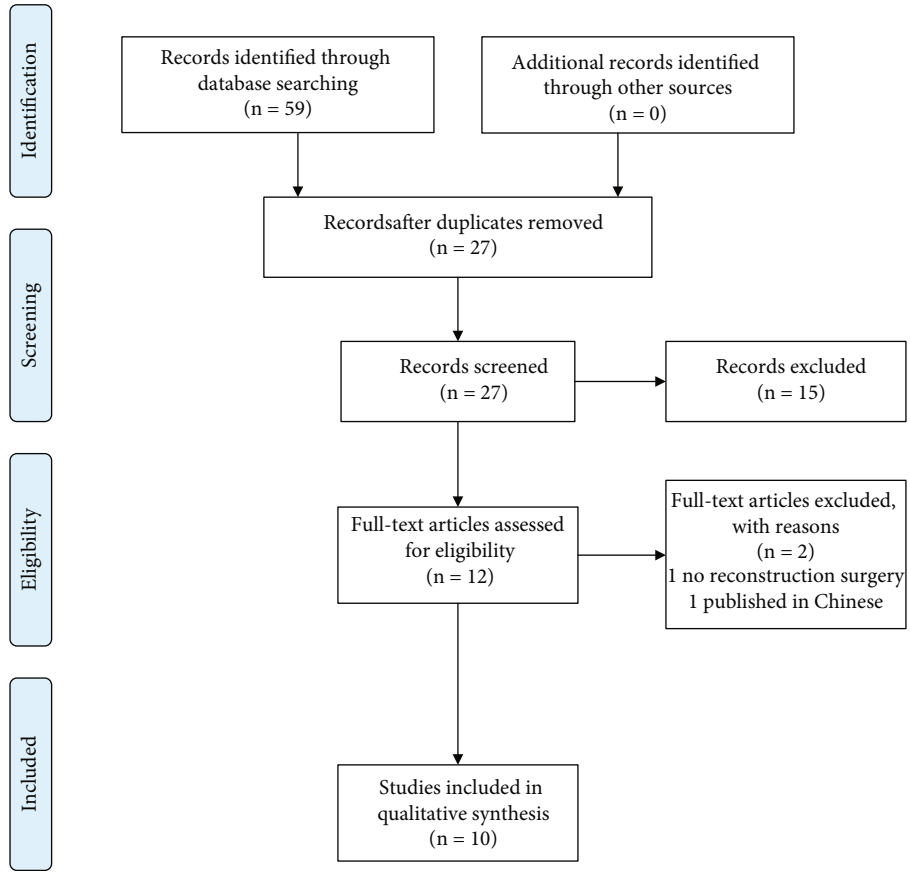

Figure 1: PRISMA flow diagram of the literature selection process.

Reference/Item	2	3	4	5	6	7	8	9	10	11	Score
Salvarani et al. 2003											6/10
Moezy et al. 2008											5/10
Fu et al. 2013											7/10
Berschin et al. 2014											6/10
Pamukoff et al. 2016											6/10
Pistone et al. 2016											6/10
Pamukoff et al. 2017											6/10
Costantino et al. 2018											6/10
Pamukoff et al. 2018											6/10
da Costa et al. 2019											6/10
	100%	10%	100%	0%	0%	40%	100%	50%	100%	100%	

Figure 2: Methodological quality assessment of the included studies with PEDro scale. (2) Subjects were randomly allocated to groups (in a crossover study, subjects were randomly allocated an order in which treatments were received); (3) allocation was concealed; (4) the groups were similar at baseline regarding the most important prognostic indicators; (5) there was blinding of all subjects; (6) there was blinding of all therapists who administered the therapy; (7) there was blinding of all assessors who measured at least one key outcome; (8) measures of at least one key outcome were obtained from more than 85%; of the subjects initially allocated to groups; (9) all subjects for whom outcome measures were available received the treatment or control condition as allocated or, where this was not the case, data for at least one key outcome was analysed by "intention to treat"; (10) the results of between-group statistical comparisons are reported for at least one key outcome; (11) the study provides both point measures and measures of variability for at least one key outcome.

identified. During the screening process, 15 publications were excluded for not being related to the research question, and the full text of 12 studies was reviewed in detail. After careful analysis, 2 studies were excluded (1 because the subjects were not subjected to a reconstruction surgery and 1 because it was published in Chinese). Finally, 10 studies were included in the systematic review. The selection process is schematized in Figure 1.

The included studies had a mean score of 6 when assessing the methodological quality with the PEDro scale (Figure 2), with a minimum of 5 points and a maximum of 7, evidencing moderate methodological quality.

Detailed description and results of the included studies are presented in Table 1. Seven out of ten studies were designed as randomized controlled trials [14, 15, 29–33], and three were designed as randomized crossover trials [16, 34, 35]. Four studies analysed the effects of a single session of WBV [16, 34, 35], and six studies analysed the effects of WBV programs with a minimum of two weeks (10 sessions) [33] and a maximum of ten weeks (30-40 sessions) [29]. Four studies investigated the effects of WBV and other programs [14, 30, 32, 33], and six investigated the effects of WBV alone [15, 16, 29, 31, 34, 35]. Only three studies had follow-up assessments at 1 week after the intervention [33], 3 months after the intervention [30], and one month after the intervention [32].

Most studies included male and female patients; however, Moezy et al. [31] and da Costa et al. [15] included only male subjects, Costantino, Bertuletti, and Romiti [14] have included only female participants and [32] have not stated the gender of the participants. In general, the sample size was small, ranging between 20 participants [16, 33–35] and 48 participants [30]. Studies evidenced a low attrition rate.

3.1. WBV Protocols. The WBV intervention protocols were heterogenous. Intervention varied in duration (as stated before), in training frequency, session duration, number of repetitions, amount of rest between repetitions, in frequency, amplitude, type of vibration (synchronous and site alternating), modality of exercises included (static or static and dynamic), and number of exercises per session. Patients were standing in all studies, with knee flexion varying from "slight" to 60° of flexion. Parameters were fixed during the protocol in some studies and varying in others, mostly based on time criteria. The timing of implementation of the WBV protocol greatly varied between studies, starting between 2 weeks [29] and 50.6 ± 21.3 months [34, 35] after surgery.

A summary of WBV protocols can be found in Table 1.

The risk of bias of included studies was assessed with the Cochrane risk of bias tool (Figure 3).

3.2. Assessed Outcomes. Several outcomes were assessed: running biomechanics (1 study: [16]), functional tests [30], Corticomotor excitability (1 study: [34]), active range of motion (1 study: [29]), motor neuron pool excitability (1 study: [34]), joint position sense (2 studiess: [30, 31]), joint laxity (2 studiess: [29, 30]), Lysholm score (2 studiess: [29, 32]), surface electromyographic signal (3 studiess: [15, 34, 35]), balance or postural stability (5 studiess: [15, 29–32]), and muscle strength (8 studiess: [14, 15, 29, 30, 32–35]).

3.2.1. Running Biomechanics. A single session of WBV improved knee flexion excursion during running in the injured limb [16]. The other outcomes assessed in the study, such as loading rate, peak knee flexion angle, peak knee flexion moment, and peak vertical ground reaction force have not significantly changed. The study also suggests that the improvement was higher in patients with more impairment at baseline.

3.2.2. Functional Tests. Fu et al. [30] described a significant improvement in the shuttle run test in the WBV group and in the single-legged hop test in the reconstructed limb in both groups. The WBV group also evidenced better limb symmetry during the tests. In the tests Carioca and triple hop, no significant differences were found between the groups.

3.2.3. Corticomotor Excitability. The motor-evoked potential amplitude has not changed after one session of WBV but significant changes in an active motor threshold occurred [34].

3.2.4. Active Range of Motion. Berschin et al. [29] reported an increment in active range of motion to full amplitude after the WBV protocol but with no significant difference between the groups.

3.2.5. Motor Neuron Pool Excitability. Regarding *H*-reflex and maximal muscle response (*M*-wave), in the study of Pamukoff et al. [34], no significant differences were found after the intervention.

3.2.6. Joint Position Sense. Moezy et al. [31] reported significant improvements in proprioceptive acuity after WBV intervention in both testing amplitudes 30° and 60° of knee flexion and both limbs (injured and uninjured) except in uninjured knee at 30°, but not in the control group. However, Fu et al. [30] reported no significant differences in proprioceptive acuity when repositioning to 30° and 60° of knee flexion after intervention and between groups in both lower limbs.

3.2.7. Joint Laxity. Both ([29, 30] reported no significant side-to-side differences in joint laxity in WBV and control groups before and after the intervention.

3.2.8. Lysholm Score. Berschin et al. [29] reported that knee function improved in both WBV and control group, with no significant differences between the groups but [32] reported significantly higher functional gains in the treatment group both at post-intervention and follow-up.

3.2.9. Surface Electromyographic Signal. Pamukoff et al. [34] reported significant changes in quadriceps electromyographic amplitude but not in the hamstrings after WBV, and electromechanical delay has not changed after intervention in the study of Pamukoff et al. [35]. However, in the study of da Costa et al. [15], the electromyographic amplitude of the *vastus lateralis* and *vastus medialis* has not changed after intervention.

3.2.10. Balance or Postural Stability. Moezy et al. [31] observed a significant improvement in overall stability, anteroposterior, and mediolateral indexes in both opened and closed eyes conditions after WBV, which was statistically greater than in the control group. Fu et al. [30] have also reported significantly higher improvements in overall, anteroposterior and mediolateral stability indexes in the WBV group both after intervention and at follow-up (3 months). Berschin et al. [29] have also reported significant improvements in stability index after WBV, but not in the control group. Significant changes between groups were observed in the 8^{th} and 11^{th} weeks. Another study reported significant improvements in stability in balance tests with eyes opened, with better results in the WBV group, but not with eyes

Table 1: Summary table of the included studies in the review with main findings.

Study	Study design	Demographics	Graft	Intervention protocol	WBV intervention	Follow-up after intervention	Results
Salvarani [33]	RCT	20 subjects (17 males/3 females) TG: 10 subjects (29.7 ± 7.8 years; 174.1 ± 7.7 cm; 72.0 ± 7.6 kg) CG: 10 subjects (26.8 ± 5.2 years; 175.2 ± 8.3 cm; 73.2 ± 7.9 kg)	Patellar tendon	1 month after surgery: TG: standard treatment + WBV 10 sessions 1 daily session/2 weeks CG: standard + isometrics in the same position of TG 10 sessions 1 daily session/2 weeks	Synchronous vibration Freq: 30 Hz Duration: 1 min/repetition, 5 repetitions Rest: 1 min rest/set Isometric contraction with position: Knee flexion of 25°	1 week	TG: significant increase in extensor strength after intervention. Significant increase from baseline to follow-up but not between postintervention and follow-up CG: significant increase in extensor strength after intervention. Significant increase from baseline to follow-up but not between postintervention and follow-up.
Moezy [31]	RCT	20 male subjects (23 initially, 3 dropped out during intervention, 2 in TG and 1 in CG) TG: 12 subjects (24.51 ± 3.38 years; 1.74 ± 0.05 m; 74.30 ± 10.61 kg; 24.51 ± 3.38 kg/m2) CG: 11 subjects (22.70 ± 3.77 years; 1.78 ± 0.07 m; 78.00 ± 10.12 kg; 24.62 ± 2.78 kg/m2)	Patellar tendon	12 weeks after surgery: TG: WBV 12 sessions 3x/week for 1 month CG: conventional strength, flexibility, and proprioceptive training program 12 sessions 3x/week for 1 month	Synchronous vibration Parameters changed during intervention Freq: 30-50 Hz Duration: 30-60 secs/set Rest: 30-60secs Amplitude: 2.5–5 mm Modality: static-static and dynamic Session duration: 4-16 min Position: several exercises, different knee position	None	TG: significant improvement in overall stability, anteroposterior and mediolateral indexes in opened and closed eye tests. Significant improvements in absolute angular errors in both knees in both testing amplitudes (except in healthy knee at 30°) CG: significant improvements in overall stability in opened and closed eyes and significant improvement in mediolateral index in closed eye test. No significant differences in proprioceptive acuity. The improvement in stability and proprioceptive acuity scores was significantly higher in the TG, except in absolute angular error in healthy knees at 30°
Fu [30]	RCT	48 subjects (32 males/16 females, 9 dropped out, 5 in TG and 4 in CG but were included in the analysis) TG: 24 subjects (18 males, 23.3 ± 5.2 years; 66.5 ± 12.8 *kg*; 1.71 ± 0.08 m; 22.75 ± 3.44 kg/m2) CG: 24 subjects (14 males, 25.2 ± 7.3 years; 66.7 ± 10.5 kg; 1.70 ± 0.07 m; 23.11 ± 2.84 kg/m2)	Hamstrings	1 month after surgery: TG: WBV+conventional training 16 sessions 2x/week for 2 months CG: conventional training	Synchronous vibration Parameters changed during intervention Freq: 35-50 Hz Duration of sets: 30-45 secs Rest: 15-30 secs Amplitude: 4 mm Modality: static-static and dynamic Session duration: 4-16 min Position: several exercises, different knee position	3 months	No significant differences regarding joint position sense throughout 6 months between groups, in both limbs. With eyes closed, the TG had significantly better overall anteroposterior and mediolateral stability indexes than the CG. The TG evidenced significant improvements in overall anteroposterior and mediolateral stability indexes 3 months after surgery, but the anteroposterior index significantly decreased in the CG. Reconstructed limb's knee extensors in the TG evidenced significantly higher peak torques than the CG in all velocities (60, 180, and 300°/s) at 6 months after surgery.

Table 1: Continued.

Study	Study design	Demographics	Graft	Intervention protocol	WBV intervention	Follow-up after intervention	Results
							Reconstructed limb's knee flexors in the TG evidenced significantly higher peak torques than the CG at 60 and 300°/s. 3 months after training only the TG evidenced significant improvement in knee extensors and flexors at 300°/s. The TG also evidenced better limb symmetry throughout the rehabilitation process. The TG performed significantly better in the shuttle run test. In the single-legged hop test, the reconstructed limb in both groups performed significantly better. Subjects in the TG had better limb symmetry throughout the rehabilitation process. No significant differences between both groups regarding triple hop and carioca tests. No significant differences regarding joint laxity between the two groups and both groups achieved full range of motion.
Berschin [29]	RCT	40 subjects (29 males/11 females) TG: 20 subjects (14 males; 27 ± 4.2 years; 23.2 ± 3.4 kg/m2) CG: 20 subjects (15 males; 28 ± 6.8 years; 24.3 ± 2.8 kg/m2)	Patellar tendon	2 weeks after surgery: TG: WBV exercise protocol average 40 ± 2.3 min/session Unclear number of sessions 3-4x/week for 10 weeks CG: standard strengthening protocol average 85 ± 4.4 min/session Unclear number of sessions 3-4x/week for 10 weeks	Side alternating vibration Parameters changed during intervention (3 phases) Freq: 10-30 Hz Duration of sets: 1-2 min Rest: not clearly stated Amplitude: 5-9 mm Modality: static-dynamic Position: slight knee flexion in static, varying in dynamic exercise	None	Range of motion increased in both groups to full motion with no significant differences between groups. No significant changes in joint laxity in both groups after intervention. Extensor and flexor strength improved significantly in both groups with similar results in isometric and isokinetic testing, except for isometric extensor testing at 11 weeks which was significantly higher in the CG. The TG evidenced a significant increase in stability index, but not the CG. Significant differences in this outcome between groups in the 8th and 11th weeks. Knee function (Lysholm score) improved significantly in both groups without significant differences between groups.

Table 1: Continued.

Study	Study design	Demographics	Graft	Intervention protocol	WBV intervention	Follow-up after intervention	Results
Pamukoff [35]	Randomized crossover trial	20 subjects (6 males, 21.1 ± 1.2 years; 168.4 ± 9.5 cm; 68.3 ± 14.9 kg)	16 patellar tendon 3 hamstrings 1 allograft	50.6 ± 21.3 months after surgery TG: WBV, 1 session TG2: local muscle vibration, 1 session CG: no intervention	Synchronous vibration Freq: 30 Hz Duration: 1 min/repetition 6 repetitions Rest: 2 min between repetitions Amplitude: not stated Acceleration: 2 g Modality: static Position: knee flexion 60°	None	No significant changes were observed in the rate of torque development, motor-evoked potential amplitude, *H*-reflex amplitude, hamstrings electromyographic amplitude, and quadriceps *M*-wave amplitude. Significant improvements in active motor threshold (corticomotor excitability), central activation ratio, quadriceps peak torque, and quadriceps electromyographic amplitude. Improvements after WBV were not significantly different from those observed in local muscle vibration.
Pistone [32]	RCT	34 subjects (gender not specified) TG: 17 subjects (27 ± 7 years; 1.76 ± 0.08 m; 73.3 ± 11.9 kg) CG: 17 subjects (29 ± 7 years; 1.75 ± 0.08 m; 73.0 ± 10.7 kg)	Semitendinous	1 month after surgery: TG: traditional rehabilitation program and WBV 5 days/week TRP+12 sessions, 3 sessions/week for 4 weeks, of WBV CG: traditional rehabilitation program 5 days/week TRP	Synchronous vibration Freq: optimal vibration frequency—frequency (Hz) with maximal muscle activation Duration: 1 min/repetition; number of repetitions increased during protocol from 3 to 10 Rest: 1 min between repetitions Amplitude: 2 mm Modality: static Position: knee flexion of 60°	1 month	Limb symmetry index in knee extension MVC increased significantly between baseline and postintervention and between baseline and follow-up in both groups equally. Limb symmetry in knee flexor MVC increased significantly between baseline and follow-up in the CG and between baseline and postintervention, between baseline and follow-up, and between postintervention and follow-up in the TG. LSI of knee flexion in the TG was significantly higher than CG at postintervention and follow-up. During balance trials with eyes open, significant changes were observed over time in both groups, but at follow-up, the TG performed significantly better. During balance trials with eyes closed, there were no significant changes over time, but at follow-up, the TG performed significantly better. Improvements in the Lysholm score were greater in TG than in the CG at postintervention and follow-up.

Table 1: Continued.

Study	Study design	Demographics	Graft	Intervention protocol	WBV intervention	Follow-up after intervention	Results
Pamukoff [35]	Randomized crossover trial	20 subjects (6 males, 21.1 [20.6-21.6] years; 168.4 [164.2-172.6] cm; 68.3 [61.8-74.8] kg) (mean [95% CI])	16 patellar tendon 3 hamstrings 1 allograft	50.6 (95% CI: 41.3-59.9) months after surgery TG: WBV, 1 session TG2: local muscle vibration, 1 session CG: no intervention	Synchronous vibration Freq: 30 Hz Duration: 1 min/repetition 6 repetitions Rest: 2 min between repetitions Amplitude: not stated Acceleration: 2 g Modality: static Position: knee flexion 60°	None	WBV, but not the other conditions, significantly increased the early rate of torque development (0-100 ms) during a maximal isometric knee extension. Late rate of torque development and electromechanical delay has not changed significantly. No differences between conditions were observed after intervention.
Costantino [14]	RCT	38 female subjects (39 initially, 1 dropped during intervention in the TG) TG: 19 subjects (25.47 ± 2.01 years; 166.16 ± 5.18 cm; 56.00 ± 3.92 kg; 20.29 ± 1.28 kg/m2) CG: 19 subjects (25.42 ± 2.39 years; 166.11 ± 5.34 cm; 55.32 ± 5.18 kg; 20.06 ± 1.80 kg/m2)	Patellar tendon	13 weeks after surgery: TG: 2 static exercises with WBV in addition to the rehabilitation protocol 3 sessions/week for 8 weeks. CG: 2 static exercises without WBV in addition to the rehabilitation protocol 3 sessions/week for 8 weeks.	Synchronous vibration Freq: 26 Hz Duration: 1 min/repetition, 6 repetitions/exercise Rest: 1 min between repetitions, 2 min between sets Amplitude: 4 mm Modality: static Position: knee flexion of 25°	None	All strength parameters (peak torque and maximum power) in knee extensors and knee flexors improved significantly in both groups. TG had a significantly higher improvement than the CG.
Pamukoff [16]	Randomized crossover trial	20 subjects (15 females, 22.3 ± 3.3 years; 173.0 ± 9.1 cm; 71.8 ± 15.3 kg)	10 patellar tendon 7 hamstrings 3 allograft	44.9 ± 22.8 months after surgery TG: WBV, 1 session CG: no intervention	Synchronous vibration Freq: 30 Hz Duration: 1 min/repetition 6 repetitions Rest: 2 min between repetitions Amplitude: not stated Acceleration: 2 g Modality: static Position: knee flexion 60°	None	WBV vibration significantly increased knee flexion excursion in the injured limb but not loading rate, peak knee flexion angle, peak knee flexion moment, and peak vertical ground reaction force. Subjects with more baseline impairment had larger changes in knee flexion excursion.

Table 1: Continued.

Study	Study design	Demographics	Graft	Intervention protocol	WBV intervention	Follow-up after intervention	Results
da Costa [15]	RCT	44 male subjects (48 initially, 4 dropped out during evaluation due to fatigue and/or discomfort, before intervention) TG: 22 subjects (28.0 ± 5.52 years; 1.75 ± 0.79 m; 27.1 ± 4.49 kg/m2) CG: 22 subjects (26.8 ± 6.83 years; 1.74 ± 0.63 m; 26.5 ± 2.96 kg/m2)	Gracilis-semitendinosus	Postoperative time: TG: 16.8 ± 1.55 weeks CG: 17.0 ± 1.26 weeks TG: WBV squat 1 session CG: squat without vibration	Synchronous vibration Freq: 50 Hz Duration: 10 sets of 30 secs Rest: 30 secs between sets Amplitude: 4 mm Modality: static Position: knee flexion of 40°	None	No significant improvements in any of the outcome variables (peak torque, total work, electromyographic activity, and oscillation of the centre of pressure) and no significant differences between groups were observed.

RCT: randomized controlled trial; COP: centre of pressure; Freq: frequency; CG: control group; LSI: limb symmetry index; MVC: maximal voluntary contraction; TG: training group; ROM: range of motion; TRP: traditional rehabilitation program; WBV: whole-body vibration.

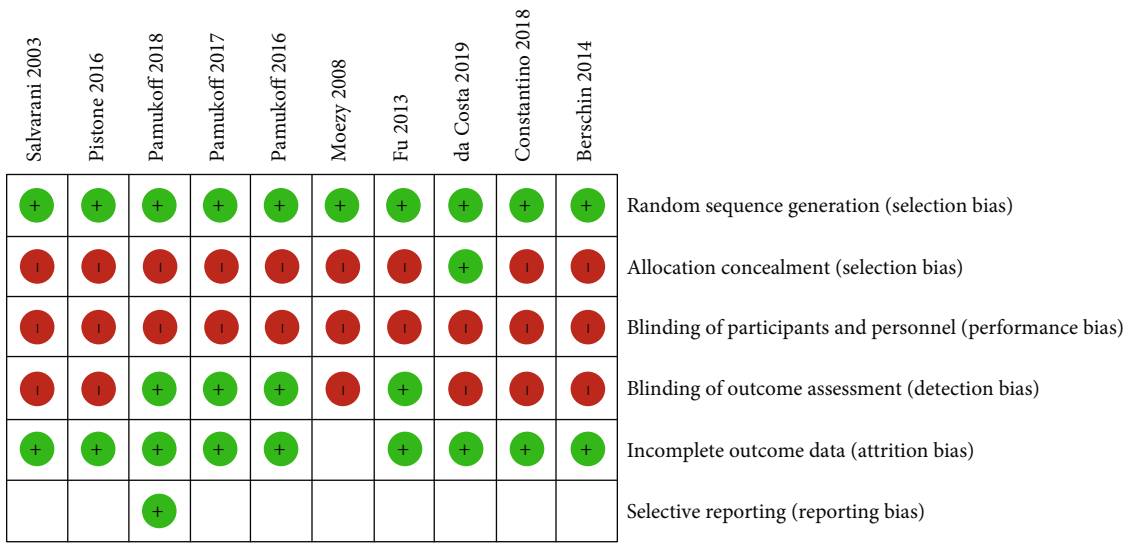

Figure 3: Risk of bias summary: authors assessment for each risk of bias criterion.

closed. However, in eyes closed tests at follow-up, the WBV group performed better [32]. The study of da Costa et al. [15] was the only not reporting significant improvements after intervention with WBV.

3.2.11. Muscle Strength. In studies analysing the effects of a single WBV session, Pamukoff et al. [34] reported significant improvements in central activation ratio and knee extensor peak torque but no significant changes in the rate of torque development. However, the same authors reported that WBV induced a significant increase in early (0-100 ms) rate of torque development but not in late (100-200 ms) rate of torque development [35]. Finally, da Costa et al. [15] found no significant differences in knee extensor peak torque after a single WBV session.

In studies analysing the effects of WBV programs with several sessions, Salvarani et al. [33] reported an increase in knee extensor strength in both WBV and control groups, but an increase in the mid-second of contraction only occurred after WBV. Fu et al. [30] observed an increase in knee extensor strength in the reconstructed limb in all analysed velocities (60°/s, 180°/s, and 300°/s) at the 3-month follow-up assessment, when compared to the control group, and an increase in flexor strength in the reconstructed limb at 60°/s, when compared to the control group. Three months after the rehabilitation program, only the WBV group had higher peak torque at 300°/s. Berschin et al. [29] verified an increase in extensor and flexor strength in both control and WBV groups. In the 11th week, isometric extensor strength was significantly higher in the control (conventional strengthening program) group. In another study, limb symmetry index in knee extension maximal voluntary contraction (MVC) increased significantly in both WBV and control group, and limb symmetry index in knee flexor MVC increased significantly in the WBV group at postintervention and follow-up [32]. Finally, Costantino, Bertuletti, and Romiti [14] reported significant improvements in peak torque and maximum power in knee extensors and flexors, with significantly higher improvements in the WBV group.

4. Discussion

The main goal of this systematic review was to assess the effect of WBV in the rehabilitation of patients with RACL. After analysing the included studies and considering their limitations, the results suggest that WBV may be a valid intervention in this population.

4.1. Methodological Quality of the Studies. The methodological quality of the included studies was moderate. Regarding concealed allocation, only one study stated the use of numbered, sealed, and opaque envelopes that were only opened at the moment of the intervention [15]. None has blinded participants and therapy administrators and only four referred blinded assessors in outcome measurement [16, 30, 34, 35]. The impact of these issues is well known and discussed [36].

4.2. Effects on Running Biomechanics, Functional Tests, Active Range of Motion, Corticomotor, and Motor Neuron Pool Excitability. Positive findings in these outcomes were reported. However, the limited number of studies addressing each of the outcomes limits the ability to establish its relevance to clinical practice. More studies, with high methodological quality, are needed to address these effects in the future and allow to establish solid recommendations.

4.3. Effects on Joint Position Sense. Conflicting evidence exists in this outcome. Moezy et al. [31] reported a significant increase in proprioceptive acuity after the WBV intervention; however, Fu et al. [30] found no significant changes after the WBV protocol. Both studies assessed joint position sense with an isokinetic dynamometer, but the assessment modality was different. Moezy et al. [31] used active repositioning during the assessment, and Fu et al. used passive repositioning in the assessment. This difference alone may explain the divergence in outcomes. Active repositioning is known to increase the activation of muscle receptors when compared to passive repositioning [37]. WBV may increase muscle activity in knee extensors [34] which may be related to a

higher activity of muscular mechanoreceptors, contributing to a decrease in absolute errors while assessing joint position sense actively. The WBV protocol was similar in both studies, but the timing of the implementation was different. Fu et al. [30] started 1 month after surgery and Moezy et al. [31] started 12 weeks after surgery, which also may have contributed to the observed differences. However, more studies are needed to understand the impact of the modality of limb repositioning and the timing of protocol implementation in proprioceptive acuity outcomes.

4.4. Effects on Joint Laxity. Two studies [29, 30], using different kinds of vibration—vertical synchronous and side alternating, respectively—failed to evidence significant changes in side-to-side differences in joint laxity, assessed with the KT 1000 arthrometer, in both WBV and conventional or standard rehabilitation groups. However, no study has assessed the effects of WBV in dynamic joint stability, which is a functionally more interesting parameter and should be addressed in future research.

4.5. Effects of Knee Function. Two studies [29, 32] have found that WBV increases knee function. However, when compared to the respective control groups (standard strengthening program and traditional rehabilitation program), only the study of Pistone et al. [32] reported significantly higher functional improvement in the WBV group. Several aspects can justify this difference, the nature of the control group, the timing of implementation, and the WBV parameters. Berschin et al. [29] compared the effects of the WBV to a group performing a standard strengthening program and this focus on strengthening may have contributed to the lack of differences between the groups as strength is a key parameter to increase functional status after ACL injury [38]. On the other hand, the timing of implementation of the WBV program may have been an important factor. Berschin et al. [29] started the WBV program 2 weeks after surgery, and Pistone et al. [32] started the program 1 month after surgery. Considering the natural differences in functional status between 2 weeks and 1 month after surgery this may have played an important role in the differences in outcomes between the studies. However, further research should analyse the impact of the timing of implementation of the WBV program in functional status. Finally, the differences in the WBV program parameters should be discussed. Pistone et al. [32] have not used a fixed WBV frequency, but rather the optimal vibration frequency was previously determined, which may explain why results in the WBV group were significantly better. The optimal vibration frequency has been defined as the vibration frequency at which maximal muscle activation arises, and according to Giombini et al. [18], it is advisable to prescribe individualized vibration parameters to maximize the improvement in outcome measures.

4.6. Effects on Surface Electromyographic Signal. More research is needed to understand the effect of WBV on parameters related to the electromyographic activity of knee extensors and flexors. No study has assessed the long-term effects of WBV on electromyographic activity in patients with RACL, and only three studies have analysed the acute effects of WBV in parameters in this domain, but the parameters and/or methodologies were distinct. Pamukoff et al. [34] reported a significant increase in the electromyographic amplitude of knee extensors but not in knee flexors, and da Costa et al. [15] reported no significant changes in knee extensor electromyographic amplitude. Previous research suggested that higher vibration frequencies and amplitudes elicited the highest changes in electromyographic signal [39, 40]. However, the studies of da Costa et al. [15], using a frequency of 50 Hz, and Pamukoff et al. [34], using a frequency of 30 Hz, suggest the opposite. It should be noted that the study populations are different, and the studies included in this review addressed a clinical population, which can suggest that healthy subjects and subjects with a condition may benefit differently from WBV. However, regarding the differences in outcomes of Pamukoff et al. [34] and da Costa et al. [15], it should be stressed that the timing of implementation of the WBV program is different, 50.6 ± 21.3 months and 16.8 ± 1.55 weeks after surgery, respectively, suggesting that early implementation may lead to better results in these parameters. WBV does not seem to decrease the time between the onset of the surface electromyographic signal and the onset of torque in knee extensors and flexors; however, as stated before, only one short-term study [35] has addressed this question, and more research is needed to increase the body of knowledge on the topic.

4.7. Effects on Balance or Postural Stability. Previous research has established that WBV training could enhance muscle spindle sensibility and excitability, which could lead to reduced reaction time of postural muscles and motor unit recruitment thresholds [17, 41] and that lower WBV frequencies could be more beneficial when training balance [42].

There is a clear positive effect of WBV training on balance in patients with RACL. Out of five studies analysing this effect [15, 29–32] only one, analysing the acute effects of WBV training, failed to provide positive effects on balance [15]. This suggests that a single session of WBV may be insufficient to elicit positive adaptations in the neuromuscular system, and this should be noticed by clinicians. Another interesting aspect is that positive effects occurred when lower [29], higher [30, 31] or custom [32] vibration frequencies were employed, and the same is true for WBV amplitude.

4.8. Effects on Muscle Strength. Two types of research articles analysed the effects of WBV on muscle strength, those assessing the effects of a single training session and those assessing the effects of several WBV sessions.

Concerning improvements knee extensor peak torque and rate of torque development. Pamukoff et al. [34] described significant improvements in knee extensor peak torque, contrary to the findings of da Costa et al. [15] that found no significant differences in peak torque after a single session of WBV. The differences in the timing of protocol implementation and protocol parameters, especially vibration frequency, may explain the discrepancy as Tseng et al. [42] states that immediate neuromuscular function is impaired when vibration frequency exceeds 40 Hz. Only the

rate of torque development in the first 100 ms maximal isometric knee extension contraction seems to improve after a single session of WBV [34, 35]. Often, dynamic tasks require force production before 300 milliseconds, but early torque production, during the first 100 milliseconds, may be a more reliable parameter for functional tasks in which the knee extensors must produce submaximal levels of force rapidly, such as immediately before ground contact during gait to attenuate the vertical ground reaction force [43].

Regarding muscle strength improvements after WBV programs with several training sessions, adding WBV to standard/conventional treatment programs [14, 30, 32, 33] provides important benefits providing better resistance to fatigue, increasing the mid-second of contraction, increasing performance in knee extensors and flexors, increasing limb symmetry indexes in knee extensors and flexors and higher improvements in peak torque and maximum power in knee extensors and flexors. Only the study of Berschin et al. [29] failed to demonstrate better results in the WBV group. This was also the only study where WBV was used alone against a control group performing a standard strengthening program, which achieved significantly higher isometric knee extensor strength at the 11^{th} week. These findings suggest that WBV should be used as a complement to rehabilitation programs to provide significantly better results.

However, considering the heterogeneity in WBV protocols, more research is needed to identify the optimal protocol to be implemented in patients with RACL to improve neuromuscular function.

4.9. Adverse Effects. Only one study [29] reported minor complications such as pain or swelling during or after WBV exercise in 12/20 (60%) participants up to the sixth week but in the control group the same complications occurred in 14/20 (70%).

4.10. Limitations. The findings of this systematic review must be interpreted with caution. Although four well-known databases were used, including more sources of data could have improved the amount of literature included in the review. The same goes for the search terms that, although inclusive, could have provided different results if a broader search strategy was used, and therefore not all relevant studies might have been identified. Moreover, within the included studies, limitations are present in terms of study design, heterogeneity of WBV protocols, heterogeneity of control groups, and cohorts. This heterogeneity makes the comparison between studies and interpretation of WBV effects very difficult. Regarding the included studies cohorts, the included trials had small sample sizes and heterogenous samples. Demographic data was not always described.

5. Conclusion

WBV interventions in patients with RACL evidenced high patient compliance. This training method demonstrated that it can have a positive impact in strength, balance, electromyographic activity, and knee function. Therefore, implementing WBV interventions in this population seems possible and effective in improving parameters that are relevant to patients recovering from RACL.

5.1. Future Research. High-quality randomized clinical trials are needed, with proper allocation concealment and blinding, and trial registration to ensure that selective reporting is not an issue. Future studies should investigate the effects of WBV, with adequate follow-up after intervention, on relevant functional parameters, and should compare the effects of different types of WBV (synchronous and side alternating) and different vibration frequencies and amplitudes, aiming to determine the best protocol for these patients.

Conflicts of Interest

The authors have no conflicts of interest to declare.

References

[1] J. Evans and J. Nielson, *Anterior Cruciate Ligament (ACL) Knee Injuries*, 2019.

[2] R. Gupta, A. Malhotra, M. Sood, and G. D. Masih, "Is anterior cruciate ligament graft rupture (after successful anterior cruciate ligament reconstruction and return to sports) actually a graft failure or a re-injury?," *Journal of Orthopaedic Surgery*, vol. 27, no. 1, 2019.

[3] R. A. G. Hoogeslag, R. W. Brouwer, B. C. Boer, A. J. de Vries, and R. Huis in 't Veld, "Acute anterior cruciate ligament rupture: repair or reconstruction? Two-year results of a randomized controlled clinical trial," *The American Journal of Sports Medicine*, vol. 47, no. 3, pp. 567–577, 2019.

[4] S. L. Logterman, F. B. Wydra, and R. M. Frank, "Posterior cruciate ligament: anatomy and biomechanics," *Current Reviews in Musculoskeletal Medicine*, vol. 11, no. 3, pp. 510–514, 2018.

[5] C. C. Prodromos, Y. Han, J. Rogowski, B. Joyce, and K. Shi, "A Meta-analysis of the Incidence of Anterior Cruciate Ligament Tears as a Function of Gender, Sport, and a Knee Injury–Reduction Regimen," *Arthroscopy*, vol. 23, no. 12, pp. 1320–1325.e6, 2007.

[6] M. Majewski, H. Susanne, and S. Klaus, "Epidemiology of athletic knee injuries: a 10-year study," *The Knee*, vol. 13, no. 3, pp. 184–188, 2006.

[7] R. C. Mather III, L. Koenig, M. S. Kocher et al., "Societal and economic impact of anterior cruciate ligament tears," *The Journal of Bone and Joint Surgery American Volume*, vol. 95, no. 19, pp. 1751–1759, 2013.

[8] B. D. Beynnon, B. S. Uh, R. J. Johnson et al., "Rehabilitation after anterior cruciate ligament reconstruction: a prospective, randomized, double-blind comparison of programs administered over 2 different time intervals," *The American Journal of Sports Medicine*, vol. 33, no. 3, pp. 347–359, 2005.

[9] T. L. Chmielewski, K. E. Wilk, and L. Snyder-Mackler, "Changes in weight-bearing following injury or surgical reconstruction of the ACL: relationship to quadriceps strength and function," *Gait & Posture*, vol. 16, no. 1, pp. 87–95, 2002.

[10] M. Solomonow, "Sensory–motor control of ligaments and associated neuromuscular disorders," *Journal of Electromyography and Kinesiology*, vol. 16, no. 6, pp. 549–567, 2006.

[11] Y. Konishi, T. Fukubayashi, and D. Takeshita, "Possible mechanism of quadriceps femoris weakness in patients with

ruptured anterior cruciate ligament," *Medicine and Science in Sports and Exercise*, vol. 34, no. 9, pp. 1414–1418, 2002.

[12] L. Laudani, A. Giombini, P. P. Mariani, F. Pigozzi, and A. Macaluso, "Application of the sit-to-stand movement for the early assessment of functional deficits in patients who underwent anterior cruciate ligament reconstruction," *American Journal of Physical Medicine & Rehabilitation*, vol. 93, no. 3, pp. 189–199, 2014.

[13] R. M. Palmieri-Smith, A. C. Thomas, and E. M. Wojtys, "Maximizing quadriceps strength after ACL reconstruction," *Clinics in Sports Medicine*, vol. 27, no. 3, pp. 405–424, 2008.

[14] C. Costantino, S. Bertuletti, and D. Romiti, "Efficacy of whole-body vibration board training on strength in athletes after anterior cruciate ligament reconstruction: a randomized controlled study," *Clinical Journal of Sport Medicine*, vol. 28, no. 4, pp. 339–349, 2018.

[15] K. S. A. da Costa, D. T. Borges, L. de Brito Macedo, C. A. de Almeida Lins, and J. S. Brasileiro, "Whole-body vibration on performance of quadriceps after ACL reconstruction: a blinded randomized controlled trial," *Journal of Sport Rehabilitation*, vol. 28, no. 1, pp. 52–58, 2019.

[16] D. N. Pamukoff, M. M. Montgomery, K. H. Choe, T. J. Moffit, and M. N. Vakula, "Effect of whole-body vibration on sagittal plane running mechanics in individuals with anterior cruciate ligament reconstruction: a randomized crossover trial," *Archives of Physical Medicine and Rehabilitation*, vol. 99, no. 5, pp. 973–980, 2018.

[17] M. Cardinale and C. Bosco, "The use of vibration as an exercise intervention," *Exercise and Sport Sciences Reviews*, vol. 31, no. 1, pp. 3–7, 2003.

[18] A. Giombini, A. Macaluso, L. Laudani et al., "Acute effect of whole-body vibration at optimal frequency on muscle power output of the lower limbs in older women," *American Journal of Physical Medicine & Rehabilitation*, vol. 92, no. 9, pp. 797–804, 2013.

[19] P. B. C. Matthews, "The reflex excitation of the soleus muscle of the decerebrate cat caused by vibration applied to its tendon," *The Journal of Physiology*, vol. 184, no. 2, pp. 450–472, 1966.

[20] R. Ritzmann, A. Gollhofer, and A. Kramer, "The influence of vibration type, frequency, body position and additional load on the neuromuscular activity during whole body vibration," *European Journal of Applied Physiology*, vol. 113, no. 1, pp. 1–11, 2013.

[21] M. Cardinale and J. Lim, "Electromyography activity of vastus lateralis muscle during whole-body vibrations of different frequencies," *The Journal of Strength & Conditioning Research*, vol. 17, no. 3, pp. 621–624, 2003.

[22] D. Perchthaler, T. Horstmann, and S. Grau, "Variations in neuromuscular activity of thigh muscles during whole-body vibration in consideration of different biomechanical variables," *Journal of Sports Science & Medicine*, vol. 12, no. 3, pp. 439–446, 2013.

[23] P. J. Marín, D. Bunker, M. R. Rhea, and F. N. Ayllón, "Neuromuscular activity during whole-body vibration of different amplitudes and footwear conditions: implications for prescription of vibratory stimulation," *The Journal of Strength & Conditioning Research*, vol. 23, no. 8, pp. 2311–2316, 2009.

[24] D. Moher, A. Liberati, J. Tetzlaff, D. G. Altman, and The PRISMA Group, "Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement," *PLoS Medicine*, vol. 6, no. 7, article e1000097, 2009.

[25] M. Cardinale and J. Wakeling, "Whole body vibration exercise: are vibrations good for you?," *British Journal of Sports Medicine*, vol. 39, no. 9, pp. 585–589, 2005.

[26] N. A. de Morton, "The PEDro scale is a valid measure of the methodological quality of clinical trials: a demographic study," *The Australian Journal of Physiotherapy*, vol. 55, no. 2, pp. 129–133, 2009.

[27] C. G. Maher, C. Sherrington, R. D. Herbert, A. M. Moseley, and M. Elkins, "Reliability of the PEDro scale for rating quality of randomized controlled trials," *Physical Therapy*, vol. 83, no. 8, pp. 713–721, 2003.

[28] J. P. T. Higgins, D. G. Altman, P. C. Gotzsche et al., "The Cochrane Collaboration's tool for assessing risk of bias in randomised trials," *BMJ*, vol. 343, article d5928, 2011.

[29] G. Berschin, B. Sommer, A. Behrens, and H. M. Sommer, "Whole body vibration exercise protocol versus a standard exercise protocol after ACL reconstruction: a clinical randomized controlled trial with short term follow-up," *Journal of Sports Science and Medicine*, vol. 13, no. 3, pp. 580–589, 2014.

[30] C. L. A. Fu, S. H. P. Yung, K. Y. B. Law et al., "The effect of early whole-body vibration therapy on neuromuscular control after anterior cruciate ligament reconstruction a randomized controlled trial," *American Journal of Sports Medicine*, vol. 41, no. 4, pp. 804–814, 2013.

[31] A. Moezy, G. Olyaei, M. Hadian, M. Razi, and S. Faghihzadeh, "A comparative study of whole body vibration training and conventional training on knee proprioception and postural stability after anterior cruciate ligament reconstruction," *British Journal of Sports Medicine*, vol. 42, no. 5, pp. 373–378, 2008.

[32] E. M. Pistone, L. Laudani, G. Camillieri et al., "Effects of early whole-body vibration treatment on knee neuromuscular function and postural control after anterior cruciate ligament reconstruction: a randomized controlled trial," *Journal of Rehabilitation Medicine*, vol. 48, no. 10, pp. 880–886, 2016.

[33] A. Salvarani, M. Agosti, A. Zanré, A. Ampollini, L. Montagna, and M. Franceschini, "Mechanical vibration in the rehabilitation of patients with reconstructed anterior cruciate ligament," *Europa Medicophysica*, vol. 39, no. 1, pp. 19–25, 2003.

[34] D. N. Pamukoff, B. Pietrosimone, M. D. Lewek et al., "Whole-body and local muscle vibration immediately improve quadriceps function in individuals with anterior cruciate ligament reconstruction," *Archives of Physical Medicine and Rehabilitation*, vol. 97, no. 7, pp. 1121–1129, 2016.

[35] D. N. Pamukoff, B. Pietrosimone, E. D. Ryan, D. R. Lee, L. E. Brown, and J. T. Blackburn, "Whole-body vibration improves early rate of torque development in individuals with anterior cruciate ligament reconstruction," *Journal of Strength and Conditioning Research*, vol. 31, no. 11, pp. 2992–3000, 2017.

[36] J. Savović, H. E. Jones, D. G. Altman et al., "Influence of reported study design characteristics on intervention effect estimates from randomized, controlled trials," *Annals of Internal Medicine*, vol. 157, no. 6, pp. 429–438, 2012.

[37] U. Proske, A. K. Wise, and J. E. Gregory, "The role of muscle receptors in the detection of movements," *Progress in Neurobiology*, vol. 60, no. 1, pp. 85–96, 2000.

[38] M. Buckthorpe, G. La Rosa, and F. D. Villa, "Restoring knee extensor strength after anterior cruciate ligament reconstruction: a clinical commentary," *International Journal of Sports Physical Therapy*, vol. 14, no. 1, pp. 159–172, 2019.

[39] T. J. Hazell, J. M. Jakobi, and K. A. Kenno, "The effects of whole-body vibration on upper- and lower-body EMG during static and dynamic contractions," *Applied Physiology, Nutrition, and Metabolism*, vol. 32, no. 6, pp. 1156–1163, 2007.

[40] R. D. Pollock, R. C. Woledge, K. R. Mills, F. C. Martin, and D. J. Newham, "Muscle activity and acceleration during whole body vibration: effect of frequency and amplitude," *Clinical biomechanics*, vol. 25, no. 8, pp. 840–846, 2010.

[41] R. D. Pollock, R. C. Woledge, F. C. Martin, and D. J. Newham, "Effects of whole body vibration on motor unit recruitment and threshold," *Journal of Applied Physiology*, vol. 112, no. 3, pp. 388–395, 2012.

[42] S.-Y. Tseng, P.-S. Hsu, C.-L. Lai, W.-C. Liao, M.-C. Lee, and C.-H. Wang, "Effect of two frequencies of whole-body vibration training on balance and flexibility of the elderly: a randomized controlled trial," *American Journal of Physical Medicine & Rehabilitation*, vol. 95, no. 10, pp. 730–737, 2016.

[43] T. Liikavainio, J. Isolehto, H. J. Helminen et al., "Loading and gait symmetry during level and stair walking in asymptomatic subjects with knee osteoarthritis: importance of quadriceps femoris in reducing impact force during heel strike?," *The Knee*, vol. 14, no. 3, pp. 231–238, 2007.

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Research Article

Low-Intensity Electrical Stimulation to Improve the Neurological Aspect of Weakness in Individuals with Chronic Anterior Cruciate Ligament Lesion

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Purpose. This study is aimed at investigating the effect of low-intensity electrical stimulation on the voluntary activation level (VA) and the cortical facilitation/inhibition of quadriceps in people with chronic anterior cruciate ligament lesion. *Methods*. Twenty former athletes with unilateral ACL deficiencies (ACL group) and 20 healthy subjects (healthy control group) participated in the study. The quadriceps VA level, motor-evoked potential (MEP), short-interval intracortical inhibition (SICI), and intracortical facilitation (ICF) elicited by transcranial magnetic stimulation were tested before and after 30 minutes of low-intensity electrical stimulation (ES). *Results*. Before ES, the quadriceps VA in the ACL lesion legs of the ACL group was lower compared to the legs of the healthy control group ($P < 0.05$). The MEP sizes in the ACL lesion legs and the healthy control were not significantly different. The ACL lesion legs showed lower SICI and higher ICF compared to the healthy control group ($P < 0.05$). After ES, the quadriceps VA level increased and the SICI-ICF was modulated only in the ACL lesion legs ($P < 0.05$) but not in the healthy controls. *Conclusions*. Low-intensity ES can normalize the modulation of intracortical inhibition and facilitation, thereby ameliorating the activation failure in individuals with ACL lesion.

1. Introduction

The anterior cruciate ligament (ACL) is vulnerable to sports injury and usually leads to severe quadriceps weakness. Weakness and atrophy persist for years even though reconstruction has been made [1–3]. Severe quadriceps weakness and atrophy restricts the functional performance of the knee joint and prevents athletes' return to sports competitions. Sixty-six percent of athletes returned to sports competition one year after surgical reconstruction [1], and only 55% of athletes returned to preinjury level post surgery [2]. The causes for severe quadriceps weakness

in the chronic phase of ACL deficiency are not clear. Knowing the mechanism of severe quadriceps weakness at the chronic phase of ACL deficiency and developing a therapeutic strategy are important.

ACL does not only serve as a mechanical stabilizer but also provides essential afferent input. Animal studies suggested that the loading of ACL has an excitatory effect on the thigh muscles [4], and the mechanism is possibly related to the feedback from mechanoreceptors in the ACL to gamma motor neurons. This mechanism is suggested to be important for recruiting high-threshold motor units during voluntary quadriceps contractions [5]. After ACL injury, feedback from the mechanoreceptors in the ACL is disrupted [6], resulting in a decrease of motor unit recruitment in the quadriceps and a decrease in quadriceps strength [5]. Therefore, an ACL lesion might cause a neurophysiological dysfunction which is generally overlooked in rehabilitation.

The maximal voluntary contraction force (MVC) is the most frequently used strength quantification variable which contains both central and peripheral neuromuscular factors. There are several potential ways to quantify the neurological deficits. By comparing the twitch force elicited by electrical stimulation at rest and during MVC, the voluntary activation level (VA) of the quadriceps can be quantified [7, 8]. It was found that the VA decreased bilaterally following ACL deficiency [9–12]. Studies reported that the motor-evoked potentials (MEPs) elicited by TMS had a tendency to decrease in subjects with ACL deficiency, and the resting motor threshold was significantly reduced in the ACL-injured group [13]. However, the integrity of the cortical inhibition and facilitation circuitries and whether these circuitries responded to training are not clear.

Training the athletes with an ACL lesion to return to games is usually challenging. Since ACL plays a role in providing afferent input, modifying compensation caused by the decrease in afferent input due to ACL injury might be essential. Electrical stimulation is one of the potential methods to provide sensory stimulation. Back in 1995, Snyder-Mackler et al. found that high-intensity ES would have better effects than high-level volitional exercise on the restoration of quadriceps strength after surgery. However, whether the improvement was from pure peripheral muscle structure changes [14] or from compensatory sensory stimulation is not clear. More recent studies showed that motor cortex excitability was enhanced after repetitive peripheral electrical stimulation (ES) in healthy subjects [15–17]. The role of ES in modulating the cortex excitability in ACL retraining remains unclear. Therefore, this study is aimed at investigating the neurological dysfunction and restoration after ACL deficiency training using low-intensity ES. The purpose of this study was (1) to investigate the difference of cortical facilitation/inhibition function between individuals with and without ACL deficiency and (2) to study the effect of providing additional afferent input by ES on the cortical facilitation/inhibition functions and VA. To clarify the role of afferent input, we used a low-intensity electrical stimulation to avoid excessive muscle contractions.

2. Materials and Methods

Twenty individuals (5 females, 15 males, aged 24.1 ± 3.55 years old) with ACL deficiency (ACL group) and twenty individuals with no physical disabilities (5 females, 15 males, aged 22.3 ± 2.62 years) (healthy control group) participated in the study. There were no significant differences in age, gender, height, and weight between the two groups (Table 1). Eighteen subjects in the ACL group had ACL reconstruction using the semitendinosus graft, patella tendon graft, or artificial ligament graft, and two subjects did not have ACL repair. All subjects of the ACL group were physically active. This was confirmed by Tegner activity level scale 4 to 5 which included recreational sports to competitive sports for 2 times per week by definition. The averaged months from ACL injury to the testing date were 30.85 ± 24.04 months, and the averaged months after reconstruction were 27.44 ± 24 months (not including two individuals with ACL deficiency). The subjects in the healthy control group had no previous history of neuromuscular disease. Subjects in both the ACL and healthy control groups revealed no pain and no knee swelling one month before the testing day. All subjects participated with informed consent, and the testing protocols had been approved by our internal review board in accordance with the Helsinki Declaration.

The ACL lesion legs of subjects in the ACL group and the dominant legs of subjects in the healthy control group were tested (Figure 1). We did not compare both legs of the healthy group since our subjects in the healthy control group did not show evidence of asymmetry on both legs. Before tests, the knee stability test was performed using a KT-2000 arthrometer and the thigh circumference was measured 10 cm above the knee joint line. Participants sat in a custom-designed chair with their hip joint fixed at 60° flexion and their knee joint fixed at 60° flexion. A force transducer maximum load of 100 kg (BA-100M, Transcell Technology Inc., IL, USA) was mounted on the custom-designed chair to measure the knee extension force. The transducer has been calibrated with the hysteresis and linearity error less than 1%. The signal from the force transducer was amplified by a transducer amplifier (Gould Inc., Valley View, OH, USA) with a gain range from 10 to 500 and a frequency response from dc to 1,000 Hz.

Surface electromyography (EMG) of the vastus medialis obliques (VMO), vastus lateralis (VL), and rectus femoris (RF) was recorded by a bipolar surface electrode with a fixed interelectrode distance of 2 cm (B&L Engineering, USA). A reference electrode was placed on the patella bone. The EMG activity was on-site preamplified with a factor of 330 and was further amplified at the mainframe. The mainframe amplifier had an input impedance greater than 10 MΩ, a common mode rejection ratio of 100 dB at 60 Hz, and a gain range from 0.5 to 100,000 times (Gould Bioelectric, Gould Instrument Systems Inc., USA). Both the force and EMG activity were monitored on an oscilloscope and digitized at 4000 Hz (InstruNet Model 200 PCI Controller, USA).

The femoral nerve was stimulated by a constant current stimulator (DS7A, Digitimer Ltd., England) with an active electrode (cathode, 2 cm diameter) placed at the femoral

Table 1: Characteristics of the participants (mean ± SD).

	ACL group	Healthy control group	P
Numbers	20	20	N/A
Gender	15 men, 5 women	15 men, 5 women	N/A
Age	24.1 ± 3.55	22.3 ± 2.62	0.192
Height (cm)	173.4 ± 6.96	168.6 ± 9.16	0.241
Weight (kg)	70.4 ± 10.91	64.9 ± 11.41	0.847
ACL deficient	2		
ACL reconstruction	18		
Semitendinosus graft	11		
Patella tendon graft	6		
Artificial ligament graft	1		
ACL injury alone	7		
ACL+complex injury	13		

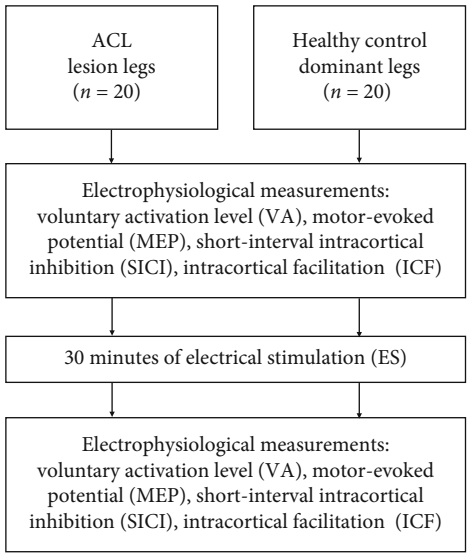

Figure 1: The flowchart of the study.

triangle and a dispersive electrode (anode, 4.5 cm × 10 cm) placed over the low back. The stimulation pulse duration was a 500 μs square wave pulse, and the stimulation intensity was supramaximal, which was 110% of the intensity that elicited maximum M waves, resting twitches, and interpolated twitches.

After five warm-up contractions of the quadriceps, subjects were instructed to fully contract the quadriceps muscles for 3 s to measure maximum voluntary contraction (MVC) forces. They were given both verbal encouragement and visual output of their force to motivate maximal effort.

For evaluating VA, the femoral nerve was stimulated at the supramaximal intensity before and during the MVC of the quadriceps to elicit unpotentiated resting twitch, interpolated twitch (Ti), and potentiated resting twitch (Figure 2(a)). The unpotentiated resting twitch and potentiated resting twitch were then averaged to obtain the control twitch (Tc) for further calculation of VA. VA was calculated from formula (1) [7, 8, 18]. The measurements of VA were repeated three times with 5 seconds in between.

$$\mathrm{VA} = \left(1 - \frac{\mathrm{Ti}}{\mathrm{Tc}}\right) * 100\%. \quad (1)$$

The motor-evoked potentials (MEPs) of VMO, VL, and RF were elicited by TMS (Magstim 200, Magstim Co., Dyfed, UK) using a double-cone coil. The optimal scalp location for consistent production of the largest MEPs in the muscle of primary interest (VMO) at the lower intensity was marked, and this location was used for the remainder of the experiment. The resting motor threshold (rMT) was defined as the minimum TMS intensity required to elicit at least five out of 10 MEPs greater or equal to 50 μV in consecutive trials [19] in the relaxed VMO [19, 20].

The testing pulse intensity was set to 120% of this threshold. For a paired pulsed protocol, the conditioning stimulation intensity was set at 80% of this threshold. The interstimulation intervals were 2 and 3 ms for measuring short-interval intracortical inhibition (SICI) and 10, 13, and 16 ms for measuring ICF [18]. The MEP was measured 6 times at intervals of 9.5 to 10.5 seconds apart and in random order. To avoid the outlier from influencing the average value, the highest value and lowest value were excluded when calculating the average. The tested MEP of the paired pulse protocol was normalized by the single pulse MEP and represented as a ratio. A ratio > 1 represents a facilitation, whereas a ratio < 1 represents an inhibition.

After the above measurements, subjects received 30 minutes of electrical stimulation (ES) with two portable stimulators (multifunctional stimulator TRIO-300; Ito Co., Tokyo, Japan) on the ACL lesion legs (ACL group) or on the dominant legs (healthy control group) to activate the VM, VL, and RF. Three pairs of surface electrodes with a size of 4 cm × 5 cm were placed along the muscle belly of VMO, VL, and RF avoiding the EMG electrodes. The stimulation frequency was 25 Hz, and the pulse duration was 200 μs. The on/off time was set at 1 s/1 s. The stimulation intensity was set above the sensory threshold and 1.2 times the minimal intensity to produce muscle contraction and was independently set for each muscle. After 30 minutes of ES, the VA and the single and paired MEPs were measured again.

For the single TMS protocol, the peak-to-peak amplitude of MEP was normalized to the peak-to-peak amplitude of the maximal M waves. For the paired TMS protocol, the testing MEPs produced by a paired TMS were expressed as a percentage of the MEP produced by a single TMS and were further averaged for each subject at each interstimulus interval (ISI) to yield individual SICI-ICF curves for an individual subject in each condition. In the individual SICI-ICI curves, ISI 2 ms and 3 ms were in the SICI range and ISI 10 ms, 13 ms, and 16 ms were in the ICF range. Since the strongest SICI and ICF might not necessarily occur in the exact same ISI for each subject in every condition, the single SICI value and ICF for each subject in each condition were extracted from the individual SICI-ICF curve. The single SICI value

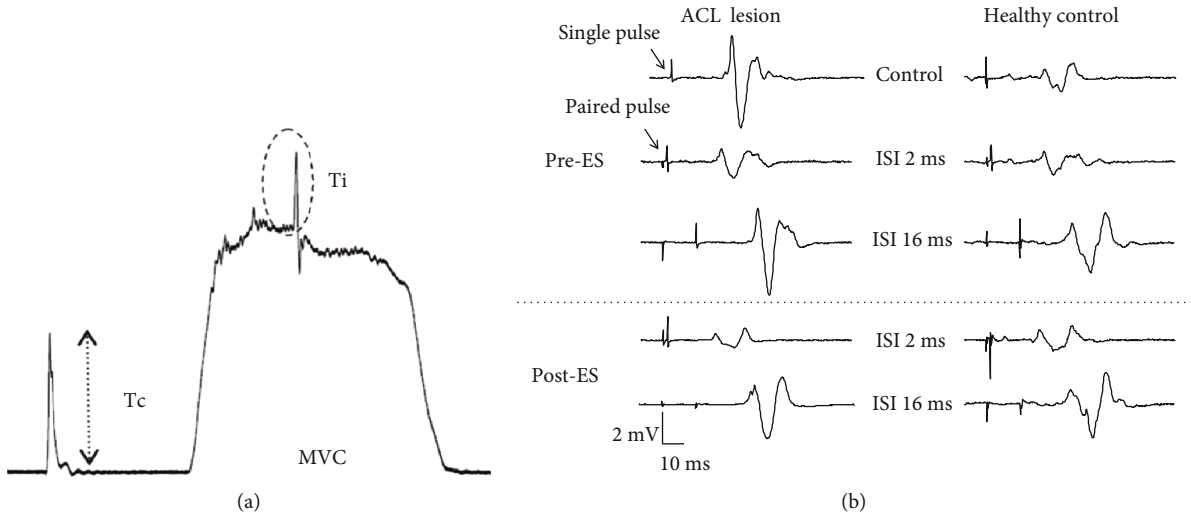

Figure 2: Examples of data recordings of voluntary activation level (a) and motor-evoked potentials (b) at an interstimulus interval (ISI) of 2 and 16 ms of pre- and postelectrical stimulation (ES).

($SICI_{max}$) and single ICF were the strongest inhibition/facilitation which were the lowest value in the SICI range and the highest value in the ICF range, respectively. These values were thus used for statistical analysis (Figure 2(b)).

Data were analyzed using SAS version 9.1. The baseline difference was analyzed using a two-sample t-test (ACL lesion legs and healthy control) and paired t-test (ACL lesion legs vs. ACL nonlesion legs). The mean ± SD was calculated for outcome variables. Two-way (group by time) repeated measures ANOVA was used to evaluate the difference between groups (ACL lesion legs, healthy control) and to determine if the dependent variables were different before and after ES in the two groups (ACL lesion legs and healthy control). If a significant interaction was detected, one-way ANOVA was then applied. Tukey's post hoc test was used for analysis whenever a significant main effect was found.

3. Results

A KT-2000 arthrometer revealed a significant displacement difference between the lesion and nonlesion sides (lesion side: 4.62 ± 1.92mm; nonlesion side: 3.15 ± 1.41mm, $P < 0.05$), confirming that ACL lesion legs had worse knee stability than the nonlesion leg. Thigh circumference showed no significant difference between sides in the ACL group (ACL lesion legs: 43.58 ± 4.74 cm; nonlesion side: 44.78 ± 4.83 cm, $P < 0.05$).

For VA (Figure 3), significant time × group interaction was shown ($F_{(1,36)} = 8.62$, $P = 0.006$), indicating that the ACL lesion legs and the legs of the healthy control group responded differently to ES. Before ES, one-way ANOVA showed that the VA of the ACL lesion legs (64.92 ± 12.46%) was significantly lower than that of the legs of the healthy control group ($F_{(1,36)} = 25.12$, $P < 0.001$).

After 30 minutes of ES, the VA of ACL lesion legs significantly increased from 64.92 ± 12.46% to 72.71 ± 12.47%

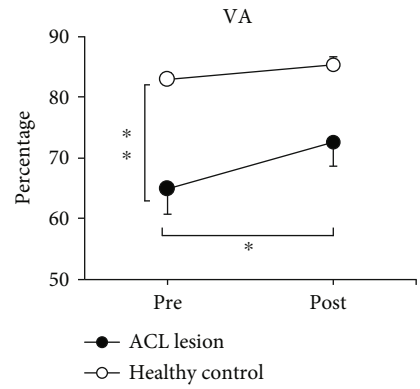

Figure 3: The mean ± SE of voluntary activation level (VA) before and after ES. The black circles (-●-) are ACL lesion legs, and the white circles (-○-) are legs of the healthy control group. VA is significantly increased following a 30-minute electrical stimulation (ES) only in ACL lesion legs. *Significant difference between pre- and post-ES ($P < 0.05$). **Significant difference between ACL lesion legs and legs of the healthy control group before ES ($P < 0.05$).

($F_{(1,19)} = 40.10$, $P < 0.001$), although the value was still lower than that of the legs of the healthy control group. The ES did not alter the VA of the legs of the healthy control group (pre: 82.95 ± 9.27%, post: 85.51 ± 8.12%, $F_{(1,17)} = 3.97$, $P = 0.063$).

For resting MEP (Figure 4(a)), there is no significant time × group interaction in the MEP of VMO ($F_{(1,38)} = 3.33$, $P = 0.076$), VL ($F_{(1,38)} = 1.95$, $P = 0.170$), or RF ($F_{(1,38)} = 0.36$, $P = 0.552$) after 30 minutes of ES, suggesting that both groups responded to ES similarly. There is no main effect of the group. These results suggested that the resting state cortical excitability was not altered in ACL lesion legs. Main effects of time showed that both ACL lesion legs and the legs of the healthy control group significantly increased MEP in VMO, VL, and RF muscles (VMO: $F_{(1,38)} = 11.78$, $P = 0.002$; VL: $F_{(1,38)} = 42.78$, $P < 0.001$; and RF: $F_{(1,38)} = 14.27$, $P < 0.001$).

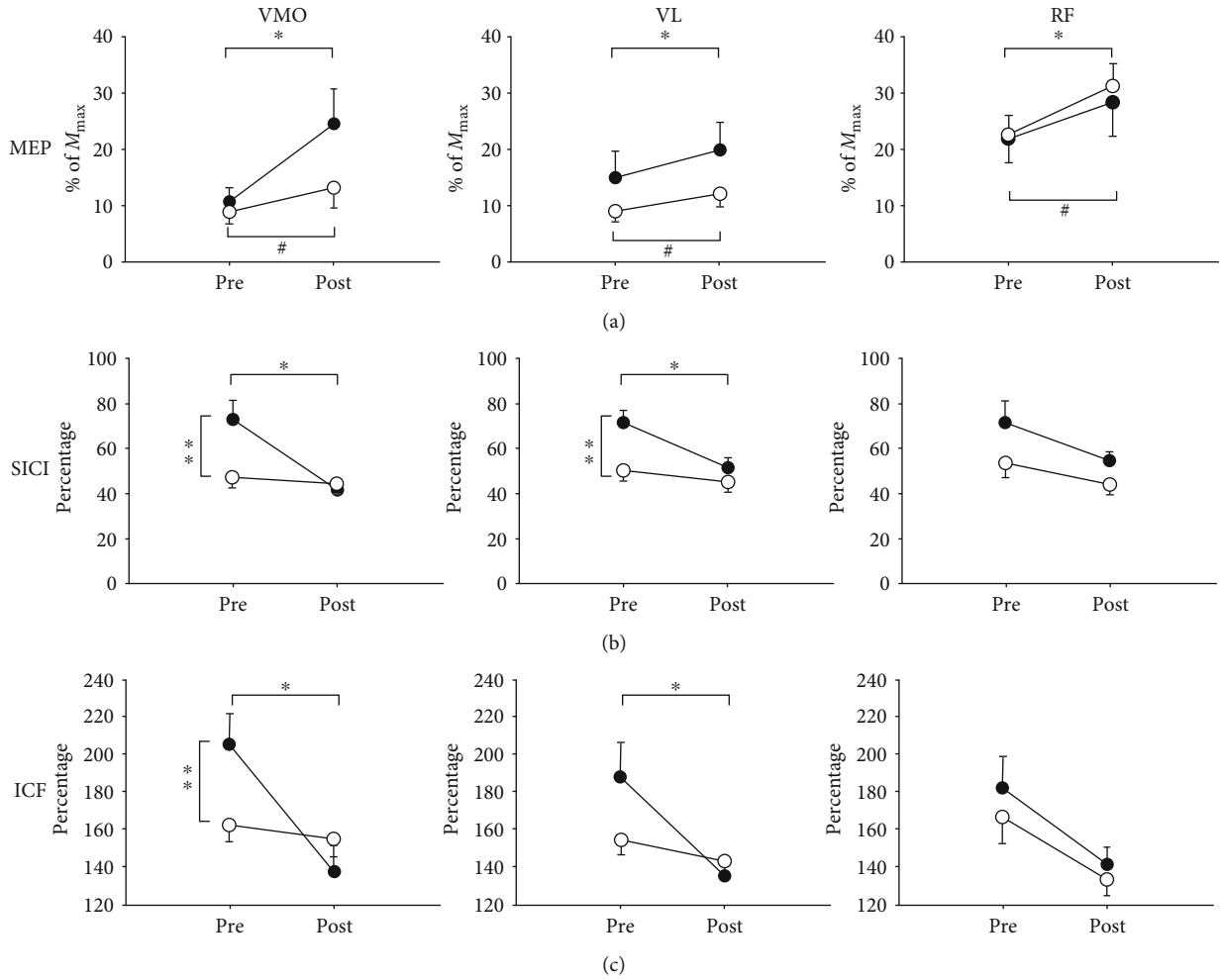

Figure 4: The mean ± SE of motor-evoked potential (MEP) (a), short-interval intracortical inhibition (SICI) (b), and intracortical facilitation (ICF) (c) in vastus medialis obliques (VMO), vastus lateralis (VL), and rectus femoris (RF) in the ACL lesion (-●-) and healthy control (-○-) groups before and after 30 minutes of electrical stimulation (ES) training. *Significant difference between pre- and post-ES in the ACL lesion group ($P < 0.05$). #Significant difference between pre- and post-ES in the healthy control group ($P < 0.05$). **Significant difference between ACL lesion legs and legs of the healthy control group before ES ($P < 0.05$).

For $SICI_{max}$ (Table 2), significant time × group interactions were shown in VMO ($F_{(1,38)} = 17.20$, $P < 0.001$) and VL ($F_{(1,38)} = 6.48$, $P = 0.015$). Before ES, the $SICI_{max}$ of VMO in ACL lesion legs was 72.79 ± 38.78%, which was significantly higher than that of the legs of the healthy control group (47.37 ± 19.50%, $F_{(1,38)} = 6.68$, $P = 0.013$). For VL, the value of $SICI_{max}$ in ACL lesion legs (71.67 ± 24.05%) was significantly higher than that in the legs of the healthy control group (50.46 ± 20.41%, $F_{(1,38)} = 9.04$, $P = 0.005$). A higher value of $SICI_{max}$ represents a weaker SICI. The above results suggested that the ACL lesion legs had a weaker SICI than healthy control legs.

After 30 minutes of ES, in ACL lesion legs, the $SICI_{max}$ significantly decreased from 72.79 ± 38.78% to 41.53 ± 23.99% ($F_{(1,19)} = 26.71$, $P < 0.001$) for VMO and decreased from 71.67 ± 24.05% to 51.49 ± 20.78% for VL ($F(1, 19) = 17.92$, $P < 0.001$). These results indicate that the SICI become stronger and approached that of the healthy control group after 30 minutes of ES. No significant changes in $SICI_{max}$ after ES were observed in the healthy control group (Figure 4(b)).

For ICF_{max} (Table 2), interactions were shown in VMO ($F_{(1,38)} = 11.91$, $P < 0.001$) and VL ($F_{(1,38)} = 4.18$, $P = 0.048$). Before ES, the ICF_{max} of VMO in ACL lesion legs (205.02 ± 73.47%) was significantly higher than the legs of the healthy control group (162.04 ± 38.97%, $F_{(1,38)} = 5.43$, $P = 0.026$). The ICF_{max} of VL did not reach statistical significance ($F_{(1,38)} = 2.70$, $P = 0.109$) between the ACL lesion legs (187.61 ± 83.95%) and the legs of the healthy control group (154.11 ± 35.65%). A higher value of ICF_{max} represents a stronger ICF.

After 30 minutes of ES, in ACL lesion legs, ICF_{max} significantly decreased from 205.02 ± 73.47% to 137.89 ± 59.85% ($F_{(1,19)} = 18.68$, $P < 0.001$) in VMO and from 187.61 ± 83.95% to 135.12 ± 25.74% in VL ($F_{(1,19)} = 7.58$, $P = 0.013$). These results indicate that the ICF become weaker and

Table 2: The mean, standard deviation, and results of ANOVA of the maximal short-interval intracortical inhibition (SICI), intracortical facilitation (ICF), and *M* wave on vastus medialis obliques (VMO), vastus lateralis (VL), and rectus femoris (RF) muscles before and after 30 minutes of electrical stimulation (ES) training in different groups. The main effect is not shown if the interaction is significant ($P < 0.05$).

	Pre-ES		Post-ES		2-way ANOVA (*P*)		
	ACL lesion	Health control	ACL lesion	Healthy control	Interaction	Main effect time	Main effect group
Maximal SICI (%)							
VMO	72.79 ± 38.78	47.37 ± 19.50	41.53 ± 23.99	44.93 ± 16.17	<0.001**	—	—
VL	71.67 ± 24.05	50.46 ± 20.41	51.49 ± 20.78	45.11 ± 18.38	0.015**	—	—
RF	72.15 ± 42.87	54.31 ± 29.72	55.44 ± 16.68	45.13 ± 23.07	0.446	0.012*	0.088
Maximal ICF (%)							
VMO	205.02 ± 73.47	162.04 ± 38.97	137.89 ± 59.85	155.02 ± 43.80	0.001**	—	—
VL	187.61 ± 83.95	154.11 ± 35.65	135.12 ± 25.74	142.77 ± 25.20	0.048**	—	—
RF	181.81 ± 74.87	166.44 ± 64.56	141.41 ± 40.10	133.31 ± 39.01	0.731	0.001*	0.426
M wave (mv)							
VMO	3.28 ± 2.34	2.40 ± 1.85	3.04 ± 2.03	2.36 ± 1.78	0.237	0.114	0.225
VL	1.54 ± 1.20	1.67 ± 1.12	1.37 ± 1.08	1.57 ± 1.09	0.545	0.010*	0.642
RF	0.70 ± 0.27	0.83 ± 0.36	0.72 ± 0.30	0.82 ± 0.37	0.569	0.935	0.261

*Significant main effect ($P < 0.05$). **Significant interaction ($P < 0.05$) between time and group.

approached that of the healthy control group after 30 minutes of ES. Thirty minutes of ES did not change ICF_{max} in the healthy control group (Figure 4(c)).

In RF (Table 2), no significant time × group interactions were shown in either $SICI_{max}$ ($F_{(1,38)} = 0.59$, $P = 0.446$) or ICF_{max} ($F_{(1,38)} = 0.12$, $P = 0.731$). A significant main effect was shown on time (SICI: $F_{(1,38)} = 7.01$, $P = 0.012$; ICF: $F_{(1,38)} = 12.3$, $P = 0.001$) but not on group (SICI: $F_{(1,38)} = 3.07$, $P = 0.088$; ICF: $F_{(1,38)} = 0.65$, $P = 0.426$). After 30 minutes of ES, both the ACL and healthy control groups showed a significant decrease in the $SICI_{max}$ and ICF. These results indicated that ES influenced the SICI and ICF of RF to a similar extent in the ACL and healthy control groups (Figure 4).

4. Discussion

The results of this study showed that the ACL lesion legs had lower VA, weaker SICI, and stronger ICF in comparison to healthy people. This study also showed that the VA, MEP, SICI, and ICF can be modulated by surface ES. After 30 minutes of ES on the quadriceps muscle of the ACL lesion legs, VA was increased with the SICI and ICF approaching normal values (the SICI become stronger and the ICF become weaker).

This study provides evidences of that in the chronic phase of the ACL lesion; a severe activation failure was shown in ACL lesion legs (VA = 64.9%), even though the surgical repair had been done and the thigh circumference was not obviously different [9–12]. The amount of activation failure found in our study is comparable to a previous study which measured VA in the chronic phase but is more severe than that measured in the acute phase of the ACL lesion [10]. In Urbach et al.'s study, the subjects received 7 months of rehabilitation and still showed activation failure, suggesting that rehabilitation in acute and subacute phases of the ACL lesion might not be enough to prevent the VA loss in the chronic phase of ACL injury. In our study, all subjects had received routine rehabilitation in the acute and subacute stages but still showed VA deficits. This result suggests that activation failure should not be overlooked while performing ACL rehabilitation in the chronic phase.

The cortical reorganization might be the major contributing factor for the decrease of VA in the chronic phase of ACL injury. Our results showed a weaker intracortical inhibition and stronger intracortical facilitation in ACL lesion subjects, confirming that there is a neurological aspect of deficit and, more specifically speaking, a brain reorganization after an ACL lesion. Our study showed that the SICI and ICF changed in the ACL lesion legs. The reorganization of SICI and ICF following an ACL lesion could be related to the decrease of afferent input from the mechanoreceptors within ACL. A sensory-evoked potential study revealed a reorganization of the somatosensory cortex in a patient with an ACL lesion [21]. Deafferentation has been shown to change SICI and ICF. In subjects who had deafferentation due to amputation, decreased SICI had been reported in lower limb [22], upper limb, and forearm amputees [23, 24] and increased SICI had been reported in proximal arm amputees [23].

Our study showed that peripheral ES could increase MEP in ACL lesion subjects. Previous studies showed that ES on the upper [25] and lower extremities [15, 26] increased the MEP to 26%-50% in healthy humans [15, 25, 26]. The source of MEP facilitation was proposed within the motor cortex [27], but the changes in subcortical neural structures might not be excluded [28]. The facilitation of MEP might relate to the NMDA receptor-related synaptic plasticity and might reflect the effect of long-term potentiation in the motor cortex [25]. The present study suggests that the ACL lesion subjects showed ES-induced cortical plasticity similar to the

ACL-intact subjects with the value of increment in the ACL lesion group (50-150%) somewhat greater than that in ACL-intact subjects (30-50%). The major finding of the present study was that a 30-minute ES could improve VA and normalize the abnormal SICI and ICF in individuals with an ACL lesion.

SICI and ICF are functionally important in generating muscle voluntary contraction. Zoghi et al. suggested that the SICI circuits assist the corticospinal system in producing muscle activity [29]. They suggested that selective activation of a muscle is accompanied by a selective suppression of SICI effects on the corticospinal neurons controlling that muscle. According to our results, the pre-ES SICI and ICF in ACL lesion subjects were at a less inhibited and more facilitated status. Thus, the SICI could not be further depressed to assist muscle activation and results in a decreased VA. After ES, the SICI and ICF were downregulated to the normal value and could be modulated to assist muscle activation.

Unlike the response of VMO and VL, the SICI and ICF of RF muscle were not significantly different between the ACL lesion and healthy control groups. It is possible that RF is a two-joint muscle which is different from VMO and VL which are one-joint muscles. RF in the ACL lesion group might have fewer adaptation changes due to more afferent input than VMO and VL since RF is activated during both hip and knee movements. Further study is needed to clarify this issue.

The subjects in our study were all physically active albeit VA deficient. This result suggested that people in the chronic phase of ACL injury might require a special training program other than regular physical activities to maintain VA. One might be concerned that ES might have caused fatigue that affected the results of this study. However, this should not be a concern in our study. A relatively high intensity is required as shown by a previous study using ES to induce fatigue, such as maximal or maximal tolerable intensity [30–32]. Our intensity of ES was very low which was least likely to cause fatigue. This was supported by no decrease of *M* waves shown after ES in this study.

Two of the subjects with no surgical ACL reconstruction in the ACL lesion group showed a deficit of VA that was similar to those who had ACL reconstruction. Slightly weaker SICI and stronger ICF were observed in the two subjects who did not receive ACL reconstruction when compared to the subjects with ACL reconstruction, but no statistical analysis was performed due to the small sample number. On that matter, surgical reconstruction of ACL might help preserve the functional organization of SICI and ICF but could not prevent the reorganization which is an issue that is worth further investigation.

5. Conclusion

After an ACL lesion, both activation failure and cortical reorganization occurred. Providing additional afferent input by 30 minutes of peripheral ES could enhance the VA of quadriceps and normalize the SICI and ICF. Preventing cortical reorganization after an ACL lesion should not be overlooked in clinical rehabilitation. Peripheral ES providing additional afferent input to compensate for the loss of afferent input due to an ACL lesion is a potential rehabilitation program.

Data Availability

The data are available from the corresponding author upon request.

Conflicts of Interest

The authors declare no conflict of interest.

Acknowledgments

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References

[1] C. L. Ardern, K. E. Webster, N. F. Taylor, and J. A. Feller, "Return to the preinjury level of competitive sport after anterior cruciate ligament reconstruction surgery," *The American Journal of Sports Medicine*, vol. 39, no. 3, pp. 538–543, 2011.

[2] C. L. Ardern, N. F. Taylor, J. A. Feller, and K. E. Webster, "Fifty-five per cent return to competitive sport following anterior cruciate ligament reconstruction surgery: an updated systematic review and meta-analysis including aspects of physical functioning and contextual factors," *British Journal of Sports Medicine*, vol. 48, no. 21, pp. 1543–1552, 2014.

[3] A. J. Arundale, K. Cummer, J. J. Capin, R. Zarzycki, and L. Snyder-Mackler, "CORR Insights®: Report of the clinical and functional primary outcomes in men of the ACL-SPORTS Trial: similar outcomes in men receiving secondary prevention with and without perturbation training 1 and 2 years after ACL reconstruction," *Clinical Orthopaedics and Related Research*, vol. 475, no. 10, pp. 2535–2537, 2017.

[4] M. Miyatsu, Y. Atsuta, and M. Watakabe, "The physiology of mechanoreceptors in the anterior cruciate ligament. An experimental study in decerebrate-spinalised animals," *The Journal of Bone and Joint Surgery British*, vol. 75, pp. 653–657, 1993.

[5] Y. Konishi, T. Fukubayashi, and D. Takeshita, "Possible mechanism of quadriceps femoris weakness in patients with ruptured anterior cruciate ligament," *Medicine & Science in Sports & Exercise*, vol. 34, no. 9, pp. 1414–1418, 2002.

[6] N. Adachi, M. Ochi, Y. Uchio, J. Iwasa, K. Ryoke, and M. Kuriwaka, "Mechanoreceptors in the anterior cruciate ligament contribute to the joint position sense," *Acta Orthopaedica Scandinavica*, vol. 73, no. 3, pp. 330–334, 2002.

[7] Y. M. Huang, M. J. Hsu, C. H. Lin, S. H. Wei, and Y. J. Chang, "The non-linear relationship between muscle voluntary activation level and voluntary force measured by the interpolated twitch technique," *Sensors*, vol. 10, no. 1, pp. 796–807, 2010.

[8] Y. J. Chang, M. J. Hsu, S. M. Chen, C. H. Lin, and A. M. K. Wong, "Decreased central fatigue in multiple sclerosis patients after 8 weeks of surface functional electrical stimulation," *The Journal of Rehabilitation Research and Development*, vol. 48, no. 5, pp. 555–564, 2011.

[9] D. Urbach, W. Nebelung, H.-T. Weiler, and F. Awiszus, "Bilateral deficit of voluntary quadriceps muscle activation after unilateral ACL tear," *Medicine & Science in Sports & Exercise*, vol. 31, no. 12, pp. 1691–1696, 1999.

[10] D. Urbach, W. Nebelung, R. Becker, and F. Awiszus, "Effects of reconstruction of the anterior cruciate ligament on voluntary activation of quadriceps femoris," *The Journal of Bone and Joint Surgery British Volume*, vol. 83-B, no. 8, pp. 1104–1110, 2001.

[11] D. Urbach and F. Awiszus, "Impaired ability of voluntary quadriceps activation bilaterally interferes with function testing after knee injuries. A twitch interpolation study," *International Journal of Sports Medicine*, vol. 23, no. 4, pp. 231–236, 2002.

[12] T. L. Chmielewski, S. Stackhouse, M. J. Axe, and L. Snyder-Mackler, "A prospective analysis of incidence and severity of quadriceps inhibition in a consecutive sample of 100 patients with complete acute anterior cruciate ligament rupture," *Journal of Orthopaedic Research*, vol. 22, no. 5, pp. 925–930, 2004.

[13] M. E. Heroux and F. Tremblay, "Corticomotor excitability associated with unilateral knee dysfunction secondary to anterior cruciate ligament injury," *Knee Surgery, Sports Traumatology, Arthroscopy*, vol. 14, no. 9, pp. 823–833, 2006.

[14] L. Snyder-Mackler, A. Delitto, S. L. Bailey, and S. W. Stralka, "Strength of the quadriceps femoris muscle and functional recovery after reconstruction of the anterior cruciate ligament. A prospective, randomized clinical trial of electrical stimulation," *The Journal of Bone & Joint Surgery*, vol. 77, no. 8, pp. 1166–1173, 1995.

[15] S. Khaslavskaia and T. Sinkjaer, "Motor cortex excitability following repetitive electrical stimulation of the common peroneal nerve depends on the voluntary drive," *Experimental Brain Research*, vol. 162, no. 4, article 2153, pp. 497–502, 2005.

[16] S. Khaslavskaia, M. Ladouceur, and T. Sinkjaer, "Increase in tibialis anterior motor cortex excitability following repetitive electrical stimulation of the common peroneal nerve," *Experimental Brain Research*, vol. 145, no. 3, pp. 309–315, 2002.

[17] M. C. Ridding, B. Brouwer, T. S. Miles, J. B. Pitcher, and P. D. Thompson, "Changes in muscle responses to stimulation of the motor cortex induced by peripheral nerve stimulation in human subjects," *Exp Brain Res*, vol. 131, no. 1, pp. 135–143, 2000.

[18] Y. Z. Huang, F. Y. Chang, W. C. Liu, Y. F. Chuang, L. L. Chuang, and Y. J. Chang, "Fatigue and muscle strength involving walking speed in Parkinson's disease: insights for developing rehabilitation strategy for PD," *Neural Plasticity*, vol. 2017, Article ID 1941980, 9 pages, 2017.

[19] P. M. Rossini, A. T. Barker, A. Berardelli et al., "Non-invasive electrical and magnetic stimulation of the brain, spinal cord and roots: basic principles and procedures for routine clinical application. Report of an IFCN committee," *Electroencephalography and Clinical Neurophysiology*, vol. 91, no. 2, pp. 79–92, 1994.

[20] Y.-J. Chang, T.-H. Hsieh, Y.-M. Huang, M.-J. Hsu, and A. M.-K. Wong, "A lack of modulation of motor evoked potential in sensory-impaired individuals with spinal cord injuries," *Journal of Medical and Biological Engineering*, vol. 31, no. 1, pp. 37–43, 2011.

[21] M. Valeriani, D. Restuccia, V. D. Lazzaro, F. Franceschi, C. Fabbriciani, and P. Tonali, "Central nervous system modifications in patients with lesion of the anterior cruciate ligament of the knee," *Brain*, vol. 119, no. 5, pp. 1751–1762, 1996.

[22] R. Chen, B. Corwell, Z. Yaseen, M. Hallett, and L. G. Cohen, "Mechanisms of cortical reorganization in lower-limb amputees," *The Journal of Neuroscience*, vol. 18, no. 9, pp. 3443–3450, 1998.

[23] P. Schwenkreis, K. Witscher, F. Janssen et al., "Changes of cortical excitability in patients with upper limb amputation," *Neuroscience Letters*, vol. 293, no. 2, pp. 143–146, 2000.

[24] C. Dettmers, J. Liepert, T. Adler et al., "Abnormal motor cortex organization contralateral to early upper limb amputation in humans," *Neuroscience Letters*, vol. 263, no. 1, pp. 41–44, 1999.

[25] A. Kaelin-Lang, A. R. Luft, L. Sawaki, A. H. Burstein, Y. H. Sohn, and L. G. Cohen, "Modulation of human corticomotor excitability by somatosensory input," *The Journal of Physiology*, vol. 540, pp. 623–633, 2002.

[26] M. E. Knash, A. Kido, M. Gorassini, K. M. Chan, and R. B. Stein, "Electrical stimulation of the human common peroneal nerve elicits lasting facilitation of cortical motor-evoked potentials," *Experimental Brain Research*, vol. 153, no. 3, pp. 366–377, 2003.

[27] K. Irlbacher, M. Voss, B. U. Meyer, and J. C. Rothwell, "Influence of ipsilateral transcranial magnetic stimulation on the triphasic EMG pattern accompanying fast ballistic movements in humans," *The Journal of Physiology*, vol. 574, pp. 917–928, 2006.

[28] C. D. Mac Kinnon and J. C. Rothwell, "Time-varying changes in corticospinal excitability accompanying the triphasic EMG pattern in humans," *The Journal of Physiology*, vol. 528, pp. 633–645, 2000.

[29] M. Zoghi, S. L. Pearce, and M. A. Nordstrom, "Differential modulation of intracortical inhibition in human motor cortex during selective activation of an intrinsic hand muscle," *The Journal of Physiology*, vol. 550, pp. 933–946, 2003.

[30] R. K. Shields, Y. J. Chang, S. Dudley-Javoroski, and C. H. Lin, "Predictive model of muscle fatigue after spinal cord injury in humans," *Muscle Nerve*, vol. 34, no. 1, pp. 84–91, 2006.

[31] R. K. Shields and Y. J. Chang, "The effects of fatigue on the torque-frequency curve of the human paralysed soleus muscle," *Journal of Electromyography and Kinesiology*, vol. 7, no. 1, pp. 3–13, 1997.

[32] R. K. Shields, Y. J. Chang, and M. Ross, "Neuromuscular propagation after fatiguing contractions of the paralyzed soleus muscle in humans," *Muscle Nerve*, vol. 21, no. 6, pp. 776–787, 1998.

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Review Article

Effects of Robot-Assisted Gait Training in Individuals with Spinal Cord Injury: A Meta-analysis

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Background. To investigate the effects of robot-assisted gait training (RAGT) on spasticity and pain in people with spinal cord injury (SCI). *Material and methods*. Four electronic databases (PubMed, Scopus, Medline, and Cochrane Central Register of Controlled Trials) were searched for studies published up to November 2019. Only human trials and of English language were included. The searched studies were reviewed and extracted independently by two authors. Randomized controlled trials (RCTs) and non-RCTs were pooled separately for analyses. Primary outcome measures included spasticity assessed by Ashworth scale (AS) or modified Ashworth scale (MAS) and pain assessed by VAS. Secondary outcome measures included lower extremity motor score (LEMS) and walking ability (i.e., 6-minute walk test, 10-meter walk test). *Results*. A total of 225 studies were identified. Eighteen studies (7 RCTs and 11 non-RCTs) including 301 subjects met inclusion criteria. The outcome measure of spasticity significantly improved in favor of RAGT group in non-RCTs (AS: 95%CI = −0.202 to -0.068, $p \leq 0.001$; MAS: 95%CI = −2.886 to -1.412, $p \leq 0.001$). The results on pain did not show significant change after RAGT in either RCTs or non-RCTs. LEMS and walking ability significantly increased in favor of RAGT. *Conclusions*. RAGT can improve spasticity and walking ability in people with SCI. The probable reason for no significant change in pain after RAGT is floor effect. RAGT is beneficial for normalizing muscle tone and for improving lower extremity function in people with SCI without causing extra pain.

1. Introduction

Spinal cord injury (SCI) usually causes unreversible motor and sensory impairments. The incidence of SCI is 40 to 80 new cases per million people per year from all causes, depending on the country. For traumatic SCI, the ratio of male-to-female is around 2 : 1 [1]. SCI results in weak or paralyzed muscles, atrophy, walking disability, sensory dysfunction, and autonomic disorders such as autonomic dysreflexia [2]. Spasticity and pain are also some consequences of SCI affecting locomotor and quality of life [3].

The prevalence of spasticity after SCI is 65% at discharge from hospital [4]. In chronic stage, the prevalence is higher. Andresen et al. reported that, in chronic SCI, 71% of patients had spasticity, from the self-reported questionnaire [5]. Severe spasticity is not only detrimental to patients' walking and motor function [6] but is also related to the presence of pain, lower quality of life, and daily activities [7, 8]. Dipiro and colleagues reported that the self-reported frequency of medication usage on spasticity did not significantly decrease from baseline to 5 years of follow-up in chronic SCI [9]. Therefore, finding a treatment strategy that can decrease

spasticity and the use of medication might be beneficial to people with SCI.

The prevalence of chronic pain is high in people with SCI. Previous studies reported that the prevalence was around 84% and 73% in Canada and Denmark, respectively [5, 10]. Musculoskeletal pain is the most common type of chronic pain and presents early following spinal cord injury [11, 12]. The proportion of patients feeling at-level neuropathic pain is higher than below-level neuropathic pain [12]. Pain is highly correlated with poor mood, self-perceived health [12], physical functioning [13], and low quality of life [5] in SCI.

Walking ability is one of the rehabilitation goals of people with SCI, especially in people with incomplete injury. To achieve functional walking, patients require not only appropriate muscle strength and nerve innervation but also proper endurance and less fatigue. Fatigue impacts on function in 57% of individuals with SCI [14]. It is also more prevalent among younger SCI and SCI with shorter duration of disability [15]. Clinically, there are several commonly used measurement tools, such as 6-minute walk test (6MWT), 10-meter walk test (10MWT), timed up and go (TUG), Walking Index for Spinal Cord Injury (WISCI), and Functional Independence Measure-Locomotion (FIM-L), each assesses different aspects of walking ability. For example, 10MWT and 6MWT have been shown to be valid and reliable to measure ambulatory ability for individuals with SCI [16], and 6MWT has been suggested to be a good assessment tool of endurance [16, 17]. TUG is a simple and quick test to assess a person's mobility and balance and correlates well with gait speed for frail elderly [18] and endurance in chronic stroke [19]. FIM-L and WISCI address on the need of assistance when performing functional tasks. FIM-L measures the functional status (walking/wheelchair and stairs) of a person based on the level of assistance he or she requires [20]; it can be considered as an evaluation of the gait ability in activities of daily living. WISCI scores the walking ability according to the need for physical assistance, braces, and walking aids [21]. Manual muscle testing (MMT) assesses lower extremity motor score (LEMS) according to American Spinal Injury Association (ASIA).

Rehabilitation for improving pain, spasticity, and walking ability is always a challenge for clinicians. The use of robot-assisted gait training (RAGT) in the field of rehabilitation has become more widespread since this training is not limited by the individuals' muscle paralysis level. Current systems of RAGT include Lokomat (Hocoma AG, Switzerland), G-EO systemTM (Reha Technology AG, Switzerland), Walkbot (P&S Mechanics Co., Ltd, Korea), and ReoAmbulatorTM (Motorika, USA Inc.) [22]. RAGT provides repetitive and functional task training which induces greater activation of the sensorimotor cortex (S1, S2) and cerebellar regions [23]. A meta-analysis revealed that RAGT improved walking endurance, walking independence, and lower limb muscle strength, but did not reduce spasticity [24]. Other than task-specific training, RAGT provides proprioceptive inputs to lower extremities. According to gate control theory, large fiber activation might be able to block noxious small fiber afferents which cause pain and spasticity. Previous studies revealed that sensorimotor activity by treadmill training decreased pain behavior and nociceptive fiber density in the spinal dorsal horn in acute, subchronic, and chronic SCI mice model [25, 26]. Previous studies also reported that rhythmic passive movement could induce spinal circuitry reorganization, restore postactivation depression, and decrease spasticity in patients with SCI [27]. Therefore, it is plausible to hypothesize that RAGT can reduce pain and spasticity. In the past, much work has been done on investigating the effect of RAGT on walking performance, but reports of its effect on pain and spasticity were rare.

The purpose of this meta-analysis was to compare the effects of RAGT on spasticity and pain with those of other treatments after SCI.

2. Methods

This review integrated the results from relevant studies by following the systematic review and meta-analysis guidelines outlined in the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) statement [28].

2.1. Types of Participants. This study included only SCI subjects, regardless of traumatic or nontraumatic lesion, the time since injury, age, and sex.

2.2. Types of Interventions. Any kind of RAGT compared with other training modalities or no training for lower limbs was included.

2.3. Outcome Measures. Primary outcome measures were spasticity and pain. Spasticity was assessed by modified Ashworth scale (MAS) or Ashworth scale (AS) for lower limbs. Pain was assessed by the visual analog scale (VAS). The VAS is widely used to assess self-perceived pain [29]. It is a 10-centimeter line in which 0 represents no pain and 10 at the right edge means intolerable pain. Participants subjectively reported their pain condition on the VAS scale.

Secondary outcome measures were LEMS and walking ability assessed by 6MWT, 10MWT, TUG, WISCI, and FIM-L. LEMS assessed motor score for lower limbs according to ASIA standard. 6MWT measured the walking distance in 6 minutes. 10MWT assessed the walking speed measuring the time necessary to walk 10 meters. 6MWT and 10MWT were reliable and responsive tools in assessing walking ability in incomplete SCI [30]. TUG assessed the time that a subject took to rise from a chair, walk three meters, turn around, walk back to the chair, and sit down. WISCI measured improvements in ambulation in persons with SCI by evaluating the amount of physical assistance, braces, or devices required to walk 10 meters. WISCI I scored from 1 to 19 and WISCI II from 1 to 20 [31]. FIM was an 18-item assessment of physical, psychological, and social function. The assessor graded the functional status of a person based on the need of assistance [32].

2.4. Type of Studies. RCT, non-RCT, and crossover trials (only the RAGT period) were included in analysis.

2.5. Searching Criteria. The searching criteria were limited to human studies and English language.

2.6. Data Sources. Four electronic databases (PubMed, Scopus, Medline (Proquest), and Cochrane Central Register of Controlled Trials (CENTRAL)) before November 2019 using Medical Subject Heading terms combined with keywords, such as robotics, spinal cord injury, pain, and spasticity, were processed in title, abstract, and keywords. Appendix 1 shows the combinations used.

2.7. Study Selection. Two authors independently searched and screened the titles, abstracts, and literatures to identify potentially relevant studies. Then, full texts of relevant studies were obtained and assessed to determine whether the articles met the inclusion criteria. Any disagreement was discussed and solved with the third author to reach a consensus in every relevant detail.

2.8. Data Extraction and Management. Two authors extracted data independently from included studies and filled into an extraction form. The following data were extracted: (1) authors; (2) year of publication; (3) study design; (4) inclusion/exclusion criteria; (5) subject demographics (age, gender, number of subjects, level of lesion, classification of ASIA, duration of injury); (6) intervention; (7) outcome measures; and (8) summary of the results.

Data at baseline and at the end of the intervention were extracted for the analysis of the effect of training. Measurements during the intervention or at follow-up were excluded due to inconsistent measuring time points used across different studies. Studies were excluded if necessary outcome measures were missing or not measured.

2.9. Quality Assessment. The methodological quality of the selected RCTs was independently assessed by two authors using the Cochrane risk of bias assessment tool [33]. For the assessment of the methodological quality of the selected cohort studies and clinical trials, the Newcastle Ottawa Scale [34, 35] was employed and done by two authors independently. Any disagreement was resolved through discussion and consensus with the third author.

2.10. Statistical Analysis. RCTs and non-RCTs were grouped and analyzed separately. Statistical analysis was performed using Comprehensive Meta-Analysis (CMA) version 3 to analyze the treatment effect. Mean differences and 95% confidence interval (CI) were calculated for each primary and secondary outcome. Random effect models were used to calculate the pooled mean difference estimates if heterogeneity occurred. Fixed effects models were used to calculate the pooled mean difference estimates if no heterogeneity occurred.

3. Results

3.1. Studies Included. A total of 223 studies from electronic databases and two studies from the reference lists of included studies were identified. In these, 105 of the selected studies were duplicates and thus were removed from analysis. Out of the retained studies, 18 studies were retained for quality synthesis which included 7 RCTs and 11 non-RCTs. The flow of studies through the review process is shown in Figure 1. Six studies were included after review for quantitative synthesis of which the characteristics are shown in Table 1 and Table 2.

3.1.1. Excluded Studies. After screening, a total of 66 studies were eliminated. The reasons for exclusion were as follows: texts not in English version, manuscripts in the form of education page, subjects of the studies included other diagnostic groups, study purpose, and outcome measures did not meet our inclusion criteria.

3.1.2. Study Location. From the 18 studies, 7 trials were done in the United States [36–42], 2 in Spain [43, 44], 2 in Switzerland [45, 46], 2 in Canada [47, 48], 2 in Italy [49, 50], 2 in Japan [51, 52], and one in Germany [53].

3.1.3. Study Participants. A total of 222 participants from 7 RCTs were included. Seventy-nine participants from 11 non-RCTs were included. Although age was not reported in all included studies, the participants' age of RCTs and non-RCTs ranged from 34 [46] to 59 [45] and 19 [51] to 62 [52] years, respectively. One RCT [36] and one non-RCT [39] did not report the proportion of gender. For other included RCTs, the proportion between males and females was 101 : 79. For non-RCTs, the proportion between males and females was 62 : 15.

The ASIA level was B, C, or D in RCTs and A, B, C, or D in non-RCTs. The level of injury was cervical (C1-C8) in 80 participants, thoracic in 67, C2-T9 in 46, and above T10 in 30 participants in RCTs. The cervical level of injury was C3 to C7 in 16 participants, thoracic (T3-T12) in 48, lumbar (L1-L5) in 14, and T12-L1 in one participant in non-RCTs.

3.2. Interventions. The intervention of RAGT was 3 to 5 sessions per week, 30 min to one hour for 4 to 12 weeks in RCTs. The training protocol of non-RCTs was 2 to 5 sessions, 30 min to 90 min for one week to 90 days.

The apparatus used for RAGT in these studies included Lokomat, hybrid assistive limb (HAL), Indego Exoskeleton, ReWalk, ARKE 2.0, and Ekso GT in which all included RCTs used Lokomat for training.

3.3. Risk of Bias of the Included Studies. Figure 2 summarized the risk of bias judgements related to all RCTs. In all included RCTs, only one study [36] had high risk of bias level. Five studies [37, 38, 44–46] reported randomization. Two studies did not mention randomization [36] or were unclear [47]. Allocation concealment was fulfilled by two studies [44, 45]. Three of the included studies [44, 45, 47] had blinding and the other three studies [37, 38, 46] did not report the methodology of allocation concealment. Two studies [45, 47] did intention to treat analysis and the other three studies [37, 38, 44] were unclear on the information about attrition bias. Two studies [36, 46] had high risk of attrition bias for not reporting their management on the drop-out data.

Table 3 summarized the risk of bias judgements related to non-RCTs. All studies had general to good quality. All non-RCTs recruited representative SCI subjects and no control

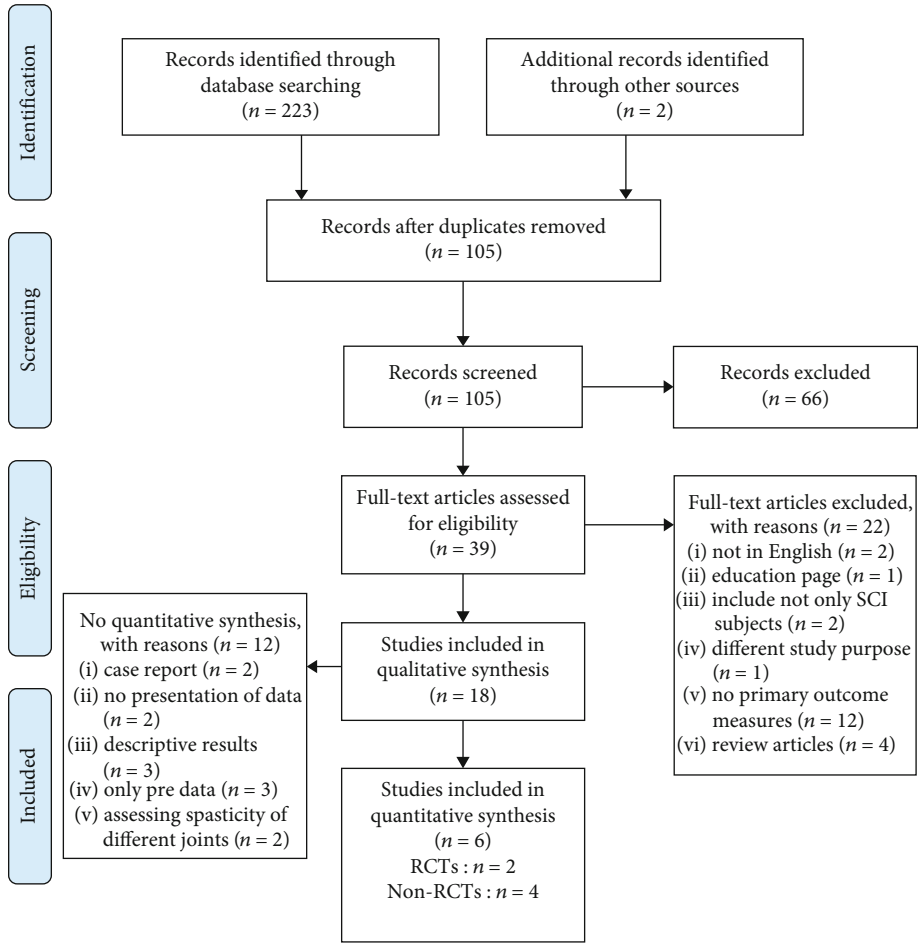

Figure 1: Flow diagram of the study selection process.

group. All studies had secure record on training protocol but one study [39] did not. All studies assessed outcomes independently. The duration of three non-RCTs [43, 50, 52] was from 40 min to 2 weeks, most trials with 8 weeks.

3.4. Effects of the Interventions. Pain and walking ability were analyzed in RCTs. Spasticity, pain, and walking ability were analyzed in non-RCTs. Summarization on spasticity and TUG in RCTs and FIM-L in non-RCTs were done without meta-analysis due to insufficient data information.

3.5. Results of Primary Outcomes: Spasticity. Four RCTs [36, 38, 44, 46] assessed spasticity. However, different muscle groups were assessed in these studies; therefore, the data could not be pooled together. In these studies, all participants' spasticity was mild (MAS 0-2) and none of them changed significantly after RAGT.

Six eligible non-RCTs were included but only 4 studies' data were retained to pool for analysis. One trial was excluded for analysis because it assessed spasticity of 36 joints together [51]. The other one trial was excluded for analysis because the participants in this trial had no spasticity [52]. Out of the four non-RCTs analyzed, 2 studies [49, 50] use MAS as their outcome measure on 28 participants. The other two studies [42, 43] used AS to assess 23 participants for spasticity (Figure 3). The robotic group showed significant decrease in MAS (95%CI = −2.886 to -1.412, $p \leq 0.001$) and AS (95%CI = −0.202 to -0.068, $p \leq 0.001$) measures. The pooled mean difference using MAS and AS (fixed effects model) were -2.149 and -0.135, respectively.

3.6. Results of Primary Outcomes: Pain. Two RCTs [44, 45] and 3 non-RCTs [43, 49, 50] were included for analysis. Eighty-four and 31 participants were involved in RCT and non-RCT studies, respectively. Figure 3 showed the results on the analysis of the primary outcomes of pain after RAGT. Although the trend for pain reduction was in favor of robotic group, there was no significant difference between robotic and control group, regardless of RCTs ($p = 0.427$) or non-RCTs ($p = 0.239$). The pooled mean difference (random effects model) of RCTs and non-RCTs were -0.890 and -1.676, respectively. The level of pain ranged from painless [44] to moderate [49, 50] in all included studies.

3.7. Results of Secondary Outcomes: LEMS and Walking Ability

3.7.1. LEMS. Three RCTs [36, 44, 45] included 104 participants, and three non-RCTs [42, 52, 53] with 30 participants were pooled for analysis. Significant positive effect in favor

Table 1: Characteristics of included RCTs.

Study	Research design	Participants	Intervention	Outcome measures
Alcobendas-Maestro et al., [44]	RCT	$n = 75$ (37 in the Lokomat training group, 38 in the conventional overground group) ASIA C or D Level of injury: C2 to T12	40 sessions over 8 weeks, 1 hour (1) Lokomat group: 30 min with the Lokomat in each session+30 min standard physical treatment (2) Overground group: one hour standard physical treatment	AS VAS 6MWT, 10MWT WISCI II FIM-L, LEMS
Hornby et al., [36]	RCT	$n = 30$ ASIA B, C, D Level of injury: above T10	(1) Robotic-assisted BWSTT (2) Therapist-assisted BWSTT (3) Overground ambulation with a mobile suspension system three 30-minute sessions per week, 8 weeks	AS SCATS 6MWT, 10MWT WISCI FIM-L LEMS, TUG
Labruyère and van Hedel, [45]	RCT cross over	$n = 9$ ASIA D Level of injury: C4 to T11	(1) Group 1: 16 sessions of RAGT (Lokomat) followed by 16 sessions of strength training (2) Group 2: the same intervention in reversed order	VAS, 10MWT, WISCI LEMS, UEMS, FET, PCI, gait symmetry, BBS Body sway FES-I, SCIM
Lam et al., [47]	RCT	$n = 15$ ASIA C or D Lesion level below thoracic 11 or lower motoneuron injury was excluded	(1) Lokomat-resisted BWSTT (Loko-R) (2) Lokomat-assisted BWSTT (control) 45 min, 3 times/week for 3 mo.	Reports of pain 10MWT 6MWT SCI-FAP
Mirbagheri et al., [37]	RCT	$n = 46$ ASIA C or D Level of injury: C2 to T9	(1) RAGT group: 3 times a week over four weeks, one hour/session (2) Control group: no intervention	MAS Intrinsic stiffness K Reflex stiffness G
Varoqui et al., [38]	RCT	$n = 30$ ASIA C or D Level of injury: above T10	(1) Lokomat group: 3 times a week over four weeks, one hour/session (2) Control group	MAS 10MWT 6MWT TUG Ankle kinematic and kinetic assessments
Wirz et al., [46]	RCT	$n = 21$ ASIA B or C Level of injury: C4 to T12	(1) Intervention group: 50 min/training (2) Control group: 25 min/training Lokomat, 3-5 days/week, 8 weeks	MAS SCIM III WISCI II Penn, GICS

BWSTT: body-weight supported treadmill training; AS: Ashworth scale; MAS: modified Ashworth scale; 10MWT: 10-meter walking test; 6MWT: 6-minute walk test; WISCI: Walking Index for Spinal Cord Injury; FIM-L: Functional Independence Measure-Locomotor section; LEMS: lower extremity motor score; SCIM: Spinal Cord Independence Measure; Penn: Modified Penn Spasm Frequency Scale; TUG: timed up and go test; FET: Figure Eight Test; PCI: Physiological Cost Index; BBS: Berg balance scale; FES-I: falls efficacy scale-international version; UEMS: upper extremity motor score; SCI-FAP: Spinal Cord Injury-Functional Ambulation Profile; SCATS: Spinal Cord Assessment Tools for Spasticity; GICS: Global Impression of Change Scale.

of robotic group in both RCTs (95%CI = 1.143 to 2.732, $p \leq 0.001$) and non-RCTs (95%CI = 1.508 to 4.839, $p \leq 0.001$) were shown in the results of LEMS. The pooled mean differences (fixed effects model) were 1.938 and 3.173 for RCTs and non-RCTs, respectively (Figure 4).

3.7.2. 6MWT. Four RCTs [36, 38, 44, 47] and 4 non-RCTs [42, 43, 49, 53] assessed 6MWT. A total of 140 and 38 participants were involved in analysis in the RCTs and non-RCTs, respectively. Regardless of RCTs or non-RCTs, walking distance in 6MWT increased significantly in favor of robotic group (RCTs: 95%CI = 4.394 to 106.628, $p = 0.033$; non-RCTs: 95%CI = 7.218 to 52.586, $p = 0.010$). The pooled mean difference (random effects model) of RCTs and non-RCTs were 55.511 m and 29.902 m, respectively (Figure 4).

3.7.3. 10MWT. Five RCTs were included in this analysis, but the data of only four studies were pooled. One study [38] was excluded because no data of control group were provided. Four RCTs [44–47] and 5 non-RCTs [42, 43, 49, 52, 53] were used for subsequent data analysis (Figure 4). In these, 117 and 40 subjects of RCTs and non-RCTs were included, respectively. 10MWT significantly improved in robotic group of non-RCTs (95%CI = 0.032 to 0.213, $p = 0.008$) but not of RCTs ($p = 0.597$). The pooled mean difference (random effects model) for non-RCTs was 0.123 m/s.

Table 2: Characteristics of included non-RCTs.

Study	Research design	Participants	Intervention	Outcome measures
Aach et al., [53]	Single case experimental A-B (pre-post) design	$n = 8$ ASIA A Level of injury: T8 to L2	HAL 5 times per week, 90 days, mean number of sessions of 51.75 ± 5.6	6MWT, 10MWT TUG WISCI II LEMS Muscle volume
Del-Ama et al., [43]	Pilot study	$n = 3$ ASIA A and D Level of injury: L1, L4, L5	Kinesis system The first week intervention, the second week no intervention	VAS AS 10MWT 6MWT Penn MMT
Ekelem and Goldfarb, [39]	Case report	$n = 2$ ASIA B Level of injury: T4, T11	Indego exoskeleton practice < 4 hr per day	MAS
Esquenazi et al., [40]	Prospective, single-intervention	$n = 12$ ASIA B Level of injury: T3-T12	ReWalk Up to 24 sessions of 60 to 90 min duration over approximately 8 weeks (target was three times per week)	Pain, fatigue (VAS) AS HR, BP Skin integrity
Ikumi et al., [51]	Case report	$n = 1$ ASIA A Level of injury: C4	HAL 60 min, 2 times per week for 5 weeks in addition to standard physical and occupational therapy	MAS Walking time and distance
Lemaire et al., [48]	Case report	$n = 2$ ASIA B Level of injury: T6, T12	ARKE 2.0 LEPE 12 half-hour training sessions, four or more weeks	Ten-point scale: pain, fatigue Number of steps Distance travelled Standing duration Walking duration Number of partial steps
Manella et al., [41]	Case report	$n = 1$ ASIA A Level of injury: T7	Lokomat 40 mins, 3 times per week, 12 weeks	AS Pendulum test of quadriceps spasticity Spasm frequency and severity ASIA sensory scores LEMS FIM
Mazzoleni et al., [49]	Single group	$n = 7$ ASIA A Level of injury: T4-T12	20 sessions, 3 sessions/week, FES-cycling system (Pegaso) followed by 20 sessions, 3 sessions/wk, overground robotic exoskeleton (Ekso GT)	MAS PSFS SCIM Spasticity and pain through a 0-10 points NRS ISCI 6MWT, 10MWT TUG
Stampacchia et al., [50]	Single group	$n = 21$ ASIA A, B, D Level of injury: C7, L1-L2, dorsal	Ekso GT 40 min	Pain and spasticity (0-10 points scale) MAS PSFS PGIC

Table 2: Continued.

Study	Research design	Participants	Intervention	Outcome measures
Watanabe et al., [52]	Case report	$n = 2$ ASIA C, D Level of injury: T8-T10, T12-L1	HAL 3-4 times per week, for a total of 8 sessions, in addition to conventional physical therapy, 20-30 min/session	MAS LEMS WISCI II FIM CGS Stride, cadence Right and left leg swing time Hip and knee joint angle BI, mRS and adverse effects
Wirz et al., [42]	Single group	$n = 20$ AISA = C or D Level of injury: L1 or higher	Lokomat (DGO) 8 weeks, 3 to 5 sessions each week, 45 min	Primary: WISCI II, 10MWT, 6MWT, TUG Secondary: at 1 center, $n = 10$ LEMS, AS, SCATS

AS: Ashworth scale; MAS: modified Ashworth scale; 10MWT: 10-meter walking test; 6MWT: 6-minute walk test; WISCI: Walking Index for Spinal Cord Injury; FIM: Functional Independence Measure; LEMS: lower extremity motor score; HR: heart rate; BP: blood pressure; SCIM: Spinal Cord Independence Measure; Penn: Modified Penn Spasm Frequency Scale; TUG: timed up and go test; SCATS: Spinal Cord Assessment Tools for Spasticity; PSFS: Penn Spasm Frequency Scale; ISCI: International Spinal Cord Injury Pain Data Set; PGIC: patient's global impression of change; CGS: comfortable gait speed; BI: Barthel index; mRS: modified Rankin Scale.

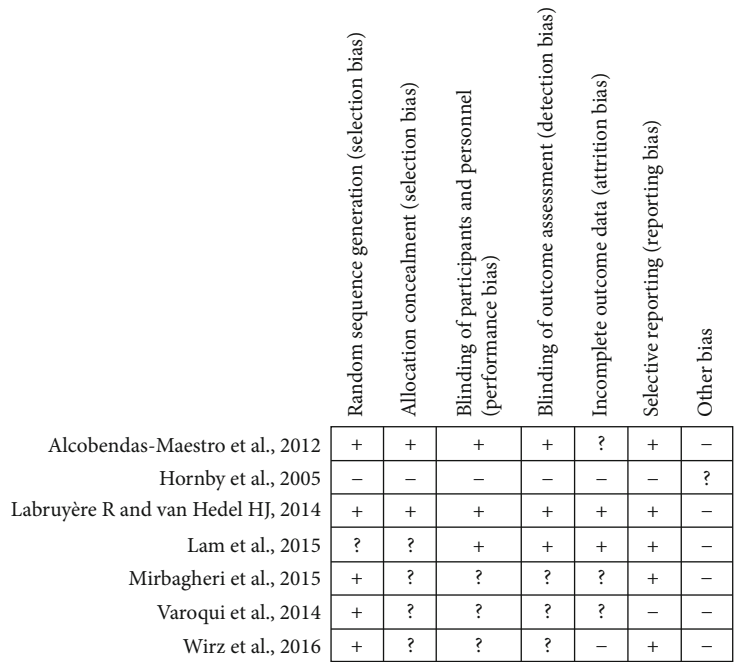

Figure 2: Risk of bias summary for all included RCTs. +: low risk of bias; -: high risk of bias; ?: unclear risk of bias.

3.7.4. TUG. Though one RCT [38] used this outcome measure, there was no sufficient data for analysis. Data from three non-RCTs [42, 49, 53] included 35 participants who were pooled for analysis. The result showed significant improvement in favor of robotic group (95%CI = −33.232 to -15.659, $p \leq 0.001$). The pooled mean difference (fixed effects model) was -24.446 s (Figure 4).

3.7.5. WISCI. Five RCTs and 3 non-RCTs were included for this analysis, but 2 RCTs and one non-RCT were excluded for insufficient data provided (one RCT [38] and one non-RCT [42]). Data variability of one RCT [46] was too dispersed. Data of three RCTs [36, 44, 45] and 2 non-RCT ones [52, 53] with 104 and 10 participants for RCT and non-RCT, respectively, were finally pooled into analysis, and the results showed no significant difference ($p = 0.265$ for RCTs; $p = 0.228$ for non-RCTs) (Figure 4).

3.7.6. FIM-L. Only 2 RCT studies [36, 44] assessed FIM-L scale. The analysis included 95 subjects. The pooled result

Table 3: Assessment of study quality with Newcastle-Ottawa scale.

		Selection						Outcome			Comparability
Study ID	Year	S1	S2	S3	S4	C1	C2	O1	O2	O3	No. of star
Aach et al.	2014	★		★	★			★	★	★	6
del-Ama et al.	2014	★		★	★			★		★	5
Ekelem and Goldfarb	2018	★			★			★			3
Esquenazi et al.	2012	★		★	★			★	★	★	6
Ikumi et al.	2017	★		★	★			★	★	★	6
Lemaire et al.	2017	★		★	★			★	★	★	6
Manella et al.	2010	★		★	★			★	★	★	6
Mazzoleni	2017	★		★	★			★	★	★	6
Stampacchia	2016	★		★	★			★		★	4
Watanabe	2017	★		★	★			★		★	4
Wirz et al.	2005	★		★	★			★	★	★	6

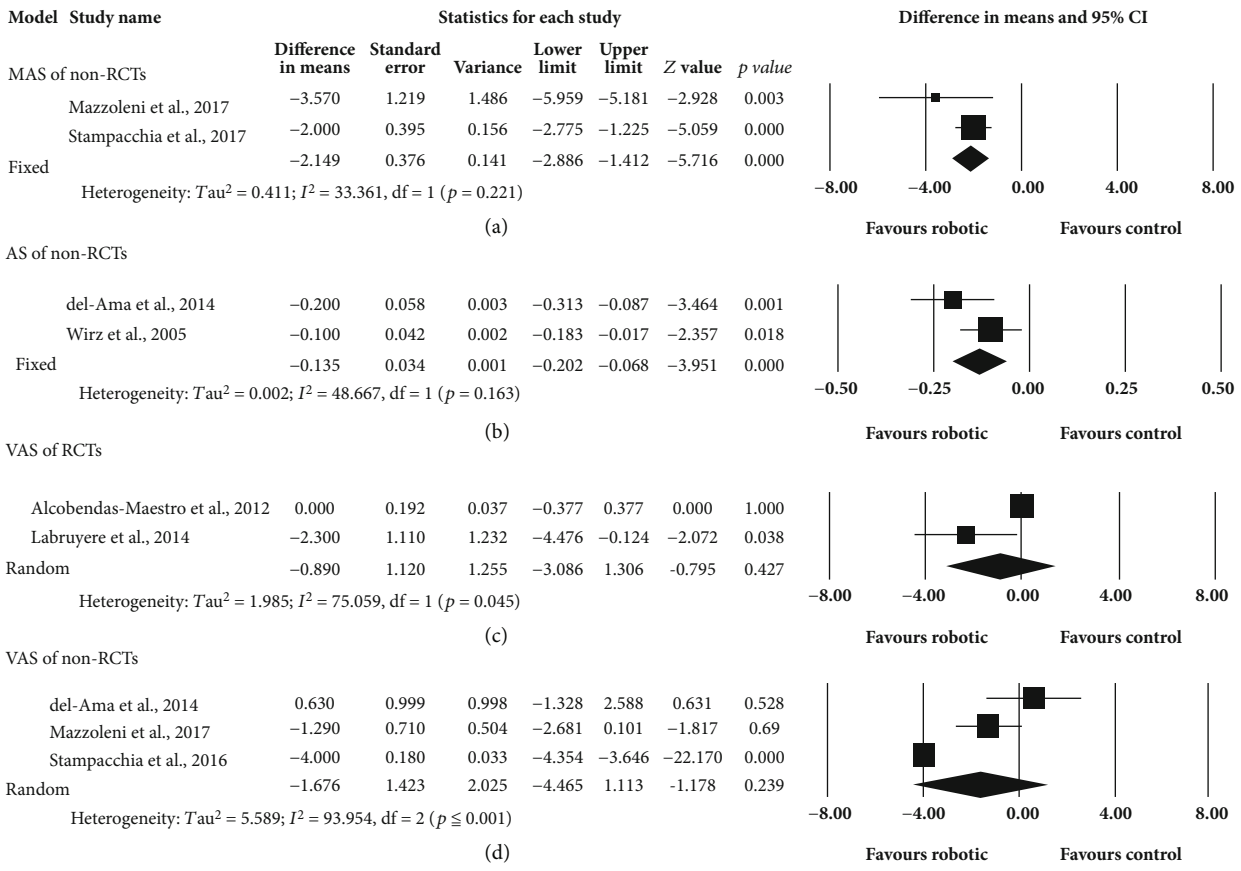

Figure 3: Forest plots of spasticity- (MAS and AS) and pain- (VAS) related variables.

showed no significant difference between two groups ($p = 0.122$). The pooled mean difference (random effects model) was 1.853 (Figure 4). For the included non-RCTs, none of them reported FIM-L.

3.8. Publication Bias. Appendix 2 demonstrated the funnel plots of VAS, 6MWT, 10MWT, TUG, WISCI, and LEMS. There were no funnel plots of MAS and AS due to only two studies of each measurement. It seemed a symmetrical funnel plot of VAS, but small study bias was identified in Egger's test ($p = 0.03289$). No small study bias was found in other measurements.

4. Discussion

This meta-analysis showed RAGT decreased spasticity and improved walking ability in individuals with SCI. Furthermore, the level of pain showed no change after RAGT.

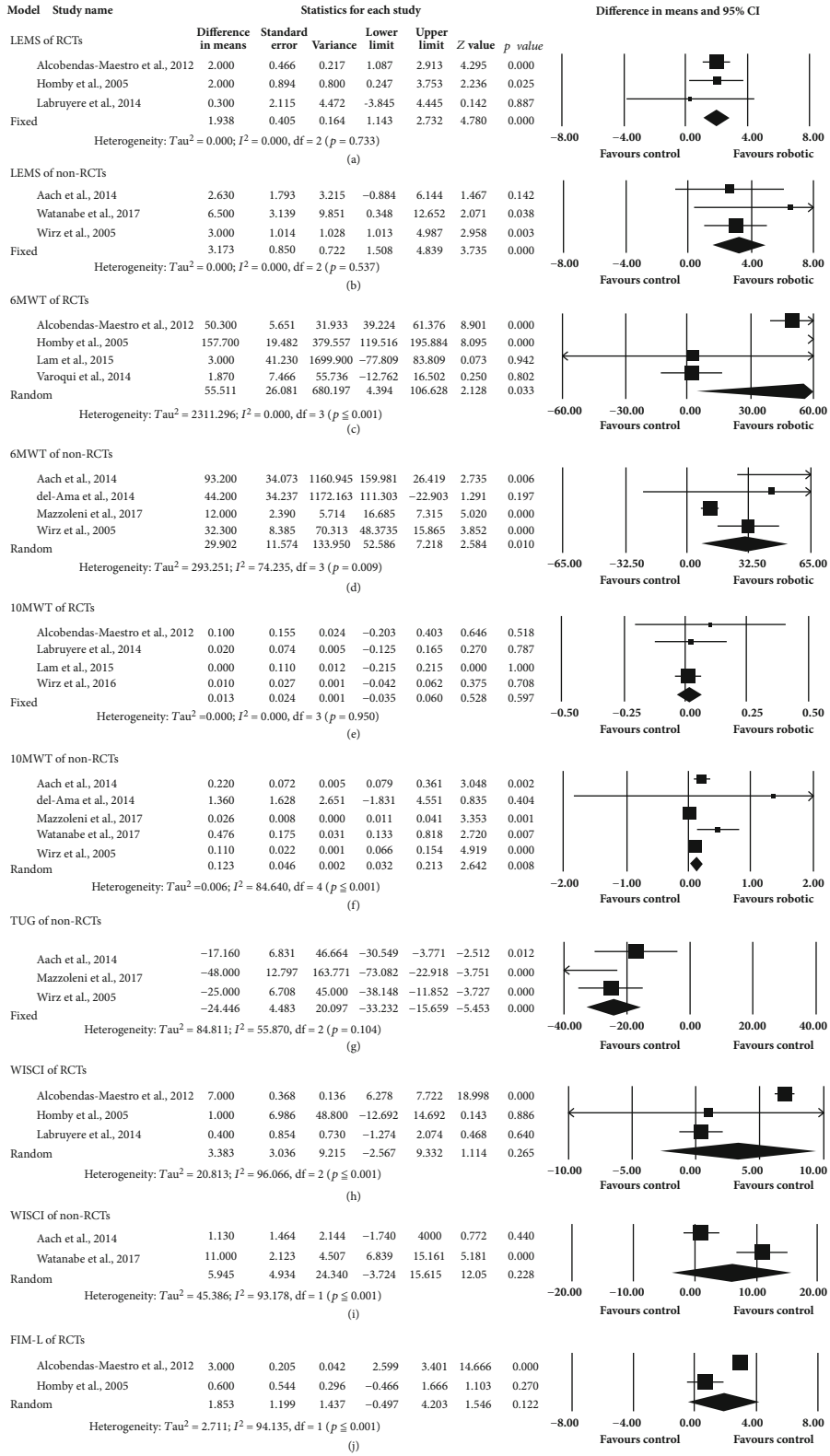

Figure 4: Forest plots of muscle strength of lower limbs (LEMS) and walking ability-related variables (6MWT, 10MWT, TUG, WISCI, and FIM-L).

4.1. Spasticity. The current meta-analysis revealed that spasticity decreased after RAGT in non-RCTs. Several possible mechanisms could explain the reduction of spasticity after RAGT. Spasticity is defined as a velocity-dependent increase in tonic stretch reflexes with exaggerated tendon jerks [54]. However, spasticity also involves nonreflex component such

as intrinsic muscular properties [54]. Mirbagheri et al. reported that RAGT reduced reflex and intrinsic stiffness of ankle in individuals with SCI [37].

RAGT produces rhythmic movements of lower limbs and provides sensory inputs. Previous studies reported that rhythmic passive exercise could induce spinal circuitry reorganization and decrease spasticity in patients with SCI [27, 55]. Improving spasticity and locomotor function by the activation of spinal locomotor centers might also be influenced by the repetitive elements of the therapeutic program [56]. RAGT is a type of repetitive functional task training. These above mechanisms might possibly explain the finding that RAGT reduces spasticity.

The reasons that the RCTs did not show significant reduction in spasticity in the RAGT group might be due to the floor effect [44, 46] (MAS 0 to 1) and the measurements done on different joints [38, 44, 46]. In the included studies, the subjects' initial spasticity level was not high enough to show change after RAGT. It is suggested that subjects with more severe spasticity could be recruited for further investigation of RAGT.

4.2. Pain. Pain and spasticity are intricate consequences of spinal cord injury [57]. Researchers suggested that pain and spasticity are closely linked [57]. In addition, pain and spasticity might share similar pathophysiological mechanisms [5]. Hence, it is reasonable to expect a reduction of pain with spasticity reduction after RAGT. However, the result of this meta-analysis did not show significant decrease of pain accompanying reduced spasticity following RAGT. This might be that the pain suffered by the participants in these included trials was not mainly from spasticity. Some other potential sources, such as muscle soreness due to excess exercise, joint pain due to malposture, or poor biomechanics, might be the cause of pain. One should also note that the neuropathic pain, more than 50% prevalence in spinal cord injured persons [58], was not reported in the included studies. Therefore, they lacked source of data for meta-analysis. It is suggested to be investigated in future studies.

Although, the included RCTs and non-RCTs did not show significant change in pain, the trend favored RAGT group. Past studies revealed that physical activities could relieve musculoskeletal and neuropathic pain [59, 60]. However, participants in the current meta-analysis did not subjectively feel significant alteration in pain level with VAS assessment. The baseline floor effect of mild [44] to moderate [50] intensity of pain felt by the participants might account for the nonsignificant result. Future studies that include participants with higher level of pain at baseline are suggested.

4.3. LEMS. This study showed that LEMS significantly improved after RAGT. As discussed previously, rhythmic muscle activations could be detected during RAGT. In addition, weight bearing may be an important factor. RAGT provides support which allows users to load their weight on lower limbs during training. Lower limbs weight bearing and the enhancement of muscle activation may contribute to the improvement of LEMS.

Decreasing guiding force as RAGT progresses might increase the muscle strength of lower extremities. Subjects needed greater engagement to activate muscles and participate in the training program. Since the guiding force has not been quantified in the included studies, investigation of the relationship between guiding force and the improvement of LEMS is suggested in future studies.

4.4. 6MWT. This meta-analysis showed that 6MWT increased significantly in favor of the RAGT group. 6MWT is an indicator of endurance. Clinically meaningful change (CMC) of 6MWT was 19-22 m in healthy older adults [61]. The 95% CI of the current meta-analysis includes the range 4.394-106.628 m for included RCTs and 7.218-52.586 m for included non-RCTs. Hence, RAGT can be clinically practical for endurance training.

In physiological point of view, endurance could be improved by multiple sessions of submaximal voluntary exercises [62]. RAGT, due to its lack of active participation from the users during training, was doubted to increase cardiopulmonary fitness in subjects [63]. However, increased 6MWT in this meta-analysis indicates it could improve endurance without emphasizing voluntary muscle contraction. According to Mazzoleni et al. [64], bilateral muscular activity increased after RAGT in people with SCI. Thus, the activation of muscles might increase the challenge to cardiopulmonary systems and, thus, increase the endurance of participants with SCI.

4.5. Walking Speed (10MWT and TUG). TUG is commonly used to assess functional mobility. It was correlated with muscle strength of the lower extremities and gait speed [18, 65]. The current meta-analysis showed that both parameters improved after RAGT in SCI. The results of 10MWT also supported that RAGT increased walking speed in SCI. The CMC of 10MWT was 0.04-0.06 m/s in healthy older adults [61]. The pooled mean difference (0.123 m/s) was above CMC in included non-RCTs in this meta-analysis.

Kim et al. [66] reported that muscle strength of the lower extremities was correlated with walking speed in chronic incomplete SCI. As shown with the result of LEMS's improvement, lower extremity strength might be the cause of improved walking speed.

Another explanation for improved walking speed was the strengthening of central pattern generator (CPG). Previous studies supported that RAGT, which involved rhythmic activations of lower extremities, could strengthen CPG [67]. CPG is an essential neural mechanism of walking. Enhanced CPG would lead to increase walking ability. The other explanation was the reduction of spasticity. Spasticity could increase the resistance of movement and interfere with gait. As shown in the above result, spasticity reduced after RAGT and, thus, resulted in less resistance during walking.

4.6. WISCI and FIM-L. WISCI and FIM-L showed no significant difference after RAGT in this meta-analysis. The reason might be that studies investigated that WISCI and FIM-L were few in the current meta-analysis. However, the CMC for the WISCI was 1 point [68]. The pooled mean differences

of included studies all exceed CMC (3.383 for RCTs and 5.945 for non-RCTs).

FIM was graded according to the assistance required by a subject. People with SCI might experience fear of falling that impeded transferring the improved walking abilities to functional tasks after RAGT.

4.7. Study Limitations. The first limitation of this current review is no classification of subgroups according to the level and severity of SCI. More trials and subjects are needed for subgroup analysis. The second limitation is the risk of bias exists in all studies. Compared with the non-RCTs, the number of RCTs studies is relatively few. The third limitation is that the training protocol used in each study is not identical. Further reviews are suggested to compare effects of different protocols with increased trials.

5. Conclusions

This meta-analysis concluded that RAGT had positive effects in improvements of spasticity and walking ability. In RCTs, walking distance and muscle strength of lower limbs improved after RAGT. RAGT can be applied in individuals with SCI without increasing pain.

Abbreviations

SCI: Spinal cord injury
RAGT: Robot-assisted gait training.

Conflicts of Interest

We have no conflict of interest.

Acknowledgments

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Supplementary Materials

Appendix 1: searching keywords. Appendix 2: funnel plots and Egger's test of (a) VAS for non RCTs, (b) 6MWT for 3 RCTs, (c) 6MWT for non RCTs, (d) 10MWT for RCTs, (e) 10MWT for non RCTs, 4 (f) TUG for non RCTs, (g) WISCI for RCTs, (h) LEMS for RCTs, and (i) LEMS for non 5 RCTs. *(Supplementary Materials)*

References

[1] J. B. C. Bickenbach, D. Brown, A. Burns et al., *WHO-international perspectives on SCI.pdf*, 2013.

[2] M. F. Somers, "Spinal cord injuries," in *Spinal Cord Injury: Functional Rehabilitation*, M. F. Somers, Ed., pp. 27–34, Pearson Education, Upper Saddle River, N.J, 2010.

[3] H. Barbeau, M. Ladouceur, K. E. Norman, A. Pépin, and A. Leroux, "Walking after spinal cord injury: evaluation, treatment, and functional recovery," *Archives of Physical Medicine and Rehabilitation*, vol. 80, no. 2, pp. 225–235, 1999.

[4] K. A. Holtz, R. Lipson, V. K. Noonan, B. K. Kwon, and P. B. Mills, "Prevalence and effect of problematic spasticity after traumatic spinal cord injury," *Archives of Physical Medicine and Rehabilitation*, vol. 98, no. 6, pp. 1132–1138, 2017.

[5] S. R. Andresen, F. Biering-Sorensen, E. M. Hagen, J. F. Nielsen, F. W. Bach, and N. B. Finnerup, "Pain, spasticity and quality of life in individuals with traumatic spinal cord injury in Denmark," *Spinal Cord*, vol. 54, no. 11, pp. 973–979, 2016.

[6] C. Sköld, R. Levi, and Å. Seiger, "Spasticity after traumatic spinal cord injury: nature, severity, and location," *Archives of Physical Medicine and Rehabilitation*, vol. 80, no. 12, pp. 1548–1557, 1999.

[7] W. B. McKay, W. M. Sweatman, and E. C. Field-Fote, "The experience of spasticity after spinal cord injury: perceived characteristics and impact on daily life," *Spinal Cord*, vol. 56, no. 5, pp. 478–486, 2018.

[8] K. Milinis, C. A. Young, and on behalf of the Trajectories of Outcome in Neurological Conditions, "Systematic review of the influence of spasticity on quality of life in adults with chronic neurological conditions," *Disability and Rehabilitation*, vol. 38, no. 15, pp. 1431–1441, 2015.

[9] N. D. DiPiro, C. Li, and J. S. Krause, "A longitudinal study of self-reported spasticity among individuals with chronic spinal cord injury," *Spinal Cord*, vol. 56, no. 3, pp. 218–225, 2018.

[10] J. J. Cragg, F. M. Warner, M. S. Shupler et al., "Prevalence of chronic pain among individuals with neurological conditions," *Health Reports*, vol. 29, no. 3, pp. 11–16, 2018.

[11] R. Müller, for the SwiSCI Study Group, M. W. G. Brinkhof et al., "Prevalence and associated factors of pain in the Swiss spinal cord injury population," *Spinal Cord*, vol. 55, no. 4, pp. 346–354, 2017.

[12] P. J. Siddall, J. M. McClelland, S. B. Rutkowski, and M. J. Cousins, "A longitudinal study of the prevalence and characteristics of pain in the first 5 years following spinal cord injury," *Pain*, vol. 103, no. 3, pp. 249–257, 2003.

[13] K. N. Alschuler, M. P. Jensen, S. J. Sullivan-Singh, S. Borson, A. E. Smith, and I. R. Molton, "The association of age, pain, and fatigue with physical functioning and depressive symptoms in persons with spinal cord injury," *The Journal of Spinal Cord Medicine*, vol. 36, no. 5, pp. 483–491, 2013.

[14] T. M. Fawkes-Kirby, M. A. Wheeler, H. A. Anton, W. C. Miller, A. F. Townson, and C. A. O. Weeks, "Clinical correlates of fatigue in spinal cord injury," *Spinal Cord*, vol. 46, no. 1, pp. 21–25, 2008.

[15] M. A. McColl, R. Arnold, S. Charlifue, C. Glass, G. Savic, and H. Frankel, "Aging, spinal cord injury, and quality of life: structural relationships," *Archives of Physical Medicine and Rehabilitation*, vol. 84, no. 8, pp. 1137–1144, 2003.

[16] S. Amatachaya, S. Naewla, K. Srisim, P. Arrayawichanon, and W. Siritaratiwat, "Concurrent validity of the 10-meter walk test as compared with the 6-minute walk test in patients with spinal cord injury at various levels of ability," *Spinal Cord*, vol. 52, no. 4, pp. 333–336, 2014.

[17] A. Jackson, C. Carnel, J. Ditunno et al., "Outcome measures for gait and ambulation in the spinal cord injury population," *The Journal of Spinal Cord Medicine*, vol. 31, no. 5, pp. 487–499, 2016.

[18] D. Podsiadlo and S. Richardson, "The timed "Up & Go": a test of basic functional mobility for frail elderly persons," *Journal of the American Geriatrics Society*, vol. 39, no. 2, pp. 142–148, 1991.

[19] S. S. Ng and C. W. Hui-Chan, "The timed up & go test: its reliability and association with lower-limb impairments and locomotor capacities in people with chronic stroke," *Archives of Physical Medicine and Rehabilitation*, vol. 86, no. 8, pp. 1641–1647, 2005.

[20] K. J. Ottenbacher, Y. Hsu, C. V. Granger, and R. C. Fiedler, "The reliability of the functional independence measure: a quantitative review," *Archives of Physical Medicine and Rehabilitation*, vol. 77, no. 12, pp. 1226–1232, 1996.

[21] L. Harvey and R. Marino, "The walking index for spinal cord injury," *The Australian Journal of Physiotherapy*, vol. 55, no. 1, p. 66, 2009.

[22] A. V. Aguirre-Guemez, A. I. Perez-Sanpablo, J. Quinzanos-Fresnedo, R. Perez-Zavala, and A. Barrera-Ortiz, "Walking speed is not the best outcome to evaluate the effect of robotic assisted gait training in people with motor incomplete spinal cord injury: a systematic review with meta-analysis," *The Journal of Spinal Cord Medicine*, vol. 42, no. 2, pp. 142–154, 2019.

[23] P. Winchester, R. McColl, R. Querry et al., "Changes in supraspinal activation patterns following robotic locomotor therapy in motor-incomplete spinal cord injury," *Neurorehabilitation and Neural Repair*, vol. 19, no. 4, pp. 313–324, 2005.

[24] E. Y. Y. Cheung, T. K. W. Ng, K. K. K. Yu, R. L. C. Kwan, and G. L. Y. Cheing, "Robot-assisted training for people with spinal cord injury: a meta-analysis," *Archives of Physical Medicine and Rehabilitation*, vol. 98, no. 11, pp. 2320–2331.e12, 2017.

[25] C. Sliwinski, T. A. Nees, R. Puttagunta, N. Weidner, and A. Blesch, "Sensorimotor activity partially ameliorates pain and reduces nociceptive fiber density in the chronically injured spinal cord," *Journal of Neurotrauma*, vol. 35, no. 18, pp. 2222–2238, 2018.

[26] T. A. Nees, A. Tappe-Theodor, C. Sliwinski et al., "Early-onset treadmill training reduces mechanical allodynia and modulates calcitonin gene-related peptide fiber density in lamina III/IV in a mouse model of spinal cord contusion injury," *Pain*, vol. 157, no. 3, pp. 687–697, 2016.

[27] Y. J. Chang, J. N. Liang, M. J. Hsu, H. Y. Lien, C. Y. Fang, and C. H. Lin, "Effects of continuous passive motion on reversing the adapted spinal circuit in humans with chronic spinal cord injury," *Archives of Physical Medicine and Rehabilitation*, vol. 94, no. 5, pp. 822–828, 2013.

[28] D. Moher, PRISMA-P Group, L. Shamseer et al., "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement," *Systematic Reviews*, vol. 4, no. 1, p. 1, 2015.

[29] M. D. Reed and W. Van Nostran, "Assessing pain intensity with the visual analog scale: a plea for uniformity," *Journal of Clinical Pharmacology*, vol. 54, no. 3, pp. 241–244, 2014.

[30] H. J. A. van Hedel, M. Wirz, and A. Curt, "Improving walking assessment in subjects with an incomplete spinal cord injury: responsiveness," *Spinal Cord*, vol. 44, no. 6, pp. 352–356, 2006.

[31] J. F. Ditunno Jr., P. L. Ditunno, G. Scivoletto et al., "The Walking Index for Spinal Cord Injury (WISCI/WISCI II): nature, metric properties, use and misuse," *Spinal Cord*, vol. 51, no. 5, pp. 346–355, 2013.

[32] J. M. Linacre, A. W. Heinemann, B. D. Wright, C. V. Granger, and B. B. Hamilton, "The structure and stability of the Functional Independence Measure," *Archives of Physical Medicine and Rehabilitation*, vol. 75, no. 2, pp. 127–132, 1994.

[33] J. P. Higgins and D. G. Altman, "Assessing risk of bias in included studies," *Cochrane Handbook for Systematic Reviews of Interventions: Cochrane Book Series*, pp. 187–241, 2008.

[34] A. Stang, "Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses," *European Journal of Epidemiology*, vol. 25, no. 9, pp. 603–605, 2010.

[35] G. A. Wells, B. Shen, D. O'Connell et al., *The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis*, 2000, http://www.ohri.ca/programs/clinical_epidemiology/oxford_web.ppt.

[36] G. Hornby, D. Campbell, D. Zemon, and J. Kahn, "Clinical and quantitative evaluation of robotic-assisted treadmill walking to retrain ambulation after spinal cord injury," *Topics in Spinal Cord Injury Rehabilitation*, vol. 11, no. 2, pp. 1–17, 2005.

[37] M. Mirbagheri, M. Kindig, and X. Niu, "Effects of robotic-locomotor training on stretch reflex function and muscular properties in individuals with spinal cord injury," *Clinical Neurophysiology*, vol. 126, no. 5, pp. 997–1006, 2015.

[38] D. Varoqui, X. Niu, and M. M. Mirbagheri, "Ankle voluntary movement enhancement following robotic-assisted locomotor training in spinal cord injury," *Journal of Neuroengineering and Rehabilitation*, vol. 11, no. 1, pp. 46–56, 2014.

[39] A. Ekelem and M. Goldfarb, "Supplemental stimulation improves swing phase kinematics during exoskeleton assisted gait of SCI subjects with severe muscle spasticity," *Frontiers in Neuroscience*, vol. 12, pp. 374–382, 2018.

[40] A. Esquenazi, M. Talaty, A. Packel, and M. Saulino, "The Rewalk powered exoskeleton to restore ambulatory function to individuals with thoracic-level motor-complete spinal cord injury," *American Journal of Physical Medicine & Rehabilitation*, vol. 91, no. 11, pp. 911–921, 2012.

[41] K. J. Manella, J. Torres, and E. C. Field-Fote, "Restoration of walking function in an individual with chronic complete (AIS A) spinal cord injury," *Journal of Rehabilitation Medicine*, vol. 42, no. 8, pp. 795–798, 2010.

[42] M. Wirz, D. H. Zemon, R. Rupp et al., "Effectiveness of automated locomotor training in patients with chronic incomplete spinal cord injury: a multicenter trial," *Archives of Physical Medicine and Rehabilitation*, vol. 86, no. 4, pp. 672–680, 2005.

[43] A. J. Del-Ama, A. Gil-Agudo, J. L. Pons, and J. C. Moreno, "Hybrid gait training with an overground robot for people with incomplete spinal cord injusry: a pilot study," *Frontiers in Human Neuroscience*, vol. 8, pp. 298–307, 2014.

[44] M. Alcobendas-Maestro, A. Esclarín-Ruz, R. M. Casado-López et al., "Lokomat robotic-assisted versus overground training within 3 to 6 months of incomplete spinal cord Lesion," *Neurorehabilitation and Neural Repair*, vol. 26, no. 9, pp. 1058–1063, 2012.

[45] R. Labruyère and H. J. A. van Hedel, "Strength training versus robot-assisted gait training after incomplete spinal cord injury a randomized pilot study in patients depending on walking assistance," *Journal of Neuroengineering and Rehabilitation*, vol. 11, no. 1, pp. 4–15, 2014.

[46] M. Wirz, O. Mach, D. Maier et al., "Effectiveness of automated locomotor training in patients with acute incomplete spinal cord injury: a randomized, controlled, multicenter trial," *Journal of Neurotrauma*, vol. 34, no. 10, pp. 1891–1896, 2016.

[47] T. Lam, K. Pauhl, A. Ferguson et al., "Training with robot-applied resistance in people with motor-incomplete spinal cord injury: pilot study," *Journal of Rehabilitation Research and Development*, vol. 52, no. 1, pp. 113–130, 2015.

[48] E. D. Lemaire, A. J. Smith, A. Herbert-Copley, and V. Sreenivasan, "Lower extremity robotic exoskeleton training: case studies for complete spinal cord injury walking," *Neuro Rehabilitation*, vol. 41, no. 1, pp. 97–103, 2017.

[49] S. B. E. Mazzoleni, A. Rustici, and G. Stampacchia, "An integrated gait rehabilitation training based on Functional Electrical Stimulation cycling and overground robotic exoskeleton in complete spinal cord injury patients Preliminary results," in *2017 International Conference on Rehabilitation Robotics (ICORR)*, pp. 289–293, London, UK, July 2017.

[50] G. Stampacchia, A. Rustici, S. Bigazzi, A. Gerini, T. Tombini, and S. Mazzoleni, "Walking with a powered robotic exoskeleton: subjective experience, spasticity and pain in spinal cord injured persons," *Neuro Rehabilitation*, vol. 39, no. 2, pp. 277–283, 2016.

[51] A. Ikumi, S. Kubota, Y. Shimizu et al., "Decrease of spasticity after hybrid assistive limb((R)) training for a patient with C4 quadriplegia due to chronic SCI," *The Journal of Spinal Cord Medicine*, vol. 40, no. 5, pp. 573–578, 2017.

[52] H. Watanabe, A. Marushima, H. Kawamoto et al., "Intensive gait treatment using a robot suit hybrid assistive limb in acute spinal cord infarction: report of two cases," *The Journal of Spinal Cord Medicine*, vol. 42, no. 3, pp. 395–401, 2017.

[53] M. Aach, O. Cruciger, M. Sczesny-Kaiser et al., "Voluntary driven exoskeleton as a new tool for rehabilitation in chronic spinal cord injury: a pilot study," *The Spine Journal*, vol. 14, no. 12, pp. 2847–2853, 2014.

[54] M. P. Barnes, "An overview of the clinical management of spasticity," in *Upper Motor Neurone Syndrome and Spasticity: Clinical Management and Neurophysiology*, M. P. Barnes and G. R. Johnson, Eds., pp. 1–9, Cambridge University Press, New York, 2008.

[55] C. Y. Fang, M. J. Hsu, C. C. Chen, H. Y. Cheng, C. C. Chou, and Y. J. Chang, "Robot-assisted passive exercise for ankle hypertonia in individuals with chronic spinal cord injury," *Journal of Medical and Biological Engineering*, vol. 35, no. 4, pp. 464–472, 2015.

[56] V. Dietz and S. T. Spasticity, *Handbook of Clinical Neurology*, J. Verhaagen and M. D. JW, Eds., Elsevier, 2012.

[57] N. B. Finnerup, "Neuropathic pain and spasticity: intricate consequences of spinal cord injury," *Spinal Cord*, vol. 55, no. 12, pp. 1046–1050, 2017.

[58] D. Burke, B. M. Fullen, D. Stokes, and O. Lennon, "Neuropathic pain prevalence following spinal cord injury: a systematic review and meta-analysis," *European Journal of Pain*, vol. 21, no. 1, pp. 29–44, 2017.

[59] A. L. Hassett and D. A. Williams, "Non-pharmacological treatment of chronic widespread musculoskeletal pain," *Best Practice & Research Clinical Rheumatology*, vol. 25, no. 2, pp. 299–309, 2011.

[60] T. Marqueste, J. R. Alliez, O. Alluin, Y. Jammes, and P. Decherchi, "Neuromuscular rehabilitation by treadmill running or electrical stimulation after peripheral nerve injury and repair," *Journal of Applied Physiology*, vol. 96, no. 5, pp. 1988–1995, 2004.

[61] S. Perera, S. H. Mody, R. C. Woodman, and S. A. Studenski, "Meaningful change and responsiveness in common physical performance measures in older adults," *Journal of the American Geriatrics Society*, vol. 54, no. 5, pp. 743–749, 2006.

[62] C. E. Garber, B. Blissmer, M. R. Deschenes et al., "Quantity and quality of exercise for developing and maintaining cardiorespiratory, musculoskeletal, and neuromotor fitness in apparently healthy Adults," *Medicine and Science in Sports and Exercise*, vol. 43, no. 7, pp. 1334–1359, 2011.

[63] L. P. Jack, M. Purcell, D. B. Allan, and K. J. Hunt, "The metabolic cost of passive walking during robotics-assisted treadmill exercise," *Technology and Health Care*, vol. 19, no. 1, pp. 21–27, 2011.

[64] S. B. E. Mazzoleni, C. Laschi, M. C. Carrozza, G. Stampacchia, and B. Rossi, "Changes on EMG activation in healthy subjects and incomplete SCI patients following a robot-assisted locomotor training," in *2011 IEEE International Conference on Rehabilitation Robotics*, Zurich, Switzerland, July 2011.

[65] T. Chen and L. S. Chou, "Effects of muscle strength and balance control on sit-to-walk and turn durations in the timed up and go test," *Archives of Physical Medicine and Rehabilitation*, vol. 98, no. 12, pp. 2471–2476, 2017.

[66] C. M. Kim, J. J. Eng, and M. W. Whittaker, "Level walking and ambulatory capacity in persons with incomplete spinal cord injury: relationship with muscle strength," *Spinal Cord*, vol. 42, no. 3, pp. 156–162, 2004.

[67] H. Barbeau, M. Danakas, and B. Arsenault, "The effects of locomotor training in spinal cord injured subjects: a preliminary study," *Restorative Neurology and Neuroscience*, vol. 5, no. 1, pp. 81–84, 1993.

[68] A. S. Burns, J. J. Delparte, M. Patrick, R. J. Marino, and J. F. Ditunno, "The reproducibility and convergent validity of the walking index for spinal cord injury (WISCI) in chronic spinal cord injury," *Neurorehabilitation and Neural Repair*, vol. 25, no. 2, pp. 149–157, 2011.

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Research Article

Respiratory Muscle Training Improves Functional Outcomes and Reduces Fatigue in Patients with Myasthenia Gravis: A Single-Center Hospital-Based Prospective Study

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Background. Myasthenia gravis (MG) is an immune-mediated disorder characterized by muscle fatigue and fluctuating weakness. Impairment in respiratory strength and endurance has been described in patients with generalized MG. We tested the hypothesis that respiratory muscle training (RMT) can improve functional outcomes and reduce fatigue in patients with MG. *Methods*. Eighteen patients with mild to moderate MG participated in this study. The training group underwent home-based RMT three times a week for 12 weeks. Sixteen patients with MG without RMT were enrolled as a disease control group. Lung function, autonomic testing, Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF), and functional outcome measurement by using quantitative myasthenia gravis (QMG) score and myasthenia gravis composite (MGC) scale were measured before and after the 12-week RMT. *Results*. The 12-week RMT significantly increased forced vital capacity (FVC) from 77.9 ± 12.6% to 83.8 ± 17.7% ($p = 0.03$), forced expiratory volume in one second (FEV1) from 75.2 ± 18.3% to 83.3 ± 19.0% ($p = 0.002$), and 6-minute walking distance from 403.4 ± 72.2 m to 466.1 ± 68.5 m ($p = 0.003$). The QMG score improved from 9.6 ± 4.1 to 8.1 ± 4.3 ($p = 0.04$) and the MGC scale from 4.4 ± 3.5 to 2.7 ± 2.9 ($p = 0.02$). The fatigue score (MFSI-SF) reduced from 17.1 ± 14.7 to 13.5 ± 16.9 ($p = 0.03$). *Conclusion*. The home-based RMT is an effective pulmonary function training for MG patients. The RMT can not only improve short-term outcomes but also reduce fatigue in patients with mild to moderate generalized MG.

1. Introduction

Myasthenia gravis (MG) is an immune-mediated neuromuscular junction disorder characterized by fluctuating muscle weakness and easy fatigability. In most cases, autoantibodies against the acetylcholine receptor can be found [1]. Impairment in respiratory strength and endurance has been described in patients with generalized MG [2]. Respiratory muscle dysfunction can further deteriorate patients' physical fitness and even increase the risk of respiratory failure as the characteristic feature of myasthenic crisis [3]. Improvement of respiratory muscle function is therefore an important goal in MG therapy.

The Myasthenia Gravis Foundation of America Clinical Classification divides MG into 5 main classes according to signs and symptoms [4]. Class I is defined as patients with any ocular muscle weakness and all other muscle strength as normal. Classes II to IV are defined as patients with mild to severe muscle weakness affecting other than ocular muscles, respectively. Class V is defined by the need for intubation, with or without mechanical ventilation, except when used during routine postoperative management. The effect of RMT may be performed safely and effectively in mild to moderate MG patients (classes II and III) with impairment of respiratory function [5, 6].

A previous study demonstrates that home-based respiratory muscle training (RMT) combined with breathing retraining in patients with generalized MG leads to improvements in respiratory muscle strength, chest wall mobility, and respiratory muscle endurance but does not appear to improve lung function [5, 7]. Lung function parameters such as vital capacity (VC), forced expiratory volume in one second (FEV1), and maximal expiratory pressure (MEP) are based on short maneuvers requiring maximal effort. These abilities are usually not reduced in patients with mild to moderate MG. Fatigue and weakness of respiratory muscles in MG patients are responsible for dyspnea, reduced exercise tolerance, and increased risk of respiratory failure. Therefore, improved respiratory endurance is even more important than improvement of lung function parameters in MG patients [8].

To our knowledge, few studies have demonstrated that RMT is associated with effects of functional outcome and fatigue in MG patients. The present study is therefore aimed at assessing the training effects of RMT on MG symptoms and pulmonary function in patients with mild to moderate MG. We investigated whether the RMT not only enhances the functional outcome but also reduces the fatigue in patients with MG.

2. Materials and Methods

2.1. Participants. This single-center hospital-based prospective study enrolled participants with mild to moderate generalized MG (classes II to III according to MGFA classification) [4], recruited consecutively from Chang Gung Memorial Hospital-Kaohsiung, a tertiary medical center and the main referral hospital in southern Taiwan. A diagnosis of MG is based on clinical features with serial examinations in terms of electromyography, serum autoantibodies, chest CT scan, and effect of cholinesterase inhibitors [9].

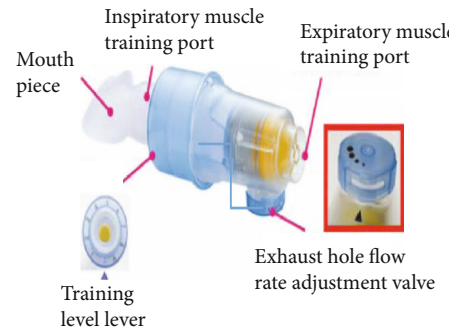

Figure 1: Dofin Breathing Trainer: the device for respiratory muscle training.

Exclusion criteria included the following: (1) presence of significant diseases (class III of MGFA classification) who would not be able to complete the training; (2) MG patients with ocular symptoms only (class I of MGFA classification); (3) MG patients in the state of myasthenic crisis; (4) presence of underlying malignancy or hematological disorders; and (5) history major systemic disease, such as end-stage renal disease, liver cirrhosis, and heart failure.

For a statistical power of 80% and the significance level of 5%, a sample size of 18 participants was calculated to determine a 15% change in myasthenia score improvement [5]. To avoid the influence of age, sex, and body mass index on the pulmonary function [10, 11], sixteen age-, sex-, and BMI-matched MG patients who were not willing to undergo RMT were included as disease controls. All participants have signed an informed consent form, and the study was conducted in accordance with the Declaration of Helsinki and approved by the hospital's Institutional Review Committees on Human Research (IRB 105-5274C). The Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) statements were used to report all the different steps of the interventions utilized in this study [12, 13].

2.2. Respiratory Muscle Training (RMT). Despite normal spirometric values, patients with generalized MG often present a characteristic pattern with a decreasing respiratory muscle strength [14] and reduced respiratory muscle endurance [2]. Due to the fatigue-prone nature of the repetitive exercise for MG patients, we choose the interval-based RMT method. The protocol of RMT was modified from previous studies as follows [15, 16]. RMT was performed by using the Dofin Breathing Trainer, a handheld pressure threshold device (Figure 1). The device can be calibrated up to a pressure range of 5-39 cmH_2O for inspiratory muscle training and 4-33 cmH_2O for expiratory muscle training. RMT was applied to generate both expiratory force for cough function and inspiratory muscle straining for the lung ventilation impairments. Patients with respiratory muscle weakness received an inspiratory muscle training from 30% to 60% of the maximum inspiratory pressures (MIP) through a respiratory trainer for two sets of 30 breaths or 6 sets of 10 repetitions. For patients with swallowing disturbance, the expiratory

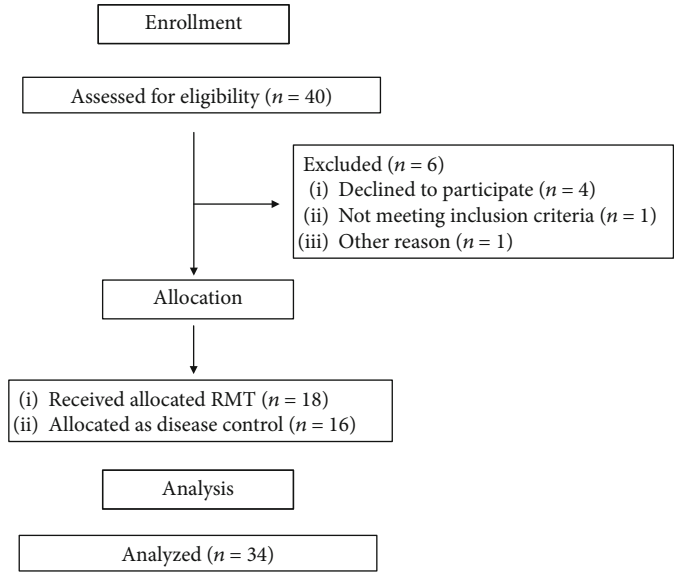

Figure 2: Flow diagram of the clinical intervention.

muscle strengthening training commences from 15% to 75% of the threshold load of an individual's maximum expiratory pressures (MEP), 5 sets of 5 repetitions with one minute of rest between sets. The training resistance was adjusted accordingly, with one or two minutes of rest between sets. RMT was conducted by an experienced respiratory therapist at the time of enrollment, and it was ensured that the participants were familiar with the device. All the participants were trained for 30 min/day twice per day, for at least 5 days a week for 12 weeks, and were monitored by making a phone call to them once a week to check the compliance of RMT at home.

2.3. Pulmonary Function Testing. The pulmonary function testing of every participant included forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and FEV1/FVC indexes using spirometry without exposure to a bronchodilator. In respiratory strengths, respiratory pressure was measured under static conditions, with MIP and MEP at a total lung capacity. Pulmonary function values were based on the best of three efforts. The procedure of spirometry completely followed the guidelines of the American Thoracic Society [17], and the results of the pulmonary function test are classified into three patterns as follows [18]: (i) obstructive pattern, which was defined as FEV1/FVC < 0.7; (ii) restrictive pattern, which was defined as FEV1/FVC ≥ 0.7 with FVC $< 80\%$; and (iii) normal pattern, which was defined as FEV1/FVC ≥ 0.7 with FVC $\geq 80\%$. The six-minute walk test was used to describe walking capability among patients with MG [19]. In previous studies, the six-minute walk test was shown to be an exercise capacity test in neuromuscular diseases [19, 20], and the normal values of the mean distance have been well defined [21, 22].

2.4. Clinical Assessment. All subjects underwent complete neurological examinations, pulmonary function, and self-administered questionnaires upon enrollment and 12 weeks after RMT. Outcomes were measured by using the quantitative myasthenia gravis (QMG) score and myasthenia gravis composite (MGC) scale. The QMG has several items that measure endurance or fatigability, taking into account the fluctuating nature of the disease. The 13 items are as follows: ptosis, diplopia, orbicularis oculi weakness, swallowing a cup of water, speech, percent predicted forced vital capacity, grip strength (2 items), arm endurance (2 items), leg endurance (2 items), and neck flexion endurance. All items are scored from 0 (no symptoms) to 3 (severe symptoms), with a total score ranging from 0 to 39; higher scores indicate greater disease severity [23].

The MGC scale contains a total of 6 physician-evaluated items, 2 ocular items (diplopia and ptosis) from the QMG, 4 items (facial, neck, deltoids, and hip flexor strength) from the Manual Muscle Test, and 4 patient-reported items (chewing, swallowing, breathing, and speech). Items are scored using a 4-level severity assessment (normal/no symptoms to severe symptoms), with weighted point scores for each item summed to generate a total MGC score ranging from 0 (no symptoms) to 50 (maximum severity) [24]. The MGC was recommended as the primary outcome measure of choice in MG trials by the MGFA scientific board [25], and it has been subsequently used as a primary or secondary outcome in several trials [26].

2.5. Measurement of Fatigue. The fatigue was measured by the self-administered questionnaire Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SF). The version has been validated in Chinese population [27]. The MFSI-SF is a 30-item short form of the MFSI that yields scores only for the empirically derived subscales, each scored from 0 (not at all) to 4 (extremely). Previous research suggests that it has acceptable psychometric properties and may be used as a substitute for the MFSI when time constraints and scale length are of concern [28]. The MFSI-SF scoring for the empirically derived scales is as follows: (1)

Table 1: Baseline characteristics between the RMT group and the disease control group.

	RMT group ($n = 18$)	Disease controls ($n = 16$)	p value
Age (years)	54.2 ± 14.6	62.4 ± 12.7	0.09
Sex (female)	11	10	0.61
Body weight (kg)	65.9 ± 9.8	64.2 ± 15.5	0.73
Body high (cm)	161.2 ± 9.8	157.7 ± 9.9	0.31
Disease duration (years)	10.7 ± 10.6	7.6 ± 7.9	0.43
Thymectomy	13	8	0.66
Cardiovascular autonomic function			
HR_DB	11.7 ± 6.8	13.8 ± 9.3	0.52
Valsalva ratio	1.4 ± 0.2	1.3 ± 0.2	0.53
BRS_seq	6.7 ± 4.2	4.6 ± 2.3	0.23
LF/HF ratio	1.8 ± 2.1	2.0 ± 2.0	0.79
Pulmonary function parameters			
FVC (%)	77.9 ± 12.6	82.9 ± 19.6	0.88
FEV1 (%)	75.2 ± 18.3	79.5 ± 21.8	0.51
FEV1/FVC	78.0 ± 10.5	75.5 ± 6.8	0.07
Maximum inspiratory pressures (MIP)	98.1 ± 44.2	80.9 ± 52.2	0.27
Maximum expiratory pressures (MEP)	82.5 ± 20.5	90.9 ± 33.6	0.67
6-minute walking distance (meter)	403.4 ± 72.2	394.9 ± 106.9	0.56
MGFA classification			0.12
IIa	10	6	
IIb	4	4	
IIIa	2	2	
IIIb	2	4	

Values are expressed as mean ± SD unless otherwise indicated. MGFA: Myasthenia Gravis Foundation of America classification; RMT: respiratory muscle training.

general scale; (2) physical scale; (3) emotional scale; (4) mental scale; (5) vigor scale; and (6) total score = (general + physical + emotional + mental) – vigor.

2.6. Statistical Analysis. Data were expressed as mean ± standard deviation (SD) or median (interquartile range (IQR)). Categorical variables were compared using chi-squared or Fisher's exact tests. Continuous variables were compared in two patient groups (the RMT group and the disease control group) by using independent t-tests. The data of cardiovascular autonomic function (HR_DB, Valsalva ratio, BRS_seg, and LF/HF ratio) that were not normally distributed were logarithmically transformed to improve normality for comparison. Second, changes between baseline and 12 weeks post-RMT on parameters of respiratory parameters, fatigue score, and outcome score were compared using a paired t-test and the Wilcoxon signed-rank test for nonparametric data. Furthermore, repeated-measure ANOVA was used to compare parameters and functional scores at two different time points (enrollment and 12 weeks follow-up). Statistical significance was set at $p < 0.05$. All statistical analyses were conducted using the SAS software version 9.1 (SAS Statistical Institute, Cary, NC, USA).

3. Results

3.1. Baseline Characteristics between the RMT Group and the Disease Control Group. The flow diagram with the enrolment of the study is shown in Figure 2. Forty individuals were recruited, and six were excluded. Consequently, thirty-four participants (18 cases in the RMT group and 16 participants in the disease control group) are enrolled in this study. They have been diagnosed with MG for 1–25 years. Table 1 shows the baseline characteristics between groups of the RMT patients and disease controls. There was no significant difference between the RMT group and the disease control group in terms of age, sex, body weight, body high, duration of disease, cardiovascular autonomic function, pulmonary function parameters, or MGFA classification.

3.2. Change of Pulmonary Function after RMT. The changes of pulmonary function parameters during the study period are shown in Table 2. The parameters of pulmonary function, including FVC (77.9 ± 12.6% to 83.8 ± 17.7%, $p = 0.03$), FEV1 (75.2 ± 18.3% to 83.3 ± 19.0%, $p = 0.002$), and 6-minute walking distance (403.4 ± 72.2 m to 466.1 ± 68.5 m, $p = 0.003$), all significantly increased after 12-week training in the RMT group. On the contrary, the pulmonary function

Table 2: Changes of pulmonary function after RMT.

	RMT group ($n = 18$)			Disease control group ($n = 16$)		
	Baseline	Follow-up	p value	Baseline	Follow-up	p value
Cardiovascular autonomic function						
HR_DB	11.7 ± 6.8	13.6 ± 8.8	0.16	13.8 ± 9.3	12.1 ± 7.1	0.62
Valsalva ratio	1.4 ± 0.2	1.4 ± 0.2	0.64	1.3 ± 0.2	1.3 ± 0.2	0.79
BRS_seq	6.7 ± 4.2	7.2 ± 4.1	0.54	4.6 ± 2.3	4.5 ± 2.5	0.91
LF/HF ratio	1.8 ± 2.1	2.1 ± 2.0	0.64	2.0 ± 2.0	1.6 ± 2.0	0.63
Pulmonary function parameters						
FVC (%)	77.9 ± 12.6	83.8 ± 17.7	0.03*	82.9 ± 19.6	85.3 ± 24.7	0.62
FEV1 (%)	75.2 ± 18.3	83.3 ± 19.0	0.002*	79.5 ± 21.8	82.3 ± 25.4	0.52
FEV1/FVC	78.0 ± 10.5	81.3 ± 8.4	0.26	75.5 ± 6.8	76.8 ± 6.7	0.54
MIP	98.1 ± 44.2	105.6 ± 42.4	0.26	80.9 ± 52.2	93.6 ± 46.5	0.12
MEP	82.5 ± 20.5	91.9 ± 31.7	0.11	90.9 ± 33.6	97.3 ± 35.2	0.22
6-minute walking distance (meter)	403.4 ± 72.2	466.1 ± 68.5	0.003*	394.9 ± 106.9	413.3 ± 104.2	0.39

HR_DB: heart rate response to deep breathing; BRS_VM: baroreflex sensitivity obtained by Valsalva maneuver; BRS_seq: baroreflex sensitivity obtained by the sequence method; LF: low frequency; HF: high frequency; FVC: forced vital capacity; FEV1: forced expiratory volume in one second; MIP: maximum inspiratory pressures; MEP: maximum expiratory pressures; RMT: respiratory muscle training. *Significant difference ($p < 0.05$) between follow-up and baseline.

Table 3: Comparison of MG outcomes and fatigue score before and after RMT.

	RMT group ($n = 18$)			Disease control group ($n = 16$)		
	Baseline	Follow-up	p value	Baseline	Follow-up	p value
Outcome measures						
QMG score	9.5 [5.5, 12.75]	7.5 [4, 12]	0.02*	12.5 [4.75, 14.75]	9.5 [5.5, 13.25]	0.11
MGC scale	4 [1.25, 6.75]	2 [0.25, 3]	0.05*	3.5 [0, 8]	3.5 [0.75, 4.75]	0.26
Fatigue scale						
MFSI_SF_general	7 [5.0, 10.75]	7 [6.0, 8.75]	0.54	6 [4.75, 8.25]	8 [5.75, 11.75]	0.21
MFSI_SF_physical	8 [5.25, 8.75]	5 [3.0, 8.0]	0.02*	7 [4.75, 9.75]	8.5 [5.75, 11.75]	0.12
MFSI_SF_emotion	6 [3.25, 7.0]	4 [3, 8.75]	0.46	5 [3, 8.25]	7 [4, 8.25]	0.63
MFSI_SF_mental	6.5 [6.0, 8.0]	7 [3.5, 8.75]	0.87	6 [5.75, 9.5]	7.5 [6, 11]	0.29
MFSI_SF_vigor	10 [8.0, 13.75]	11.5 [10, 13]	0.16	15 [11.5, 15.75]	11 [6, 15.25]	0.50
MFSI_SF_total	14 [5, 23.5]	13 [1.25, 22]	0.04*	9 [0.75, 25.75]	21.5 [6, 34.75]	0.09

QMG: quantitative myasthenia gravis; MGC: myasthenia gravis composite; MFSI-SF: Multidimensional Fatigue Symptom Inventory-Short Form; RMT: respiratory muscle training. *Significant difference ($p \leq 0.05$) between follow-up and baseline.

parameter in the two measures was not significantly different in the control group.

3.3. Comparison of MG Outcome Scale and Fatigue Score before and after RMT. Table 3 shows the results of MG outcomes and fatigue score before and after RMT. The QMG score ($p = 0.02$) and MGC score ($p = 0.05$) significantly reduced after RMT when compared to baseline, which means the MG outcomes in the RMT group were improving. However, the disease control group had similar scores at baseline and during follow-up. Figure 3 shows the comparison of MFSI-SF scoring between baseline and after RMT. The physical subscale of MFSI-SF was significantly lower than the baseline data for the RMT group during follow-up ($p = 0.02$). The total score of MFSI-SF significantly reduced after RMT when compared to the baseline score ($p = 0.04$). On the contrary, the fatigue scores in the two measures (baseline and follow-up) were not significantly different in the disease control group.

4. Discussion

The present study examined the RMT effects on pulmonary function, MG outcomes, and fatigue in MG patients. There were three main findings in this study. First, a 12-week home-based RMT may improve the pulmonary function (FVC and FVE1) and increase the 6-minute walking distance in MG patients. Second, adjunctive RMT to conventional drug treatment may enhance the short-term functional outcomes in patients with mild to moderate MG. Third, the RMT can reduce fatigue in patients with MG, especially in the physical domain.

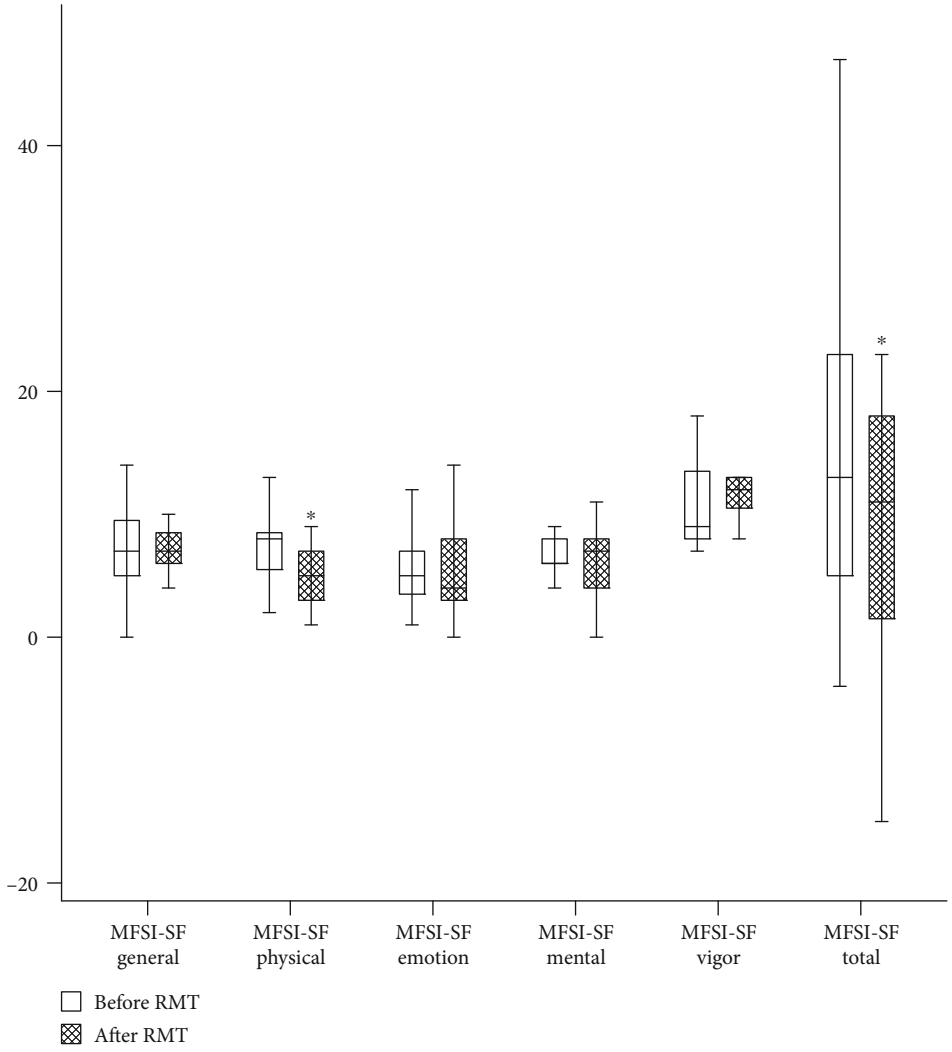

Figure 3: Comparison of MFSI-SF scoring between baseline and after RMT in patients with myasthenia gravis. $^*p < 0.05$ compared to the baseline.

Previous studies have inconsistent results for RMT in MG patients [7, 8, 29], probably because of different methodology and heterogeneity of patient groups, and there is no standard respiratory muscle training protocol for MG. Weiner et al. [29] demonstrated that 3 months of inspiratory muscle strength training performed 6 times per week significantly improved vital capacity and FEV1 in moderate to severe MG patients. Our research further demonstrated that RMT enhances the walking distance of patients with generalized MG. However, Fregonezi et al. [7] state that using the interval-based inspiratory muscle training 3 times a week for 8 weeks did not show any changes in lung function in MG patients. A recent study shows that long-term (thirteen months) respiratory muscle endurance training significantly increased respiratory endurance measured as time until exhaustion (T_{lim}) to 412% of the baseline in MG patients [6]. This can be explained by the specificity of the training of different types of RMT [30]. Respiratory muscle training mainly improves maximum strength, while respiratory muscle endurance training improves endurance but not maximum force. Moreover, all our patients perceived a benefit from the RMT in terms of improved respiratory endurance and reduced fatigue symptoms. None of them reported any adverse effects and all participants agreed to continue the training study.

The MGC and QMG are outcome measures used in clinical trials and everyday practice in MG patients [31]. Our results showed that those MG patients receiving RMT had a significant improvement not only in lung function but also in functional outcomes. The main improvement items in QMG include forced vital capacity, swallowing, and speech following counting aloud 1-50. The main improvement items in MGC include swallowing and breathing. The effect of RMT in patients with MG has been shown in several previous reports [5, 6]. Weakness and fatigue of respiratory muscles are responsible for dyspnea and reduced exercise tolerance and thus can compromise quality of life. The improvement was seen not only in respiratory muscles but also in swallowing function and speech endurance.

The other important finding in this study was the reduction in fatigue after MG patients received 3 months of RMT. To the best of our knowledge, the association between RMT

and fatigue in MG patients has not been reported previously. There are many causes of fatigue, including physical, emotional, and mental domains. Our research shows that RMT reduces fatigue in MG patients, mainly physical fatigue. The prevalence of fatigue is 70% in MG patients and influenced by depressive symptoms, disease severity, female sex, and sleep debt [32]. Fatigue in myasthenia affects quality of life and can be reduced after treatment [33]. Our results suggest that adjunctive RMT to conventional drug treatment not only reduce fatigue but also improve outcomes in patients with MG. Due to the characteristic of easily getting fatigued with repetitive exercise in MG, our study protocol did not prefer daily RMT because we consider it inappropriate for MG pathophysiology. Repeated exercise may cause a loss of K^+ ions from the contracting muscle [34] and a decrease in the gradient regulated by muscle Na^+-K^+-adenotriphosphatase that has been related to muscular fatigue [35]. Therefore, we suggest that the interval-based RMT method is feasible and benefits the MG patients.

This study has several limitations. First, we are unable to fully monitor the status of the home-based RMT, so the completion, execution rate, and efficacy of training may be different. Future research should require participants to keep a training diary and reflect on the sessions.

Second, the study regimen was strenuous and time-consuming, and several patients who were asked for participation in this study refused. For this reason, the sample size is small and the follow-up time is relatively short. Third, during the familiarization period and the first training unit, the motivations of patients were estimated to be high but briefly declined in some patients. This also affects the differences in training. Finally, there is a lack of control in medications administered to patients with MG, which may influence the efficacy of RMT. Despite these limitations, we believe this study is a good start for further large-scale investigations in this field. Future research will assess whether the RMT protocol should be restarted after the "rest" period or if intervention should continue.

In conclusion, our study shows that RMT can not only improve respiratory and functional outcomes for patients with MG but also reduce the fatigue. Further large-scale studies can be feasible to assess adjuvant RMT for conventional drug therapy in MG patients.

Abbreviations

FVC: Forced vital capacity
FEV1: Forced expiratory volume in one second
IQR: Interquartile range
MEP: Maximum expiratory pressures
MG: Myasthenia gravis
MGC: Myasthenia gravis composite
MGFA: Myasthenia Gravis Foundation of America
MIP: Maximum inspiratory pressures
MFSI-SF: Multidimensional Fatigue Symptom Inventory-Short Form
QMG: Quantitative myasthenia gravis
RMT: Respiratory muscle training
SD: Standard deviation
VC: vital capacity.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Ethical Approval

The study was approved by the Chang Gung Memorial Hospital's Institutional Review Committee on Human Research (104-9735B/105-5274C).

Conflicts of Interest

None of the authors has any commercial association, such as consultancies, stock ownership, or other equity interests or patent-licensing arrangements.

Authors' Contributions

CWH and NWT participated in the design of the study and drafted the manuscript. CCH and CEH carried out the autonomic study. HCL, WCT, and YRL participated in the clinical evaluation of patients. MCS and MCL participated in the RMT protocol and analysis. WCL interpreted the neuroimaging studies. BCC and YJS performed the statistical analysis. CLC conducted the respiratory muscle training. CHL and WNC conceived the study, participated in its design and coordination, and helped draft the manuscript. All authors read and approved the final manuscript and agreed for publication.

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References

[1] S. Berrih-Aknin and R. Le Panse, "Myasthenia gravis: a comprehensive review of immune dysregulation and etiological mechanisms," *Journal of Autoimmunity*, vol. 52, pp. 90–100, 2014.

[2] I. Heliopoulos, G. Patlakas, K. Vadikolias et al., "Maximal voluntary ventilation in myasthenia gravis," *Muscle & Nerve*, vol. 27, no. 6, pp. 715–719, 2003.

[3] A. Chaudhuri and P. O. Behan, "Myasthenic crisis," *QJM*, vol. 102, no. 2, pp. 97–107, 2009.

[4] A. Jaretzki 3rd, R. J. Barohn, R. M. Ernstoff et al., "Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America," *Neurology*, vol. 55, no. 1, pp. 16–23, 2000.

[5] B. Rassler, G. Marx, S. Hallebach, P. Kalischewski, and I. Baumann, "Long-term respiratory muscle endurance training in patients with myasthenia gravis: first results after four months of training," *Autoimmune Diseases*, vol. 2011, Article ID 808607, 7 pages, 2011.

[6] S. Freitag, S. Hallebach, I. Baumann, P. Kalischewski, and B. Rassler, "Effects of long-term respiratory muscle endurance training on respiratory and functional outcomes in patients

with myasthenia gravis," *Respiratory Medicine*, vol. 144, pp. 7–15, 2018.

[7] G. A. Fregonezi, V. R. Resqueti, R. Guell, J. Pradas, and P. Casan, "Effects of 8-week, interval-based inspiratory muscle training and breathing retraining in patients with generalized myasthenia gravis," *Chest*, vol. 128, no. 3, pp. 1524–1530, 2005.

[8] B. Rassler, G. Hallebach, P. Kalischewski, I. Baumann, J. Schauer, and C. M. Spengler, "The effect of respiratory muscle endurance training in patients with myasthenia gravis," *Neuromuscular Disorders*, vol. 17, no. 5, pp. 385–391, 2007.

[9] S. Berrih-Aknin, M. Frenkian-Cuvelier, and B. Eymard, "Diagnostic and clinical classification of autoimmune myasthenia gravis," *Journal of Autoimmunity*, vol. 48-49, pp. 143–148, 2014.

[10] E. Forno, Y. Y. Han, J. Mullen, and J. C. Celedon, "Overweight, Obesity, and Lung Function in Children and Adults—A Meta-analysis," *The Journal of Allergy and Clinical Immunology: In Practice*, vol. 6, no. 2, pp. 570–581.e10, 2018.

[11] H. I. Chen and C. S. Kuo, "Relationship between respiratory muscle function and age, sex, and other factors," *Journal of Applied Physiology*, vol. 66, no. 2, pp. 943–948, 1989.

[12] D. Sa-Caputo, L. L. Paineiras-Domingos, A. Francisca-Santos et al., "Whole-body vibration improves the functional parameters of individuals with metabolic syndrome: an exploratory study," *BMC Endocrine Disorders*, vol. 19, no. 1, article 6, 2019.

[13] D. C. Des Jarlais, C. Lyles, N. Crepaz, and T. Group, "Improving the reporting quality of nonrandomized evaluations of behavioral and public health interventions: the TREND statement," *American Journal of Public Health*, vol. 94, no. 3, pp. 361–366, 2004.

[14] S. P. Keenan, D. Alexander, J. D. Road, C. F. Ryan, J. Oger, and P. G. Wilcox, "Ventilatory muscle strength and endurance in myasthenia gravis," *The European Respiratory Journal*, vol. 8, no. 7, pp. 1130–1135, 1995.

[15] C. M. Sapienza, "Respiratory muscle strength training applications," *Current Opinion in Otolaryngology & Head and Neck Surgery*, vol. 16, no. 3, pp. 216–220, 2008.

[16] P. C. Chen, M. Y. Liaw, L. Y. Wang et al., "Inspiratory muscle training in stroke patients with congestive heart failure: a CONSORT-compliant prospective randomized single-blind controlled trial," *Medicine*, vol. 95, no. 37, article e4856, 2016.

[17] M. R. Miller, R. Crapo, J. Hankinson et al., "General considerations for lung function testing," *European Respiratory Journal*, vol. 26, no. 1, pp. 153–161, 2005.

[18] J. D. Johnson and W. M. Theurer, "A stepwise approach to the interpretation of pulmonary function tests," *American Family Physician*, vol. 89, no. 5, pp. 359–366, 2014.

[19] L. K. Andersen, K. L. Knak, N. Witting, and J. Vissing, "Two- and 6-minute walk tests assess walking capability equally in neuromuscular diseases," *Neurology*, vol. 86, no. 5, pp. 442–445, 2016.

[20] G. Crescimanno, R. Modica, R. Lo Mauro, O. Musumeci, A. Toscano, and O. Marrone, "Role of the cardio-pulmonary exercise test and six-minute walking test in the evaluation of exercise performance in patients with late-onset Pompe disease," *Neuromuscular Disorders*, vol. 25, no. 7, pp. 542–547, 2015.

[21] W. J. Gibbons, N. Fruchter, S. Sloan, and R. D. Levy, "Reference values for a multiple repetition 6-minute walk test in healthy adults older than 20 years," *Journal of Cardiopulmonary Rehabilitation*, vol. 21, no. 2, pp. 87–93, 2001.

[22] C. Casanova, B. R. Celli, P. Barria et al., "The 6-min walk distance in healthy subjects: reference standards from seven countries," *European Respiratory Journal*, vol. 37, no. 1, pp. 150–156, 2011.

[23] S. Muppidi, "Outcome measures in myasthenia gravis: incorporation into clinical practice," *Journal of Clinical Neuromuscular Disease*, vol. 18, no. 3, pp. 135–146, 2017.

[24] T. M. Burns, M. Conaway, and D. B. Sanders, "The MG composite: a valid and reliable outcome measure for myasthenia gravis," *Neurology*, vol. 74, no. 18, pp. 1434–1440, 2010.

[25] M. Benatar, D. B. Sanders, T. M. Burns et al., "Recommendations for myasthenia gravis clinical trials," *Muscle & Nerve*, vol. 45, no. 6, pp. 909–917, 2012.

[26] C. Barnett, L. Herbelin, M. M. Dimachkie, and R. J. Barohn, "Measuring clinical treatment response in myasthenia gravis," *Neurologic Clinics*, vol. 36, no. 2, pp. 339–353, 2018.

[27] L. C. Pien, H. Chu, W. C. Chen et al., "Reliability and validity of a Chinese version of the multidimensional fatigue symptom inventory-short form (MFSI-SF-C)," *Journal of Clinical Nursing*, vol. 20, no. 15-16, pp. 2224–2232, 2011.

[28] K. D. Stein, P. B. Jacobsen, C. M. Blanchard, and C. Thors, "Further validation of the multidimensional fatigue symptom inventory-short form," *Journal of Pain and Symptom Management*, vol. 27, no. 1, pp. 14–23, 2004.

[29] P. Weiner, D. Gross, Z. Meiner et al., "Respiratory muscle training in patients with moderate to severe myasthenia gravis," *Canadian Journal of Neurological Sciences*, vol. 25, no. 3, pp. 236–241, 1998.

[30] D. E. Leith and M. Bradley, "Ventilatory muscle strength and endurance training," *Journal of Applied Physiology*, vol. 41, no. 4, pp. 508–516, 1976.

[31] T. M. Burns, "The MG composite: an outcome measure for myasthenia gravis for use in clinical trials and everyday practice," *Annals of the New York Academy of Sciences*, vol. 1274, no. 1, pp. 99–106, 2012.

[32] T. M. Alekseeva, Y. V. Gavrilov, O. A. Kreis, P. O. Valko, K. P. Weber, and Y. Valko, "Fatigue in patients with myasthenia gravis," *Journal of Neurology*, vol. 265, no. 10, pp. 2312–2321, 2018.

[33] C. Tran, V. Bril, H. D. Katzberg, and C. Barnett, "Fatigue is a relevant outcome in patients with myasthenia gravis," *Muscle & Nerve*, vol. 58, no. 2, pp. 197–203, 2018.

[34] M. J. McKenna, A. R. Harmer, S. F. Fraser, and J. L. Li, "Effects of training on potassium, calcium and hydrogen ion regulation in skeletal muscle and blood during exercise," *Acta Physiologica Scandinavica*, vol. 156, no. 3, pp. 335–346, 1996.

[35] M. I. Lindinger, R. S. McKelvie, and G. J. Heigenhauser, "K+ and Lac- distribution in humans during and after high-intensity exercise: role in muscle fatigue attenuation?," *Journal of Applied Physiology*, vol. 78, no. 3, pp. 765–777, 1995.

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Research Article

Twelve-Week Gait Retraining Reduced Patellofemoral Joint Stress during Running in Male Recreational Runners

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Purpose. To explore the changes in knee sagittal angle and moment and patellofemoral joint (PFJ) force and stress before and after 12-week gait retraining. *Methods*. A total of 30 healthy male recreational runners were randomized into a control group ($n = 15$) who ran in their original strike pattern using minimalist shoes or experimental group ($n = 15$) who ran in a forefoot strike pattern using minimalist shoes during the 12-week gait retraining. The kinematic and kinetic data of the dominant leg of the participants during the 12 km/h running were collected by 3D motion capture systems and 3D force platforms. Besides, the biomechanical property of the PFJ was calculated on the basis of the joint force model and the regression equation of the contact area. *Results*. After the 12-week gait retraining, 78% of the rearfoot strikers turned into forefoot strikers. Peak knee extension moment and peak PFJ stress decreased by 13.8% and 13.3% without altering the running speed, respectively. Meanwhile, no changes in maximum knee flexion angle/extension moment and PFJ force/stress were observed for the control group. *Conclusion*. The 12-week gait retraining effectively reduced the PFJ stress, thereby providing a potential means of reducing the risk of patellofemoral pain syndrome while running.

1. Introduction

Running is a popular and prevalent way of exercising [1, 2]. In the United States alone, almost 60 million people participated in jogging, running, and trail running in 2017 [3]. Running-related injuries (RRI) have attracted the attention of researchers because of the increasing number of runners. Previous studies reported that RRI accounted for 40% of injuries caused by exercise [4]. Among RRI, those related to the knee had the highest ratio at 28%; in particular, patellofemoral joint pain accounted for the highest proportion (17%) of the specific pathologies of injury [5].

To date, high patellofemoral joint stress, overuse, trauma, decreased elasticity in quadriceps femoris, limited motion of the patella, and contracture of the patellofemoral lateral supporting band are regarded as the main causes of patellofemoral pain syndrome (PFPS) [6, 7]. Nonsurgery curative treatments are carried out through the strength training of the quadriceps, medial oblique femoris, and gluteal muscle to correct the movement trajectory of the patella [8, 9]. However, the aforementioned treatments are usually applied only after the occurrence of PFPS. PFPS caused by running is also mainly triggered by the interaction of increased patellofemoral joint stress and weak strength of the lower extremity muscles. Thus, the important factor of developing stress on the patellofemoral joint may be neglected when only muscle strength is increased.

Runners can be divided into rearfoot strikers (RFS), midfoot strikers, and forefoot strikers (FFS) based on their strike pattern [10]. A total of 75% of the runners who were used to wearing cushioned shoes correspond to rearfoot strikers [11]. In FFS, the ankle was more plantarflexed at initial contact than in RFS. The foot went through greater dorsiflexion range of motion during stance in FFS during running because of the increased plantarflexion [12]. Such change allowed shock absorption by the muscles and ligaments of the foot, which decreased loading rates and work at the knee compared with running with a rearfoot strike pattern [13–15]. Warne et al. showed that a six-week combination program of gait retraining and minimalist shoes could reduce the

loading rate and peak impact force by transforming the pattern of RFS to a nonrearfoot strike pattern [16, 17]. Female natural FFS had lower extension moment, patellofemoral joint contact force, and patellofemoral stress than those in the RFS group [18]. Researchers transversely compared the biomechanical data between these two strike patterns [18] and the acute changes in their longitudinal posture to analyze their differences [19]. Moreover, most studies of gait retraining have targeted runners with patellofemoral pain [20], ignoring the different running patterns such as greater hip adduction and internal rotation between runners with patellofemoral pain and healthy runners [21]. Meanwhile, previous studies have reported that persons with patellofemoral pain may have an abnormal joint structure (i.e., patella malalignment and patella alta) that could influence joint contact mechanics [22]. The differences in kinematics and joint structure between runners with and without patellofemoral joint pain may cause runners to adapt to gait retraining differently. Only one study done by Dos Santos et al. showed that healthy runners with the forefoot strike pattern exhibited lower patellofemoral joint stress compared with the rearfoot strike pattern [19]. However, habitual runners acutely translated to forefoot strikers by verbal instructions from the examiner. This period should not provide the participants with a process of adaptation potential changes in strike patterns and related loads. Therefore, fully understanding the biomechanical effects of patellofemoral stress in healthy runners by gait retraining is necessary.

Based on the above observation, this study was aimed at exploring the changes in knee sagittal angle, sagittal moment, and patellofemoral joint contact force (PFCF) and stress (PFS) before and after 12-week gait retraining. Thus, preventive measures of PFPS are expected to reduce injury rates. We hypothesized that the participants of the EG converted to the forefoot strike pattern with a lower foot strike angle after the 12-week gait retraining. Besides, runners would exhibit lower patellofemoral joint contact force and stress as a consequence of the 12-week gait retraining.

2. Methods

2.1. Participants. An a priori power analysis was conducted for expected outcomes with a type I error probability of 0.05 and a power of 0.8. This analysis indicated that $n = 16$ (total sample size) would provide a statistical power of approximately 80% (G∗Power v3.1.9.4). To utilize a control group and to allow attrition from the study, 30 male participants were recruited and divided into experimental (EG) and control groups (CG) (i.e., 15 participants for each group) using a random order. The type of randomization was designed for simple randomization. Randomization was performed by one researcher. The function "Rand ()" was used to generate a random number between each participant that corresponds to one "0–1" (e.g., 0.60621385), and the participants were divided into experimental and control groups in an ascending order, with 15 people in each group. No stratification or blocking factor was used. The inclusion criteria are presented as follows: (1) recreational runners who are inclined to rearfoot strike pattern and wearing cushioned shoes; (2) a weekly running distance of over 20 km in the four recent weeks and has the ability to maintain this distance for the next 3 months; and (3) should be free from lower extremity injuries within 3 months. This study, with detailed guidelines for participants' safety and experimental protocols, was approved by the Institutional Review Board of the Shanghai University of Sport (No. 2017007). The study was conducted in accordance with the declaration of Helsinki. Specifically, all procedures and potential hazards were clarified to the participants in nontechnical terms, and informed consent was signed prior to the tests. All participants were with full knowledge of test procedures and requirements.

Figure 1: INOV-8 Bare-XF 210 V2.

2.2. Experimental Design. We designed a parallel randomized control group to compare the effects of 12-week intervention in the experiment group of participants assigned to gait retraining with the effects in the control group. Participants were classified into experimental and control groups randomly with an allocation ratio of 1 : 1 according to computer-generated random numbers. The primary outcomes corresponded to changes from baseline in the patellofemoral joint stress and contact force. Secondary outcomes included the changes in knee extension moment, knee flexion angle, and foot strike angle.

2.3. Instrumentations. Two 90 cm × 60 cm × 10 cm Kistler 3D force platforms (9287B, Kistler Corporation, Switzerland) were used to collect ground reaction force (GRF) data at a sampling rate of 1000 Hz. Forty infrared retroreflective markers (diameter: 14.0 mm) were attached bilaterally to both lower extremities to define hip, knee, and ankle joints according to the plug-in gait marker set [23]. A 10-camera infrared 3D motion capture system (Vicon T40, Oxford Metrics, UK) was utilized to collect the trajectory markers at a sampling rate of 100 Hz. Running speed during the experiment was controlled by a Witty-Manual grating timing system (Microgate, Italy). The sole thickness and average weight of INOV-8 Bare-XF 210 V2 minimalist shoes (Figure 1), which did not contain any cushioning material and heel-toe drop, were 3 mm and 227 g, respectively. The size of the experimental shoes ranged from EUR 41 to 43 based on the foot size of the participants. A Podoon© pressure-sensitive intelligent shoepad, in which three flexible thin pressure sensors were inserted and could be coordinated with the Podoon© app, was used to monitor foot strike patterns during training.

Table 1: A 12-week gait retraining protocol.

Week	1	2	3	4	5	6	7	8	9	10	11	12
Time (min)	5	10	15	20	25	30	35	40	42	44	46	48
Frequency (times/week)	3	3	3	3	3	3	3	3	3	3	3	3

Table 2: A 12-week foot and ankle exercise program.

Week	1	2	3	4	5	6
Double leg heel raises (level surface)	3 × 20	3 × 20	3 × 20	3 × 20	3 × 20	N/A
Double leg heel raises (on step)	N/A	3 × 20	3 × 20	3 × 20	3 × 20	N/A
Single leg heel raise (level surface)	N/A	N/A	3 × 10	3 × 15	3 × 20	3 × 20
Towel curls	3 × 20	3 × 30	3 × 30	3 × 30	3 × 30	3 × 30
Toe spread and toe squeeze	3 × 20	3 × 25	3 × 30	3 × 30	3 × 30	3 × 30
Doming	3 × 20	3 × 25	3 × 30	3 × 35	3 × 40	3 × 40

2.4. Experimental Procedure. Basic information of the participants and informed consent forms were filled in, physical fitness was tested, and the experimental procedure was explained before training. The participants were required to wear experimental vests, shorts, and socks before the running experiment. Then, the participants underwent a 5-minute warmup at a speed of 12 km/h on a treadmill followed by 5 minutes of rest to enable participants to change into their minimalist shoes. 36 markers were attached to the bony landmarks of the body based on the plug-in-gait marker set [24]. Before the formal testing, the static models of the participants were captured. The participants ran overground at a speed of 12 km/h (±5%) using self-selected strike patterns (i.e., the grating timing system was used to control speed). The trajectory of markers and GRF data were collected simultaneously. Three successful running trials were collected for each participant with the dominant leg stepped on the force platform (the dominant leg was determined by kicking a ball [25]).

2.5. Retraining Intervention. For the EG, the participants were required to wear minimalist shoes when executing retraining to run at a self-selected speed with moderate intensity. Forefoot strike pattern was required; i.e., the participants should use the metatarsal ball of the forefoot to strike the ground first, in which the foot was placed below the hip during landing [26].

For the CG, the participants were also required to wear minimalist shoes and maintain their original strike pattern when training at a self-selected speed with moderate intensity. However, no other instructions were provided.

The intervention period lasted for 12 weeks. Time-incremental training sessions were held three times a week. Each training session lasted for 5–48 minutes across the 12 weeks (Table 1). The participants were allowed to wear habitual running shoes when out of training. During training sessions, the two groups were prevented from interacting with one another.

Matches were banned during the entire intervention period. The training plan only partly substituted for the duration of running, and the overall weekly running distance remained constant. Moreover, participants were instructed to enhance the strength and function training of their foot and lower extremity muscles to adapt to potential changes in strike patterns and related loads (Table 2) [27].

The participants were required to record the training conditions in their retraining diaries. The CG needed to record the starting time, ending time, site, and injury conditions during training. The EG needed to record the distances of running with the forefoot strike pattern in addition to the abovementioned recordings. Meanwhile, the participants of each group are required to record their own physical conditions. When the participants experience discomfort or injury, the researchers will determine whether the participants can still continue to train according to their conditions. Researchers should be informed about the specific site and starting time of training during random checks. The cloud data of intelligent insole and retraining diaries were compared during the intervention period. The experimenter would inform the participants who do not meet the requirements or with data mismatch in the cloud through telephone or online. Participants who are discontinued for more than a week will be excluded.

2.6. Data Processing. In this study, stance phase was identified from touchdown to toe-off. Marker trajectories were filtered with a cutoff frequency of 7 Hz via Visual 3D gait analysis software (v5, C-Motion, Inc., Germantown, MD, USA). Excel 2016 was used to extract characteristic values.

Foot strike pattern was identified through the curve of the vertical GRF (vGRF) during overground running [13]. Meanwhile, the foot strike angle was calculated by taking the angle of the foot at touchdown while running and subtracting the angle of the foot while standing.

In the current study, the patellofemoral stress under a dynamic condition was calculated via biomechanical modeling. Generally, a calculation model of a patellofemoral

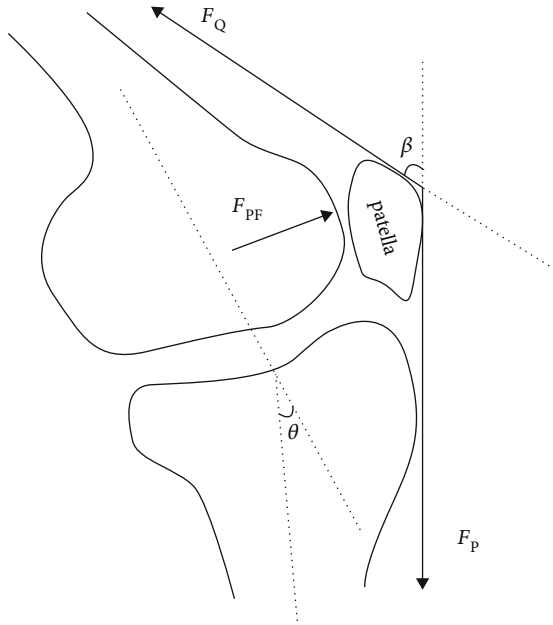

Figure 2: Free-body diagram of the patellofemoral joint and definition of angle.

contact force [28] regression equation of the contact area between the patella and the femur [29] was applied. PFS was calculated on the basis of the abovementioned studies. The details of the cited model are presented as follows.

Quadriceps force was calculated using the following equation:

$$F_Q(\theta_i) = M_{EXT}(\theta_i)/L_A(\theta_i), \quad (1)$$

where F_Q is the quadriceps force (N), M_{EXT} is the extension moment generated at the knee by ground reaction force acting on the foot (N m) [30], and θ_i is the knee sagittal angle [31] (Figure 2). L_A (m) is the effective arm of force of quadriceps, which is a function of the knee sagittal angle.

$$L_A = \begin{cases} 0.036\theta_i + 3.0 (0^\circ \le \theta_i < 30^\circ), \\ -0.043\theta_i + 5.4 (30^\circ \le \theta_i < 60^\circ), \\ -0.027\theta_i + 4.3 (60^\circ \le \theta_i < 90^\circ), \\ 2.0 (90^\circ \le \theta_i). \end{cases} \quad (2)$$

Patellofemoral joint contact force was calculated as follows:

$$F_{PF} = 2F_Q \sin\left(\frac{\beta}{2}\right), \quad (3)$$

where $\beta = 30.46 + 0.53 \cdot \theta_i$, F_{PF} (N) is PFCF, and β (°) is the angle of the quadriceps line and patellar ligament [28] (Figure 2).

Patellofemoral stress was calculated as follows:

$$P_{PFS} = F_{PF}/S_{PFCA}(\theta_i), \quad (4)$$

where P_{PFS} is the patellofemoral joint stress. The contact area (mm^2) between the patellar and the femur is a function of the knee sagittal angle [29], which is expressed as follows:

$$S_{PFCA} = 0.0781 \times \theta_i^2 + 0.06763 \times \theta_i + 151.75, \quad (5)$$

where S_{PFCA} represents the contact area between the patellar and femur.

2.7. Statistics. The basic information of the participants was tested using the t-test of paired samples. A two-way repeated measures ANOVA was used to determine the effects of the 12-week gait retraining on the dependent variables (i.e., knee sagittal moment and angle and patellofemoral joint contact force and stress) (SPSS 21.0). For the interaction parameters, dependent and independent t-tests were conducted for interclass and intergroup data, respectively. The significance level was set at 0.05.

3. Results

3.1. Dropout Rate. Overall, 17 participants (experimental group: $n = 9$; control group: $n = 8$) completed the 12-week gait retraining protocol and had a second visit to the laboratory for posttraining tests (Table 3). In detail, a participant, who was an FFS runner in a test prior to training, was excluded. In the processing of intervention, two participants quit because of injuries caused by nontraining-related incident, i.e., carelessly taking the stairs. Two other participants were excluded because of mismatch in cloud data and diaries without providing reliable evidence, such as apps or intelligent watch data. The cloud data of Podoon© were unable to observe the mismatch, and no correspondence was obtained for the three individuals. Five people who quit training after more than a week were also excluded. In addition, no participants reported that the training intensity/volume was too high/much to follow. More importantly, in the experimental group, 7 of out 9 participants transformed into forefoot strike with a rate of 78%.

3.2. Foot Strike Angle. No significant difference was observed in the foot strike angle between the EG and CG at baseline ($p = 0.126$). The main significant effect of time was observed on the foot strike angle ($p = 0.026$). The foot strike angle of the EG group decreased by 10.2° after training ($p = 0.015$); however, no difference was noted in the CG ($p = 0.753$). The foot strike angle of the EG significant differs from that of the CG group in the posttest ($p = 0.017$) (Figure 3).

3.3. Knee Sagittal Angle and Moment. After the 12-week gait retraining, in the EG, the peak knee extension moment significantly decreased by 13.8% ($p = 0.018$) (Figure 4), whereas changes were not observed for the maximum knee flexion angle during the stance phase. Meanwhile, no changes were observed for the maximum knee flexion angle and peak knee extension moment from the CG (Table 4). No between-

Table 3: Mean ± SD data for basic information of participants ($n = 17$).

Groups	Age (years)	Height (m)	Weight (kg)	Weekly volume (m)
Experimental group ($n = 9$)	**32.4 ± 6.1**	**1.75 ± 0.05**	**70.2 ± 6.0**	**28300 ± 11100**
Control group ($n = 8$)	**27.6 ± 5.2**	**1.74 ± 0.07**	**75.4 ± 11.6**	**26800 ± 10600**
t-test	$p = 0.104$	$p = 0.773$	$p = 0.262$	$p = 0.787$

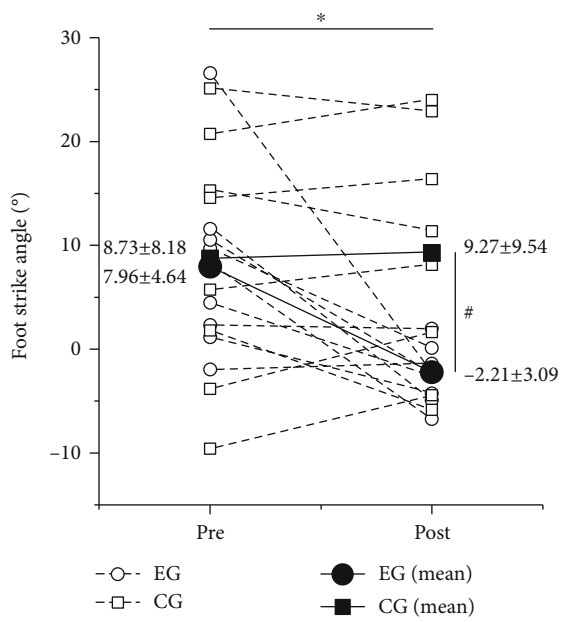

Figure 3: Effects of the 12-week gait retraining on the foot strike angle. *Significant difference from pre- to posttests in the EG group; #significant difference between groups at time point, $p < 0.05$.

group and interaction effects were observed for the maximum knee sagittal angle and moment (Table 5).

3.4. Patellofemoral Joint Contact Force and Stress. After the 12-week gait retraining, in the EG, a significant decrease of 13.3% was found in peak patellofemoral joint stress ($p = 0.018$) (Figure 5), whereas peak patellofemoral joint contact force remained the same. Meanwhile, no significant changes were observed for peak patellofemoral joint force and stress in the CG after the 12-week gait retraining (Table 4). No significant effect was observed for peak patellofemoral joint contact force and stress between the EG and CG before and after the 12-week gait retraining. In addition, no significant time × group interaction was noted on the peak patellofemoral joint contact force and stress (Table 5).

4. Discussion

This study was mainly aimed at exploring the effects of different strike patterns on the mechanism of the patellofemoral joint to provide an effective means of preventing PFPS through the 12-week gait retraining. Results showed that through gait transition and use of minimalist shoes for 12 weeks, the peak knee extension moment and peak patellofemoral joint stress decreased significantly, whereas no significant difference was observed in the CG, which only used minimalist shoes.

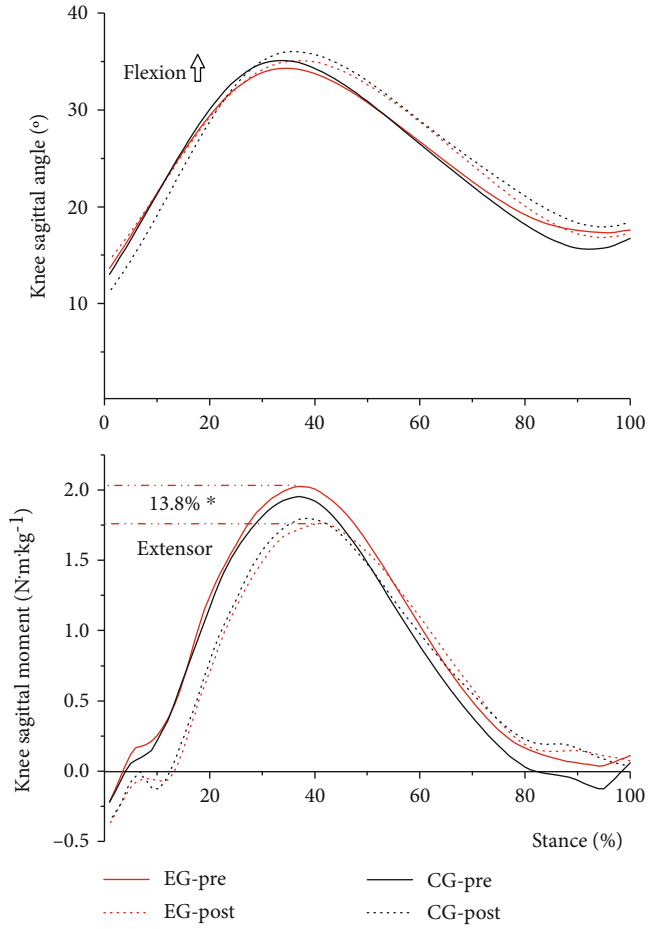

Figure 4: Effects of the 12-week gait retraining on the knee flexion angle (upper) and knee extension moment (lower) (mean values from all participants). Asterisk (*) denotes that postintervention is significantly different from preintervention.

A total of 7 out of 9 individuals changed to FFS after the 12-week gait retraining with a rate of 78%. Therefore, the 12-week gait retraining is sufficient for runners to learn gait transition and convert strike pattern. In this research, two participants dropped out because of injuries caused by nontraining-related incident (one person for each group). A total of 2 out of 15 individuals (13%) obtained injury due to training in the study of McCarthy et al. [32]. Furthermore, Warne et al. [27] showed that 2 of 14 EG participants (14%) suffered from hamstring and gastrocnemius strain, and the training time of 7 individuals was reduced due to reported calf pain. The condition of minimalist shoes for this study was also applied in McCarthy et al.'s study. Our study

Table 4: Mean ± SD data for the maximum knee flexion angle, peak knee extension moment, and patellofemoral joint contact force (PFCF) and stress (PFS) before and after the 12-week gait retraining.

Variates	Experimental group ($n = 9$)					Control group ($n = 8$)				
	Pre-	Post-	Mean difference (CI 95%)	p value	Effect size	Pre-	Post-	Mean difference (CI 95%)	p value	Effect size
Peak knee extension moment ($N\,m\,kg^{-1}$)	2.1 ± 0.4	1.8 ± 0.3	0.28 (0.09~0.47)	0.018*	0.36	2.0 ± 0.6	1.9 ± 0.6	0.11 (-0.07~0.27)	0.242	0.08
Maximum knee flexion angle (°)	34.4 ± 2.3	35.4 ± 4.8	-0.86 (-3.66~1.96)	0.569	0.14	35.4 ± 2.9	36.4 ± 4.8	-1.06 (-4.40~2.30)	0.529	0.13
Peak PFCF (BW)	4.5 ± 1.1	4.0 ± 0.9	0.51 (-0.03~1.03)	0.101	0.24	4.4 ± 1.6	4.2 ± 1.7	0.26 (-0.32~0.84)	0.359	0.08
Peak PFS (MPa)	11.6 ± 2.92	**10.1 ± 2.2**	1.05 (0.55~2.57)	0.017*	0.29	**12.1 ± 4.0**	**10.9 ± 3.2**	1.23 (-0.12~2.58)	0.098	0.17

Notes: asterisk (*) denotes significant differences between pre- and postintervention within the group ($p < 0.05$).

Table 5: Mean difference data, 95% confidence intervals, p value, effect sizes, and power for time, group, and interaction effect.

Variables	F test	Mean difference (95% confidence intervals)	p value	Effect size	Power
Peak knee extension moment (N m kg^{-1})	Time	0.19 (0.08~0.32)	0.008	0.20	0.61
	Group	0.05 (-0.19~0.27)	0.845	0.05	0.06
	Time × group		0.177	0.17	0.32
Maximum knee flexion angle (°)	Time	0.12 (-2.95~1.05)	0.386	0.12	0.27
	Group	-0.95 (-2.75~0.85)	0.542	0.12	0.09
	Time × group		0.925	0	0.05
Peak PFCF (BW)	Time	0.36 0~0.74	0.066	0.13	0.31
	Group	-0.15 (-0.81~0.53)	0.515	0.05	0.06
	Time × group		0.593	0.19	0.40
Peak PFS (MPa)	Time	1.4 (0.64~2.16)	0.004	0.23	0.73
	Group	-0.64 (-2.34~1.06)	0.668	0.10	0.08
	Time × group		0.698	0.32	0.86

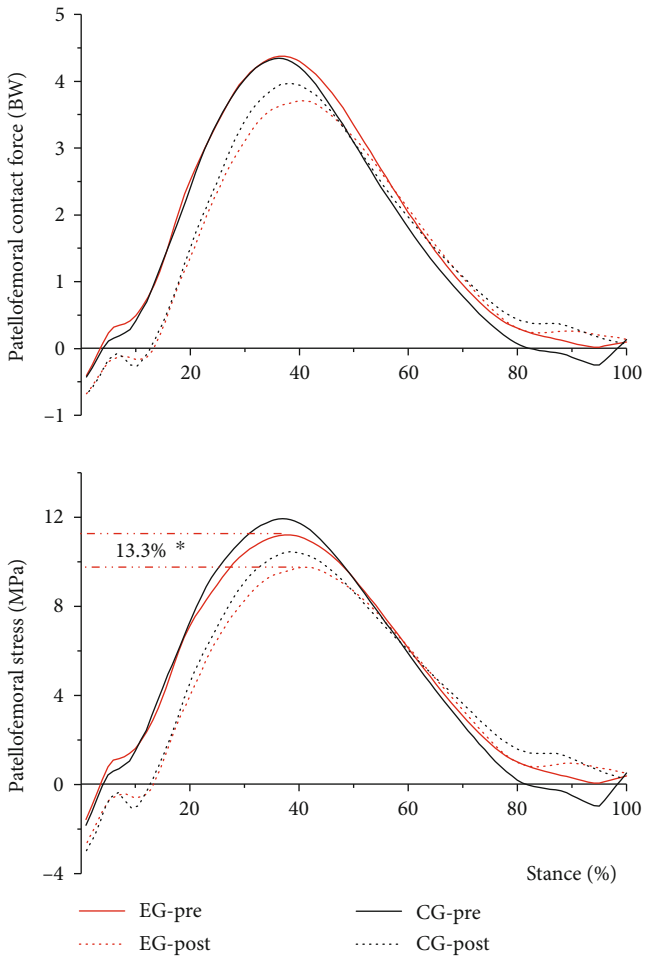

Figure 5: Effects of the 12-week gait retraining on patellofemoral joint contact force (upper) and stress (lower) (mean values from all participants). Asterisk (*) denotes post-intervention significantly different from pre-intervention.

differed because although the participants were informed that pain might be caused by a long-step length and continuous use of rearfoot strike while wearing minimalist shoes, no specific plan was made for participants to actively change their running posture. In Warne's study, the training time was increased to 40 minutes only within 6 weeks. However, in the current retraining protocol, the training volume was increased to 40 minutes in the 8th week; Afterward, a period of 2 minutes was added per week for the last 4 weeks of the research. Injuries and pain did not occur in this research because of the active changing of strike pattern, long intervention time, and low increase rate of training time, suggesting that the proposed intervention is safer for strike pattern transition compared with those of previous studies.

For the mechanical property of the patellofemoral joint, a significant decrease of 13.3% was observed in peak PFS in the EG. Similarly, Kulmala et al. [18] showed that the peak PFS of FFS decreased by 15% compared with that of RFS. In the EG, the peak knee extension moment was significantly reduced by 13.8% after the 12-week gait retraining. Lower peak knee extension moment was also found among FFS compared with RFS in other studies [19, 29, 33]. The abovementioned changes in the EG in the present study were not observed in the CG. Thus, RFS who were trained to be FFS by implementing active changes in landing strategy could decrease extension moment and patellofemoral stress at a constant speed (12 km/h ± 5%). PFS is calculated as PFCF divided by S_{PFCF}, and the knee sagittal angle is the only variable in the S_{PFCF} function. No significant changes in the maximum knee flexion angle were observed before and after retraining. Thus, no statistical difference was determined in S_{PFCF}. Similarly, changes in the β angle and LA were insignificant, suggesting that PFS decreased mainly because of the reduction in the peak knee extension moment. Liao et al. focused on the difference in patellofemoral joint stress between participants with or without patellofemoral joint pain based on the finite element model and found that the peak PFS of runners with

pain was larger than that of runners without pain and knee moment was regarded as a predictive factor [34]. Previous research suggests that FFS had lower vGRF than RFS [35], FFS could have a larger ROM of ankle [33], and the mechanical properties of the Achilles tendon can be strengthened by forefoot strike. The improvement in the loading ability of the Achilles tendon is beneficial to the calf to play a greater role in the impact phase. Lower vGRF and increased loads on the ankle using forefoot strike may cause lower peak knee extension moment [12].

Patellofemoral pain syndrome is the most common overuse injuries among runners [36]. Long-term patellofemoral joint pain can increase the probability of patellofemoral arthritis [37]. Studies showed that an increased PFS is a triggering factor of patellofemoral pain. A high PFS can lead to cartilage degeneration, which causes patellofemoral pain syndrome. Overall, the present study found that running gait retraining and wearing minimalist shoes enable runners to decrease peak PFS, and cases of injuries did not occur because of training. Therefore, the gait retraining scheme in this study was effective in preventing patellofemoral joint pain caused by large PFS while running and provided a potential means of lessening patellofemoral joint pain in runners.

Although the gait retraining scheme was effective and safe, certain limitations should be considered. The number of samples finally recruited was relatively small because of participant dropout. In the future research on recreational runners, we should focus on the training control of the participants because of work travel and other reasons, which are difficult but useful for sample preservation. In addition, intention-to-treat analysis was not conducted due to lack of second test data. Moreover, the effects caused by gait retraining in female recreational runners are unknown. Thus, female recreational runners should be recruited in future studies.

5. Conclusion

The sole use of minimalist shoes cannot influence the mechanical property of the patellofemoral joint. However, the 12-week gait retraining with minimalist shoes changed RFS to FFS and reduced knee extension moment and PFS without altering the running speed. Thus, the 12-week gait retraining intervention applied in this study can effectively decrease patellofemoral joint loads and provide a potential means of reducing the risk of patellofemoral pain syndrome caused by large PFS while running.

Data Availability

The table and figure data used to support the findings of this study are included within the article.

Conflicts of Interest

There is no conflict of interests.

Acknowledgments

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References

[1] C. A. Clermont, A. Phinyomark, S. T. Osis, and R. Ferber, "Classification of higher- and lower-mileage runners based on running kinematics," *Journal of Sport and Health Science*, vol. 8, no. 3, pp. 249–257, 2019.

[2] M. van Middelkoop, J. Kolkman, J. van Ochten, S. M. A. Bierma-Zeinstra, and B. W. Koes, "Course and predicting factors of lower-extremity injuries after running a marathon," *Clinical Journal of Sport Medicine*, vol. 17, no. 1, pp. 25–30, 2007.

[3] *Number of people who went jogging or running within the last 12 months in the United States during*2017, https://www.statista.com/topics/1743/running-and-jogging/#dossierSummary__chapter1.

[4] K. G. Hauret, S. Bedno, K. Loringer, T. C. Kao, T. Mallon, and B. H. Jones, "Epidemiology of exercise- and sports-related injuries in a population of young, physically active adults: a survey of military servicemembers," *American Journal of Sports Medicine*, vol. 43, no. 11, pp. 2645–2653, 2015.

[5] P. Francis, C. Whatman, K. Sheerin, P. Hume, and M. I. Johnson, "The proportion of lower limb running injuries by gender, anatomical location and specific pathology: a systematic review," *Journal of Sports Science and Medicine*, vol. 18, no. 1, pp. 21–31, 2019.

[6] V. Lun, W. H. Meeuwisse, P. Stergiou, and D. Stefanyshyn, "Relation between running injury and static lower limb alignment in recreational runners," *British Journal of Sports Medicine*, vol. 38, no. 5, pp. 576–580, 2004.

[7] C. Yang, S. Xiao, Y. Yang, X. Zhang, J. Wang, and W. Fu, "Patellofemoral joint loads during running immediately changed by shoes with different minimalist indices: a cross-sectional study," *Applied Sciences*, vol. 9, no. 19, p. 4176, 2019.

[8] L. Herrington and A. Al-Sherhi, "A Controlled Trial of Weight-Bearing Versus Non—Weight-Bearing Exercises for Patellofemoral Pain," *Journal of Orthopaedic & Sports Physical Therapy*, vol. 37, no. 4, pp. 155–160, 2007.

[9] G. Syme, P. Rowe, D. Martin, and G. Daly, "Disability in patients with chronic patellofemoral pain syndrome: a randomised controlled trial of VMO selective training versus general quadriceps strengthening," *Manual Therapy*, vol. 14, no. 3, pp. 252–263, 2009.

[10] P. R. Cavanagh and M. A. Lafortune, "Ground reaction forces in distance running," *Journal of Biomechanics*, vol. 13, no. 5, pp. 397–406, 1980.

[11] H. Hasegawa, T. Yamauchi, and W. J. Kraemer, "Foot strike patterns of runners at the 15-km point during an elite-level half marathon," *Journal of Strength & Conditioning Research*, vol. 21, no. 3, pp. 888–893, 2007.

[12] I. S. Davis, H. M. Rice, and S. C. Wearing, "Why forefoot striking in minimal shoes might positively change the course of running injuries," *Journal of Sport and Health Science*, vol. 6, no. 2, pp. 154–161, 2017.

[13] D. E. Lieberman, M. Venkadesan, W. A. Werbel et al., "Foot strike patterns and collision forces in habitually barefoot versus shod runners," *Nature*, vol. 463, no. 7280, pp. 531–535, 2010.

[14] D. S. Lorenz and M. Pontillo, "Is there evidence to support a forefoot strike pattern in barefoot runners? A Review," *Sports Health*, vol. 4, no. 6, pp. 480–484, 2012.

[15] J. Seay, W. S. Selbie, and J. Hamill, "In vivo lumbo-sacral forces and moments during constant speed running at different stride lengths," *Journal of Sports Sciences*, vol. 26, no. 14, pp. 1519–1529, 2008.

[16] P. A. Latorre-Román, F. García-Pinillos, V. M. Soto-Hermoso, and M. Muñoz-Jiménez, "Effects of 12 weeks of barefoot running on foot strike patterns, inversion- eversion and foot rotation in long-distance runners," *Journal of Sport and Health Science*, vol. 8, no. 6, pp. 579–584, 2019.

[17] J. P. Warne, B. P. Smyth, J. O.'. C. Fagan et al., "Kinetic changes during a six-week minimal footwear and gait-retraining intervention in runners," *Journal of Sports Sciences*, vol. 35, no. 15, pp. 1538–1546, 2016.

[18] J. P. Kulmala, J. Avela, K. Pasanen, and J. Parkkari, "Forefoot strikers exhibit lower running-induced knee loading than rearfoot strikers," *Medicine and Science in Sports and Exercise*, vol. 45, no. 12, pp. 2306–2313, 2013.

[19] A. F. dos Santos, T. H. Nakagawa, F. V. Serrão, and R. Ferber, "Patellofemoral joint stress measured across three different running techniques," *Gait & Posture*, vol. 68, pp. 37–43, 2019.

[20] J. Bonacci, M. Hall, N. Saunders, and B. Vicenzino, "Gait retraining versus foot orthoses for patellofemoral pain: a pilot randomised clinical trial," *Journal of Science and Medicine in Sport*, vol. 21, no. 5, pp. 457–461, 2018.

[21] B. Noehren, M. B. Pohl, Z. Sanchez, T. Cunningham, and C. Lattermann, "Proximal and distal kinematics in female runners with patellofemoral pain," *Clinical Biomechanics*, vol. 27, no. 4, pp. 366–371, 2012.

[22] S. R. Ward, M. R. Terk, and C. M. Powers, "Patella alta: association with patellofemoral alignment and changes in contact area during weight-bearing," *The Journal of Bone & Joint Surgery*, vol. 89, no. 8, pp. 1749–1755, 2007.

[23] R. Xia, X. Zhang, X. Wang, X. Sun, and W. Fu, "Effects of two fatigue protocols on impact forces and lower extremity kinematics during drop landings: implications for noncontact anterior cruciate ligament injury," *Journal of Healthcare Engineering*, vol. 2017, Article ID 5690519, 8 pages, 2017.

[24] T. Almonroeder, J. D. Willson, and T. W. Kernozek, "The effect of foot strike pattern on Achilles tendon load during running," *Annals of Biomedical Engineering*, vol. 41, no. 8, pp. 1758–1766, 2013.

[25] X. Zhang, R. Xia, B. Dai, X. Sun, and W. Fu, "Effects of exercise-induced fatigue on lower extremity joint mechanics, stiffness, and energy absorption during landings," *Journal of Sports Science & Medicine*, vol. 17, no. 4, pp. 640–649, 2018.

[26] H. Rice and M. Patel, "Manipulation of foot strike and footwear increases Achilles tendon loading during running," *The American Journal of Sports Medicine*, vol. 45, no. 10, pp. 2411–2417, 2017.

[27] J. P. Warne, S. M. Kilduff, B. C. Gregan, A. M. Nevill, K. A. Moran, and G. D. Warrington, "A 4-week instructed minimalist running transition and gait-retraining changes plantar pressure and force," *Scandinavian Journal of Medicine & Science in Sports*, vol. 24, no. 6, pp. 964–973, 2014.

[28] E. Bressel, "The influence of ergometer pedaling direction on peak patellofemoral joint forces," *Clinical biomechanics*, vol. 16, no. 5, pp. 431–437, 2001.

[29] C. N. Vannatta and T. W. Kernozek, "Patellofemoral joint stress during running with alterations in foot strike pattern," *Medicine and Science in Sports and Exercise*, vol. 47, no. 5, pp. 1001–1008, 2015.

[30] L. Huang, Y. Liu, S. Wei et al., "Segment-interaction and its relevance to the control of movement during sprinting," *Journal of Biomechanics*, vol. 46, no. 12, pp. 2018–2023, 2013.

[31] J. H. Brechter and C. M. Powers, "Patellofemoral stress during walking in persons with and without patellofemoral pain," *Medicine & Science in Sports & Exercise*, vol. 34, no. 10, pp. 1582–1593, 2002.

[32] C. McCarthy, N. Fleming, B. Donne, and B. Blanksby, "12 weeks of simulated barefoot running changes foot-strike patterns in female runners," *International Journal of Sports Medicine*, vol. 35, no. 5, pp. 443–450, 2014.

[33] D. Kuhman, D. Melcher, and M. R. Paquette, "Ankle and knee kinetics between strike patterns at common training speeds in competitive male runners," *European Journal of Sport Science*, vol. 16, no. 4, pp. 433–440, 2015.

[34] T. C. Liao, J. H. Keyak, and C. M. Powers, "Runners with patellofemoral pain exhibit greater peak patella cartilage stress compared with pain-free runners," *Journal of Applied Biomechanics*, vol. 34, no. 4, pp. 298–305, 2018.

[35] B. Breine, P. Malcolm, I. van Caekenberghe, P. Fiers, E. C. Frederick, and D. de Clercq, "Initial foot contact and related kinematics affect impact loading rate in running," *Journal of Sports Sciences*, vol. 35, no. 15, pp. 1556–1564, 2016.

[36] M. W. Van, "Running injuries. A review of the epidemiological literature," *Sports Medicine*, vol. 14, no. 5, pp. 320–335, 1992.

[37] M. S. Rathleff, S. K. Skuldbøl, M. N. B. Rasch, E. M. Roos, S. Rasmussen, and J. L. Olesen, "Care-seeking behaviour of adolescents with knee pain: a population-based study among 504 adolescents," *BMC Musculoskeletal Disorders*, vol. 14, no. 1, 2013.

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Review Article

Extracorporeal Shock Wave Therapy for the Treatment of Osteoarthritis: A Systematic Review and Meta-Analysis

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Background. Osteoarthritis is the most common musculoskeletal disease. Extracorporeal shockwave therapy had shown an effect on osteoarthritis in both some animal experiments and clinical studies, but there was no systematic review to confirm the value of shockwave therapy in the treatment of all types of osteoarthritis and compare it with other traditional therapies (especially traditional Chinese medicine). *Method*. PubMed, Medline, the Cochrane Central Register of Controlled Trials, Web of Science, Chinese National Knowledge Infrastructure, WANFANG database, and VIP database were searched up to December 10, 2019, to identify randomized controlled trials comparing shockwave therapy and other treatments for osteoarthritis. Visual analogue scale and the Western Ontario and McMaster Universities Osteoarthritis Index were extracted and analyzed by RevMan and STATA software as outcomes of pain reduction and functional improvement. Adverse reactions were recorded to evaluate the safety of shockwave therapy. *Results*. Shockwave therapy had significant improvement in both pain reduction and functional improvement compared with placebo, corticosteroid, hyaluronic acid, medication, and ultrasound ($P < 0.05$). In functional improvement, shockwave therapy showed statistical improvement compared with kinesiotherapy and moxibustion ($P < 0.05$) but not with acupotomy surgery ($P = 0.24$). A significant difference between shockwave therapy and platelet-rich plasma was observed in pain reduction ($P < 0.05$) but not in functional improvement ($P = 0.89$). Meanwhile, a statistical difference was found between shockwave therapy and fumigation in functional improvement ($P < 0.05$) but not in pain reduction ($P = 0.26$). Additionally, there was no statistically significant difference between shockwave therapy and manipulation in both pain reduction ($P = 0.21$) and functional improvement ($P = 0.45$). No serious adverse reaction occurred in all of studies. *Conclusions*. Extracorporeal shockwave therapy could be recommended in the treatment of osteoarthritis as a noninvasive therapy with safety and effectiveness, but the grade of recommendations needs to be discussed in a further study.

1. Background

Osteoarthritis (OA) is the most common musculoskeletal disease, ranking as the 11th highest contributor to global disability and 38th highest in the disability-adjusted life years (DALYs) in the Global Burden of Disease 2010 study [1, 2]. About 18% of women and 10% of men over 60 years of age suffered from OA and had higher mortality rates than their peers [3, 4]. In recent studies, the pathological processes of OA involve several local and systemic factors such as cytokines, chemokines, inflammatory mediators, matrix degradation, cell-derived, and/or matrix-derived products, which may cause damages to the synovium, cartilage, subchondral bone, periarticular muscles, ligaments, and other joint structures and finally lead to pain, stiffness, and disability [5, 6]. At present, the medical management of OA includes surgical therapies and nonsurgical therapies such as intra-articular injection, medication, and physical therapy. However, it was still difficult to reverse the destruction of joint structures [5]. Therefore, it is of great clinic significance to find an ideal method to relieve pain, improve function, and delay the disease progression.

As a new technique, extracorporeal shockwave therapy (ESWT) uses a single-impulse transient acoustic wave induced by pneumatic, electrohydraulic, electromagnetic, or piezoelectric generators which focuse on the area needed to

be treated [7]. ESWT has shown an effect on articular cartilage and subchondral bone development, neovascularization, tissue regeneration, and inflammatory response in some animal experiments [8–10]. ESWT also succeeds in the treatment of several musculoskeletal diseases, including tennis elbow syndrome, plantar fasciitis, tendon disease, and fracture nonunions, in some clinical studies [11–14]. More and more attention has been paid to the application of ESWT on OA because of its noninvasive nature, low rate of complications, and low cost compared with other surgical or conservative treatments in recent studies [15, 16]. Despite some systematic reviews focusing on the effect of ESWT on knee OA [17–19], there was no systematic review to confirm the value of EWST in the treatment of all types of OA (including knee OA and carpometacarpal joint OA) and compare ESWT with other traditional therapies (especially traditional Chinese medicine). Thus, this meta-analysis was performed, and the latest randomized controlled trials were included, which would contribute to the treatment of OA.

2. Method

2.1. Search Strategy. The protocol was registered in the PROSPERO database (CRD42019120534), and all searched results were evaluated according to the PRISMA statement. PubMed, MEDLINE, the Cochrane Central Register of Controlled Trials, Web of Science (WOS), Chinese National Knowledge Infrastructure (CNKI), WANFANG database, and VIP database were searched up to December 10, 2019, to identify the potential studies exploring the effect of ESWT for the treatment of OA. The searching strategy used was as follows: (((extracorporeal shock wave therapy [Title/Abstract]) OR ESWT[Title/Abstract])) AND ((osteoarthritis[-Title/Abstract]) OR OA[Title/Abstract]) Filters: Publication date to 2019/12/10. The publication language was limited to English and Chinese.

2.2. Study Selection. The inclusion criteria were the following: (1) randomized controlled trials (RCT) comparing the effect of ESWT and other treatments (including placebo) for all types of OA; (2) full text available and the outcome of experiments including mean (M), standard deviation (SD), and number (N); (3) patients aged 45 years or more and diagnosed with OA according to any clinical criteria; and (4) ESWT that had never been performed to the enrolled patients before.

The exclusion criteria were the following: (1) meta-analyses, reviews, letters, editorials, expert opinions, case reports, and nonrandomized control trials; (2) animal experiments; (3) patients with coagulopathy, pregnancy, cancer, history of fractures, cardiac pacemaker use, and neurologic conditions; and (4) including only the latest information if data were duplicated or overlapped.

2.3. Screening and Data Collection. Two researchers independently assessed the eligibility of the studies, and the disagreements were resolved by a third verdict. Titles and abstracts were screened to identify the related studies, and then full texts were assessed carefully. Moreover, the references cited in the selected articles were explored to identify the potentially relevant studies. The scores of visual analogue scale (VAS) were extracted as primary outcome. Secondary outcomes included the scores of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), which represented the functional change. If the scores were recorded in different follow-up times, we selected the time point at 3 months or available data to be nearest to 3 months to predict the efficacy.

2.4. Quality Assessment. The quality of included studies was assessed by the Cochrane Collaboration's tool for assessing the risk of bias which was recommended for systematic reviews of interventions in Cochrane Handbook version 5.1.0 [20]. We evaluated 7 domains of bias including selection bias, performance bias, detection bias, attribution bias, reporting bias, and other sources of bias. The judgements were expressed as "high risk," "low risk," or "unclear risk," and the quality assessment figure was generated by RevMan version 5.3.

2.5. Statistical Analyses. Meta-analysis Review Manager software (RevMan version 5.3; The Cochrane Collaboration 2014) and STATA (version 12.0; Stata Corporation) were used for data analysis. The analysis was performed in two respects including pain reduction and functional improvement. The heterogeneity was evaluated by Higgins I2 statistic, $I^2 > 50\%$ was defined as significant heterogeneity among studies, and the random effects model was applied for the pooled effect estimates. Otherwise, the fixed effects model was used. At the same time, subgroup analysis was used for exploring sources of heterogeneity and reassessing the results. Sensitivity analyses were performed by removing an individual study from the meta-analysis each time. If more than 10 studies were included in each meta-analysis, the possibility of publication bias would be evaluated by Egger's test and $P < 0.05$ was considered statistically significant; then the fill method and nonparametric trim were applied to correct the effect size. The results were expressed as the standard mean difference (SMD) and 95% confidence interval (95% CI) for continuous outcome data.

3. Result

3.1. Search Results. As shown in Figure 1, the initial search yielded 549 articles and 173 records were screened after removing duplicates. The title and abstract of potentially relevant studies were read carefully, and 118 records were excluded. Then 55 full-text articles were assessed, and 23 articles were excluded because they did not meet the inclusion criteria. Finally, 32 RCTs were included in this meta-analysis [21–52]. Characteristics of these studies are shown in Table 1. All of the articles were published between 2013 and 2019 in English or Chinese. The sample size ranged from 18 to 160. All experimental groups received ESWT, while control groups received different treatments including placebo [22, 23, 25, 26, 28, 30, 34, 48, 49, 51, 52], medication [31, 32, 43, 44, 50], intra-articular injections [21, 26, 27, 29, 35, 36, 39, 40], traditional Chinese medicine [38, 41, 42, 45,

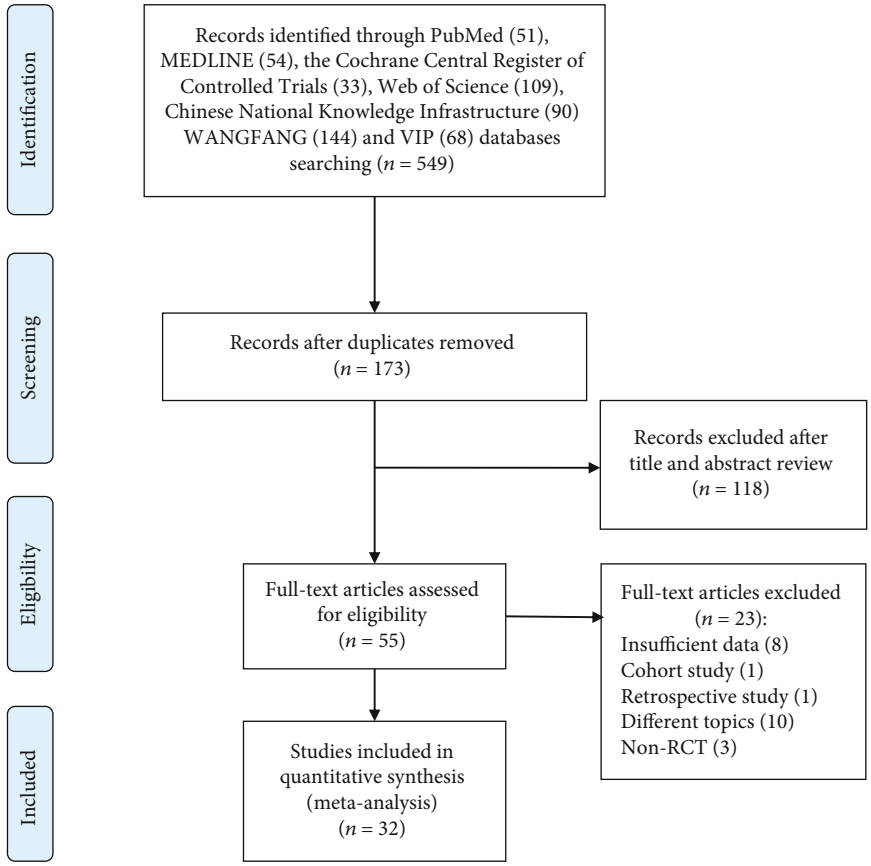

Figure 1: Flow diagram of study selection in this systematic review.

46], ultrasound [22, 24, 47], surgery [33], and kinesiotherapy (KIN) [37].

3.2. ESWT vs. Placebo. A statistically significant difference between ESWT group and placebo group was found in pain reduction (SMD = -1.44, 95% CI: -1.77 to -1.10, $P < 0.00001$) and functional improvement (SMD = -1.84, 95% CI: -2.47 to -1.20, $P < 0.00001$). As shown in Figure 2**,** high heterogeneity was observed in the analysis of pain reduction ($I^2 = 72\%$). After removing a study [25] from the meta-analysis, the heterogeneity decreased to 0%. The same phenomenon occurred in the analysis of functional improvement; the heterogeneity decreased from 89% to 30% after removing two studies [25, 26] from the meta-analysis, which suggested these two studies might be the sources of heterogeneity. The pooled effect did not change after removing these studies ($P < 0.00001$), which indicated the result was robust.

3.3. ESWT vs. Intra-Articular Injections. As shown in Figure 3, there was a statistical difference between the ESWT group and hyaluronic acid intra-articular injection (HA) group in pain reduction (SMD = -0.39, 95% CI: -0.77 to -0.01, $P = 0.04$) and functional improvements (SMD = -0.64, 95% CI: -1.24 to -0.04, $P = 0.04$). The heterogeneity decreased after subgroup analysis, which suggested that the language and dose of HA might be potential sources of heterogeneity.

A statistically significant difference between the ESWT group and platelet-rich plasma (PRP) intra-articular injection group was observed in pain reduction (SMD = -0.40, 95% CI: -0.76 to -0.03, $P = 0.03$). However, there was no statistically significant difference in functional improvement (SMD = -0.02, 95% CI: -0.38 to 0.33, $P = 0.89$).

There was a statistically significant difference between the ESWT group and corticosteroid intra-articular injection group in pain reduction (SMD = -1.68, 95% CI: -2.41 to -0.95, $P < 0.00001$) and functional improvements (SMD = -7.87, 95% CI: -9.78 to -5.95, $P < 0.00001$).

3.4. ESWT vs. Medication. There was a statistically significant difference between the ESWT group and medication group in the pain reduction (SMD = -1.67, 95% CI: -2.38 to -0.97, $P < 0.00001$) and functional improvement (SMD = -1.09, 95% CI: -1.33 to -0.85, $P < 0.00001$). High heterogeneity was found in pain reduction ($I^2 = 88\%$). In functional improvement, no heterogeneity was observed ($I^2 = 0\%$) (Figure 4).

3.5. ESWT vs. Ultrasound. As shown in Figure 5, a statistically significant difference was observed between the ESWT group and ultrasound group in pain reduction (SMD = -0.65, 95% CI: -0.92 to -0.37, $P < 0.00001$) and

Table 1: Basic characteristics of included studies.

Author	Publication year	Country	Language	Sample size	Control group	Experimental group	Outcome measures	Follow-up time	Type of OA	Type of ESWT
Ediz	2018	Turkey	English	73	Placebo	ESWT 2 times/week Total of 5 weeks	VAS, WOMAC	6 M	Knee	Focused ESWT
Ioppolo	2018	Rome	English	58	HA (3 injections of 0.5 cm^3 HA) 1 time/week Total of 3 weeks	ESWT 1 time/week Total of 3 weeks	VAS	3 M	Carpometacarpal joint	Focused ESWT
Lee	2017	Korea	English	61	HA (1 injection of 2 mL of HA) 1 time/week Total of 3 weeks	ESWT 1 time/week Total of 3 weeks	VAS, WOMAC	3 M	Knee	Focused ESWT
Lizis	2017	Poland	English	40	KIN 1 time/week Total of 3 weeks	ESWT 1 time/week Total of 5 weeks	WOMAC	5 W	Knee	Unmentioned
Zhao	2013	China	English	70	Placebo	ESWT 1 time/week Total of 4 weeks	VAS, WOMAC	3 M	Knee	Radial ESWT
Liu Y	2016	China	Chinese	86	Placebo	ESWT 1 time/week Total of 8 weeks	VAS, WOMAC	3 M	Knee	Radial ESWT
Liu MY	2017	China	Chinese	158	Medication (celecoxib) oral 200 mg qd 4 weeks	ESWT 1 time/week Total of 4 weeks	VAS, WOMAC	3 M	Knee	Unmentioned
Zhang	2017	China	Chinese	106	Ultrasound 5 times/week Total of 4 weeks	ESWT 1 time/5 days Total of 5 times	VAS	1 M	Knee	Radial ESWT
Zheng	2016	China	Chinese	48	Medication (celecoxib) oral 200 mg qd 4 weeks	ESWT 1 time/week Total of 4 weeks	VAS, WOMAC	1 M	Knee	Radial ESWT
Liu WT	2017	China	Chinese	58	Acupotomy surgery	ESWT 1 time/5 days Total of 6 times	WOMAC	5 W	Knee	Unmentioned
ZhaoAQ	2016	China	Chinese	60	Placebo	ESWT 1 time/week Total of 8 weeks	VAS, WOMAC	2 M	Knee	Unmentioned
Wu	2014	China	Chinese	53	Medication (toricoxi) oral 60 mg qd 4 weeks	ESWT 1 time/week Total of 4 weeks	VAS	6 W	Knee	Radial ESWT
Chen	2014	China	English	120	Placebo Ultrasound 3 times/week Total of 8 weeks	ESWT 1 time/week Total of 6 weeks	VAS	2 M	Knee	Focused ESWT

Table 1: Continued.

Author	Publication year	Country	Language	Sample size	Control group	Experimental group	Outcome measures	Follow-up time	Type of OA	Type of ESWT
Lee JH	2017	Korea	English	20	Placebo	ESWT 3 times/week Total of 4 weeks	VAS WOMAC	1 M	Knee	Focused ESWT
Zhong	2019	China	English	63	Placebo	ESWT 1 time/week Total of 4 weeks	VAS WOMAC	3 M	Knee	Radial ESWT
Wang	2016	China	Chinese	78	Massage manipulation 1 time/2 days 10 weeks	ESWT 1 time/5 days Total of 5 weeks	WOMAC	3 M	Knee	Radial ESWT
Zhong	2018	China	Chinese	63	Placebo	ESWT 1 time/week Total of 4 weeks	VAS WOMAC	5 W	Knee	Radial ESWT
Xie	2019	China	Chinese	60	Fumigation bid 3 weeks	ESWT 1 time/week Total of 4 weeks	VAS	3 M	Knee	Radial ESWT
Su	2018	China	Chinese	160	HA (1 injection of 2 mL of HA) 1 time/week Total of 5 weeks	ESWT 1 time/week Total of 5 weeks	VAS WOMAC	5 W	Knee	Radial ESWT
Su	2019	China	Chinese	120	PRP (1 injection of 4 mL of PRP) 1 time/week Total of 5 weeks	ESWT 1 time/week Total of 5 weeks	VAS WOMAC	5 W	Knee	Radial ESWT
Qi	2015	China	Chinese	60	Acupoint moxibustion qd 4 weeks	ESWT 1 time/week Total of 4 weeks	WOMAC	6 M	Knee	Focused ESWT
Yang	2017	China	Chinese	86	Fumigation qd 16 days	ESWT 1 time/5 days Total of 4 weeks	WOMAC	After treatment	Knee	Radial ESWT
Liu ZC	2019	China	Chinese	77	HA (1 injection of 2.5 mL of HA) 1 time/week Total of 5 weeks	ESWT 1 time/week Total of 5 weeks	VAS WOMAC	5 W	Knee	Radial ESWT
Wu TY	2018	China	Chinese	100	Medication (celecoxib) oral 200 mg qd 4 weeks	ESWT 1 time/week Total of 4 weeks	VAS WOMAC	After treatment	Knee	Radial ESWT
Cai	2018	China	Chinese	90	HA (1 injection of z.5 mL of HA) 1 time/week Total of 5 weeks	ESWT 1 time/week Total of 5 weeks	VAS WOMAC	3 M	Knee	Radial ESWT
Wei	2018	China	Chinese	40	Massage manipulation 3 times/week Total of 4 weeks	ESWT 1 time/week Total of 4 weeks	VAS WOMAC	6 W	Knee	Radial ESWT

Table 1: Continued.

Author	Publication year	Country	Language	Sample size	Control group	Experimental group	Outcome measures	Follow-up time	Type of OA	Type of ESWT
Cho	2016	Korea	English	18	Placebo	ESWT 1 time/week Total of 3 weeks	VAS	1 W	Knee	Focused ESWT
Liu YX	2018	China	Chinese	72	HA (1 injection of 20 mg of HA) 1 time/week Total of 2 months	ESWT 2 times/week Total of 2 months	VAS WOMAC	2 M	Knee	Unmentioned
Liu BZ	2019	China	Chinese	63	Placebo	ESWT 1 time/week Total of 4 weeks	VAS WOMAC	3 M	Knee	Radial ESWT
Elerian	2016	Egypt	English	60	Placebo corticosteroid injection 1 time/month Total of 2 months	ESWT 1 time/week Total of 3 weeks	VAS WOMAC	2 M	Knee	Radial ESWT
Liu WF	2019	China	Chinese	66	Medication (celecoxib) oral 200 mg qd 4 weeks	ESWT 1 time/week Total of 4 weeks	VAS	After treatment	Knee	Radial ESWT
Dou	2016	China	Chinese	121	Ultrasound 1 time/2 days for first two intervals 1 time/3 days for 2nd to 6th intervals 1 time/4 days for 6th to 8th intervals	ESWT	WOMAC	1 M	Knee	Focused ESWT

Abbreviations: RCT: randomized controlled trial; ESWT: extracorporeal shockwave therapy; HA: hyaluronic acid intra-articular injections; PRP: platelet-rich plasma; KIN: kinesiotherapy; VAS: visual analogue scale; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index; W: weeks; M: months; qd: once a day; bid: twice a day; OA: osteoarthritis.

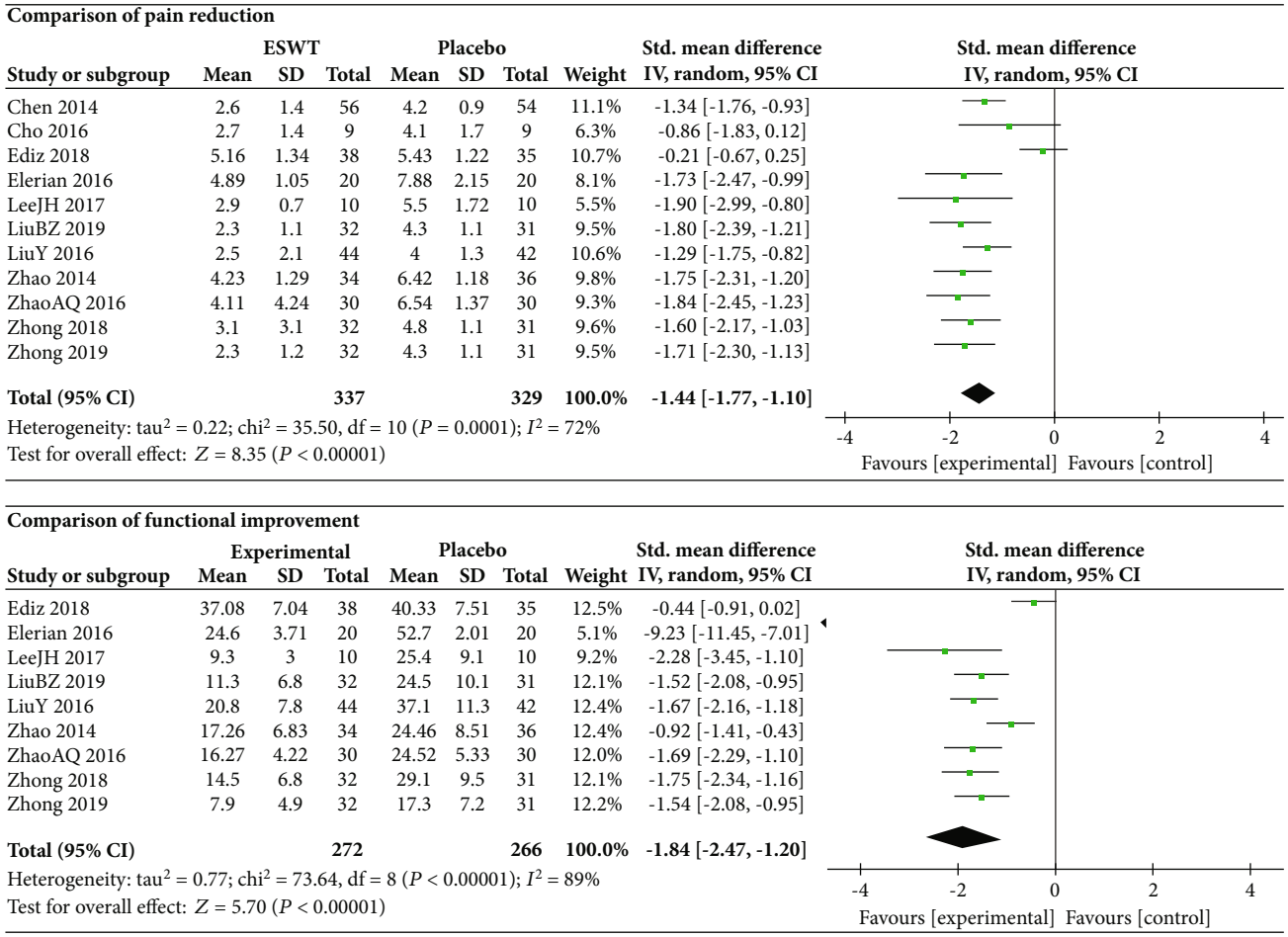

Figure 2: Forest plot comparing the ESWT group with the placebo group.

functional improvement (SMD = -1.48, 95% CI: -1.80 to -1.17, $P < 0.00001$). No heterogeneity was observed in this meta-analysis ($I^2 = 0\%$).

3.6. ESWT vs. Surgery. There was no statistically significant difference between the ESWT group and acupotomy surgery group in functional improvement (SMD = 0.31, 95% CI: -0.21 to 0.83, $P = 0.24$). (Figure 6)

3.7. ESWT vs. KIN. In Figure 7, a statistically significant difference was observed between the ESWT group and kinesiotherapy (KIN) group in functional improvement (SMD = -2.11, 95% CI: -2.90 to -1.32, $P < 0.00001$).

3.8. ESWT vs. Traditional Chinese Medicine. As shown in Figure 8, there was no statistically significant difference between the ESWT group and manipulation group in pain reduction (SMD = 0.40, 95% CI: -0.23 to 1.03, $P = 0.21$) and functional improvement (SMD = -0.47, 95% CI: -1.71 to 0.76, $P = 0.45$). A statistically significant difference was found in comparison between the ESWT group and fumigation group in functional improvement (SMD = -1.28, 95% CI: -1.74 to -0.81, $P < 0.00001$) but not in pain reduction (SMD = -0.29, 95% CI: -0.80 to 0.22, $P = 0.26$). There was a statistically significant difference between the ESWT group and acupoint moxibustion group in functional improvement (SMD = -0.60, 95% CI: -1.12 to -0.09, $P = 0.02$).

3.9. Adverse Event. Only temporary pain, minor bruising, or transient soft tissue swelling was observed in nine studies [25, 30, 34, 42, 44, 47, 50–52]. No adverse events were observed during the treatment in other six studies [27, 29, 36–38, 46], and the remaining studies did not mention it.

3.10. Sensitivity Analysis. In meta-analysis comparing ESWT with placebo, a single study was excluded each time to evaluate the impact of the individual data on the whole result. The results showed that the pooled effect was robust and no significant deviation from the overall results was detected in our study (Figure 9).

3.11. Quality Assessment and Publication Bias. In quality assessment (Figure 10), 19 studies were considered to be high risk in blinding of participants and personnel because the therapeutic properties make it hard to apply blinding. 155 of 224 domains (69.2%) were determined at low risk, and 50 of 224 domains (22.3%) were determined at unclear risk.

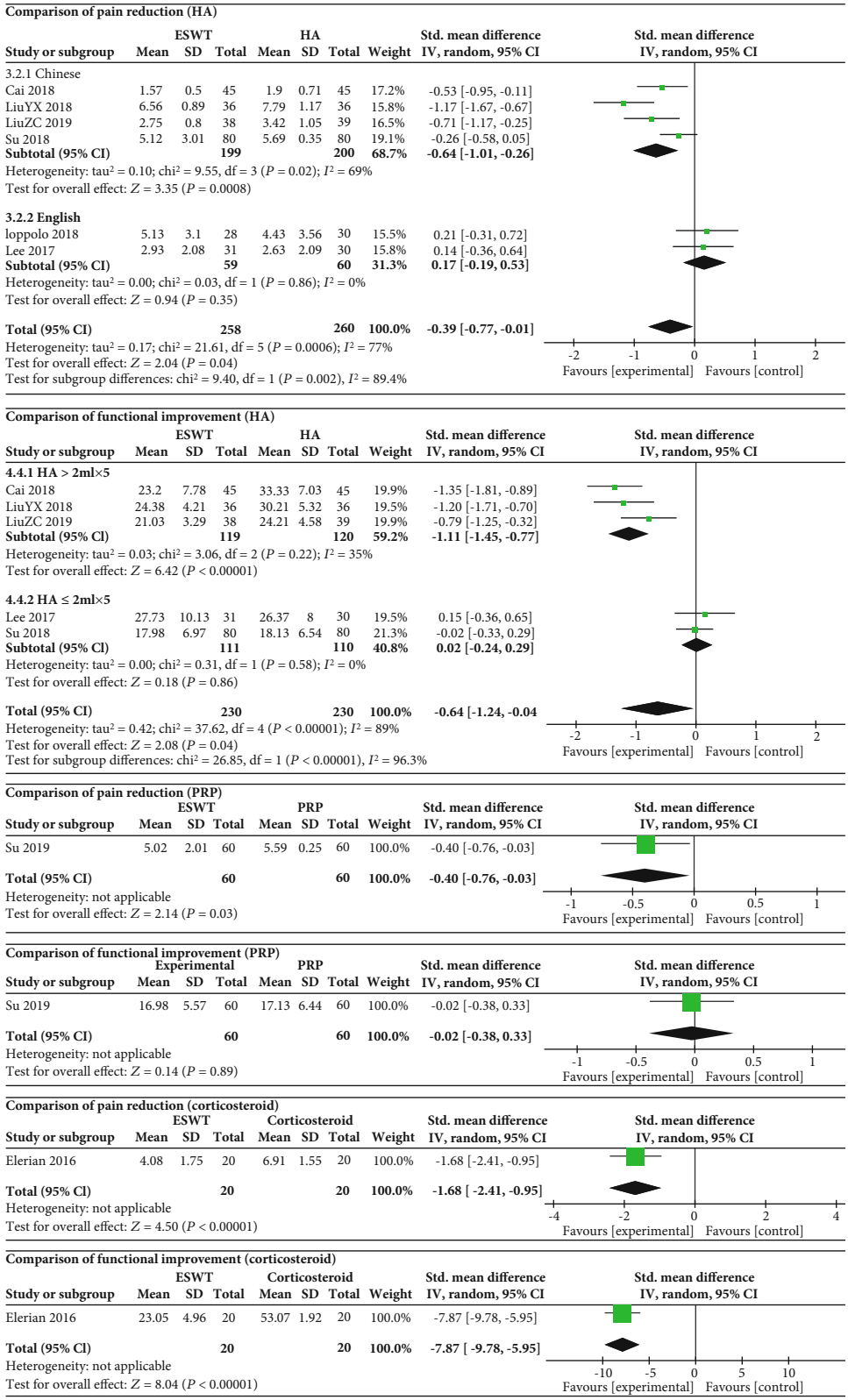

Figure 3: Forest plot comparing the ESWT group with the intra-articular injection group.

There was no publication bias in this meta-analysis (pain reduction—Begg's test: $P = 0.161$, Egger's test: $P = 0.346$; functional improvement—Begg's test: $P = 0.466$, Egger's test: $P = 0.155$).

4. Discussion

This meta-analysis included 32 studies involving 2408 patients to explore the efficacy and safety of ESWT for the

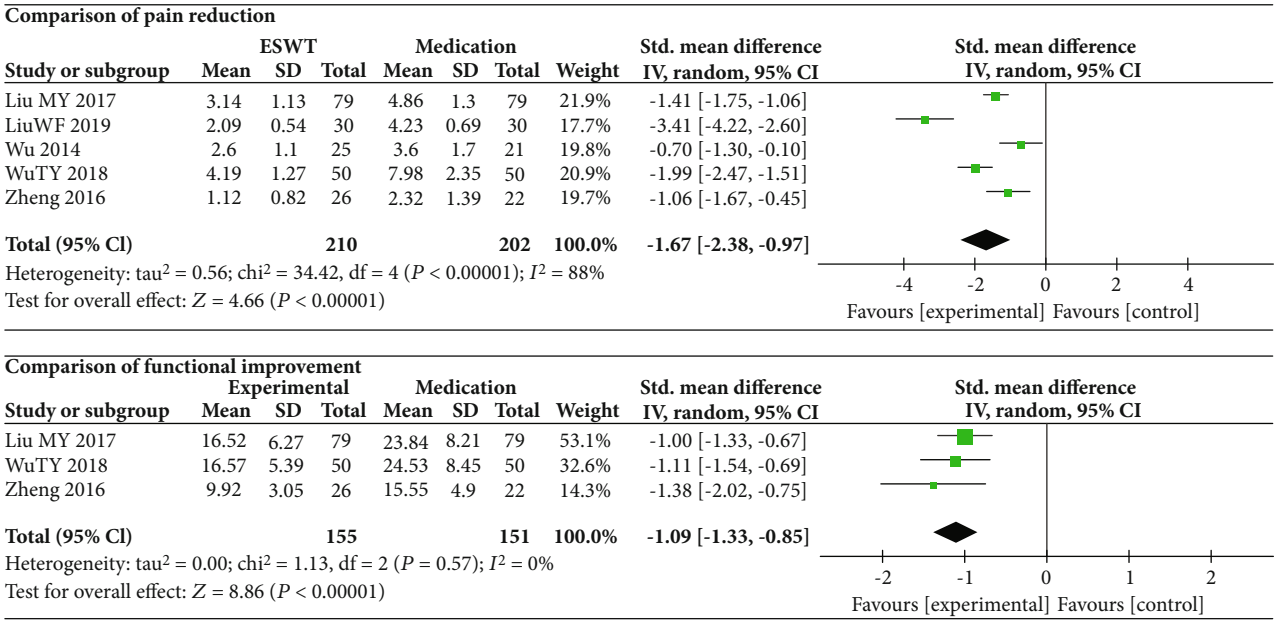

Figure 4: Forest plot comparing the ESWT group with the medication group.

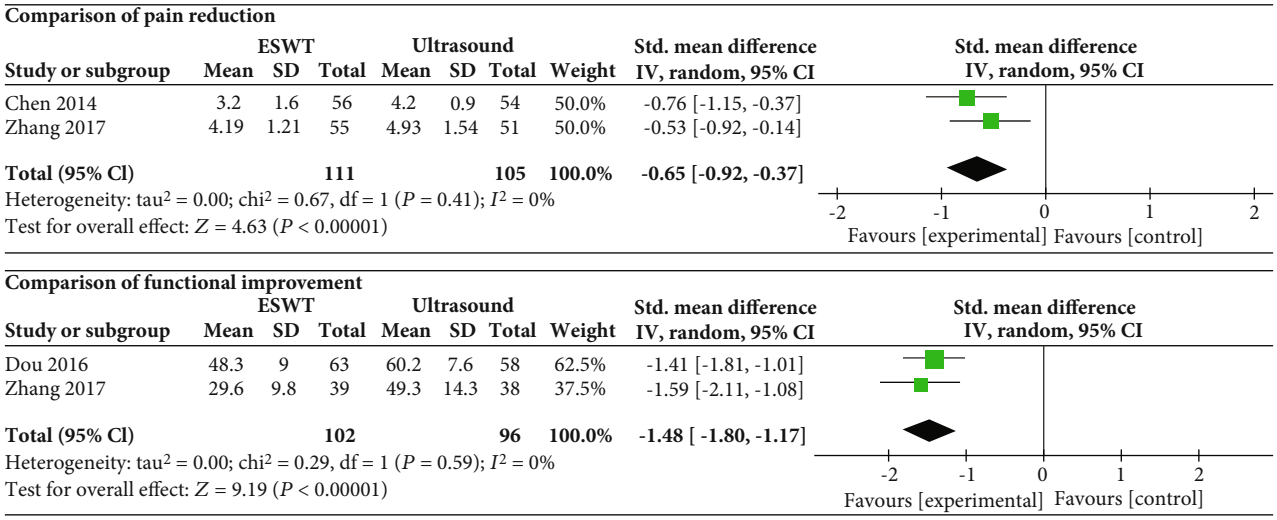

Figure 5: Forest plot comparing the ESWT group with the ultrasound group.

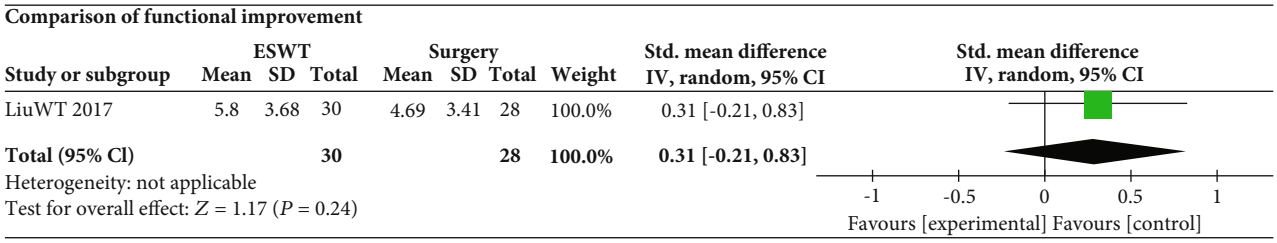

Figure 6: Forest plot comparing the ESWT group with the surgery group.

treatment of OA. In this study, the ESWT group showed a statistically significant difference compared with the placebo, corticosteroid, HA, medication, and ultrasound group in both pain reduction and functional improvement, presenting that ESWT might be a successful alternative treatment when above treatments are unavailable. In functional improvement, ESWT showed statistical improvement compared with kinesiotherapy and moxibustion but no statistical difference

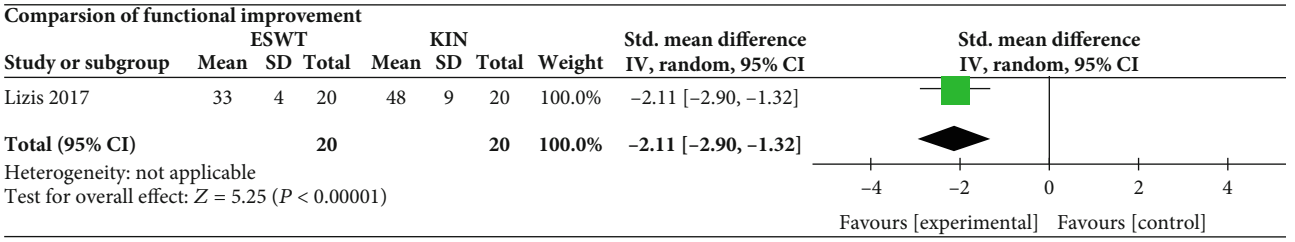

Figure 7: Forest plot comparing the ESWT group with the KIN group.

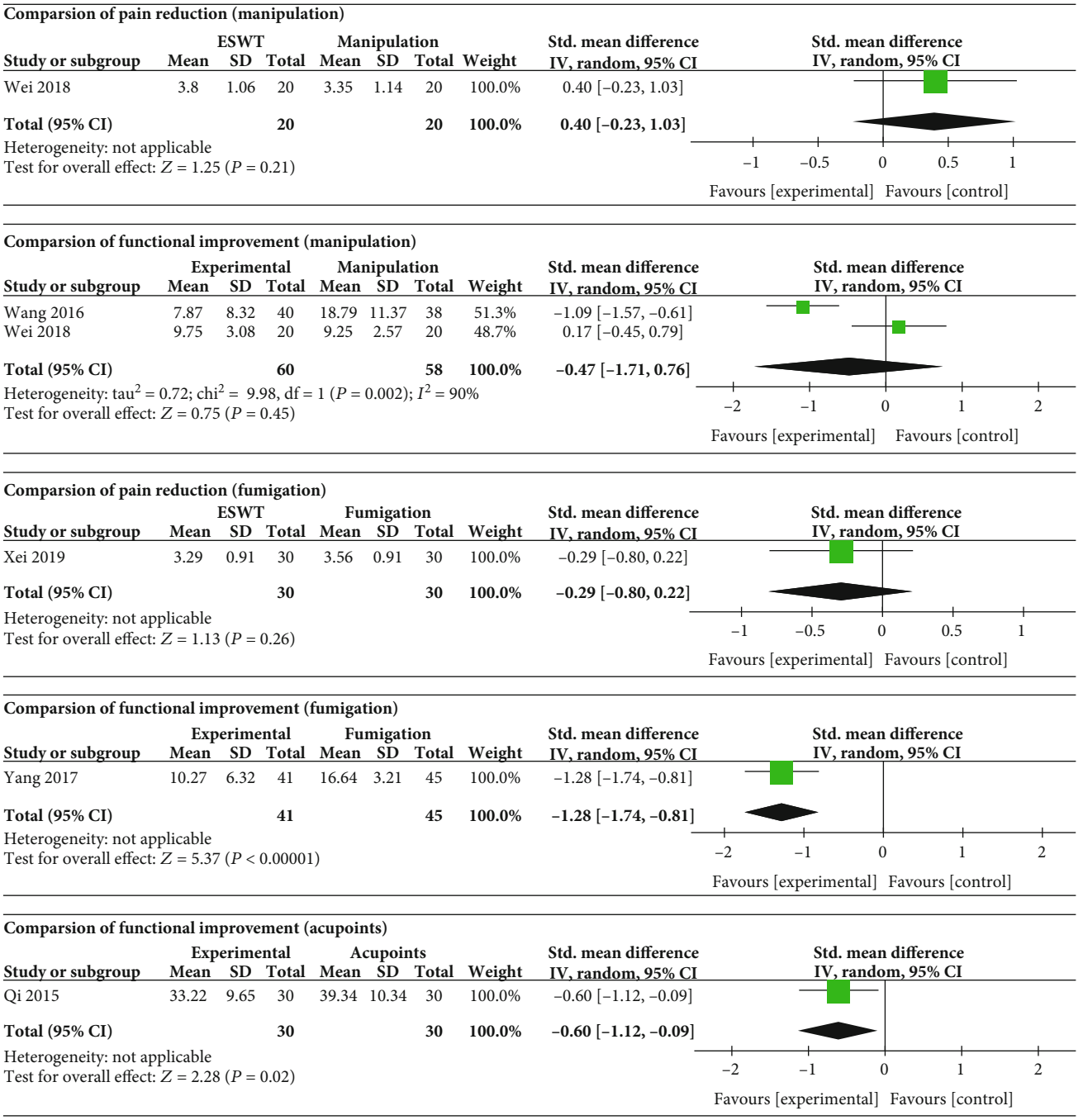

Figure 8: Forest plot comparing the ESWT group with the traditional Chinese medicine group.

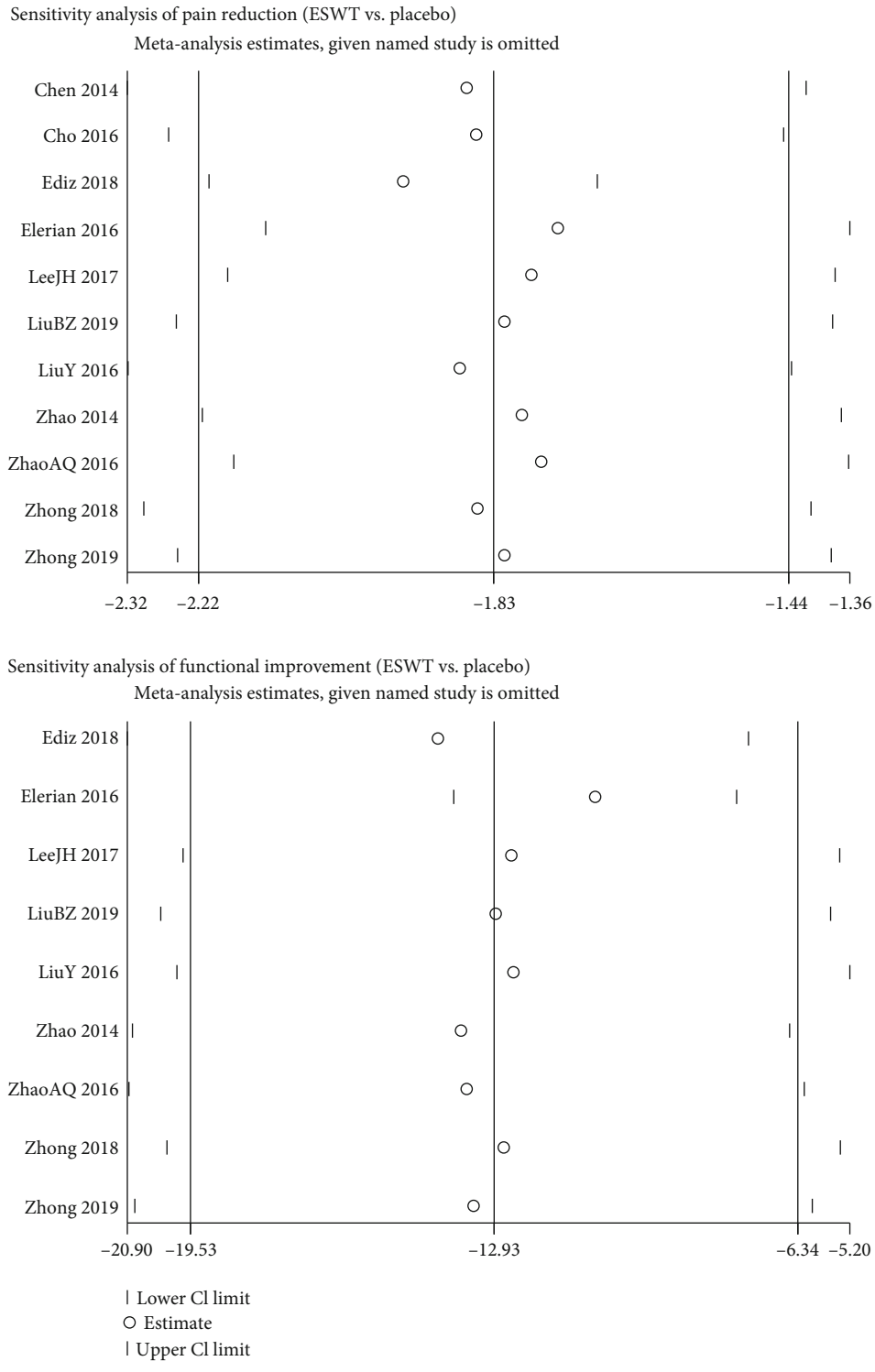

Figure 9: Sensitivity analysis of included studies comparing the ESWT group with the placebo group.

compared with acupotomy surgery. A significant difference between ESWT and PRP was observed in pain reduction but not in functional improvement. Meanwhile, a statistical difference was found between ESWT and fumigation in functional improvement but not in pain reduction. Additionally, there was no statistically significant difference between ESWT and manipulation in both pain reduction and functional improvement. No serious adverse reaction occurred in all of studies.

Osteoarthritis (OA) is the most common cause leading to musculoskeletal pain [53]. It is considered that the pathological features of OA include articular cartilage destruction, subchondral bone change, osteophyte formation remolding, ligamentous laxity, periarticular muscle weakness, and

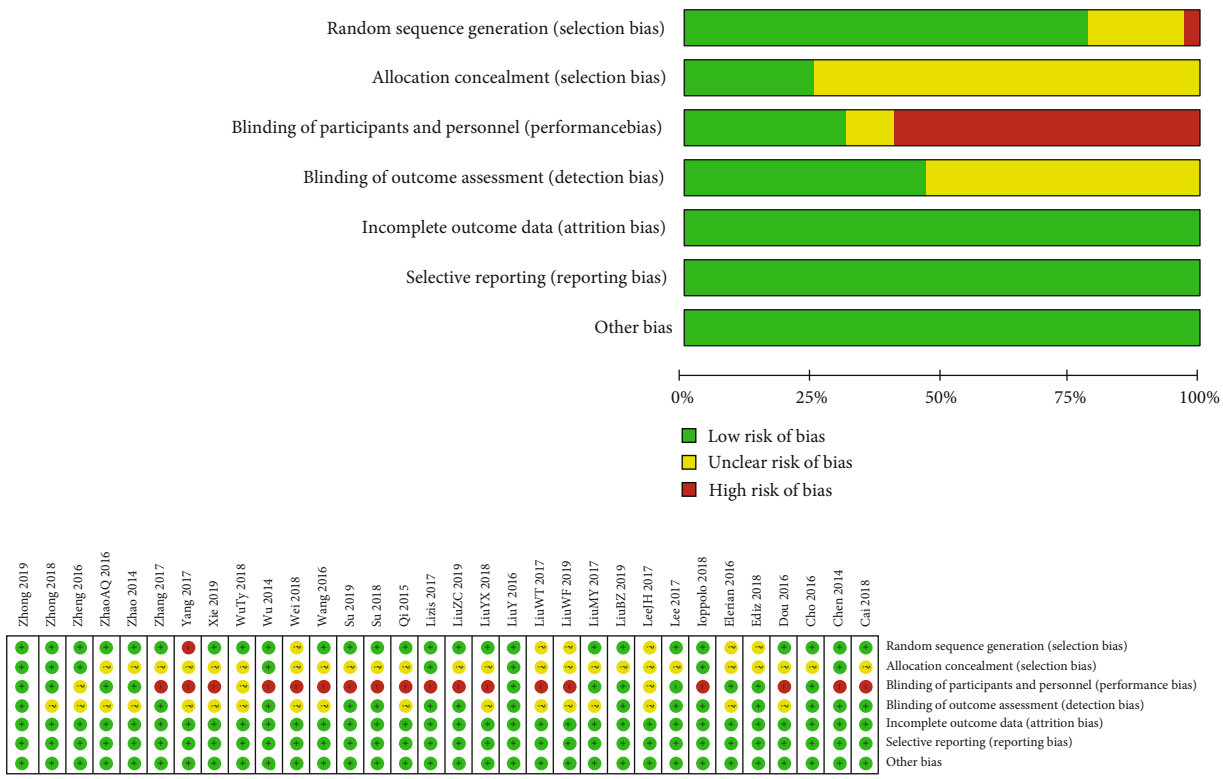

Figure 10: Quality assessment of included articles.

synovial inflammation, which could result in chronic pain, physical limitation, and joint stiffness [54, 55].

Traditional treatments of OA included nonsurgical therapies and surgical therapies. In the 2014 Osteoarthritis Research Society International guidelines for the management of knee OA, nonsurgical therapies included intra-articular corticosteroids, biomechanical interventions, exercise, education and self-management, weight management, and strength training [56]. Traditional surgical options included joint sparing procedures such as arthroscopic surgery or joint replacing procedures [57]. For treatment, nonsurgical therapy might have limited benefit and could be associated with serious adverse events such as bleeding or gastrointestinal ulcers caused by nonsteroidal anti-inflammatory drugs (NSAIDs) and infection caused by intra-articular injection [58]. As for surgery, it might be inappropriate for aged patients with limiting comorbidities. In such conditions, an effective and safe treatment was needed for patients with OA.

ESWT has been increasingly used in clinical practice over the past few years and shows significant efficacy in some clinical studies [16, 59–61]. It is suggested that ESWT can generate radial or focused pressure waves which bring energy and propagate through tissue [62]. This physical force could stimulate biological effects in a treated area, and the biochemical mechanism of ESWT in OA might be associated with neovascularization, osteogenesis, and chondrogenesis [63–65]. In recent studies, ESWT might lead to upregulation of angiogenic growth factors including endothelial nitric oxide synthase (eNOS) and vessel endothelial growth factor (VEGF), which benefit to neovascularization [66]. ESWT was also found connected with osteogenic transcription factors including VEGF-A and hypoxia inducible factor-1α (HIF-1α), affecting growth of osteoblasts [67]. Meanwhile, ESWT might elevate levels of nitric oxide (NO), bone morphogenetic protein-2 (BMP-2), protein kinase B (PKB), and transforming growth factor-beta 1 (TGF-β1), which facilitate differentiation and proliferation of osteoblasts [68–71]. Also, it was suggested that ESWT could enhance the expression of Pdia-3, a key point of 1α,25-dihydroxyvitamin D3 (1α,25$(OH)_2D_3$) signaling pathway [72]. This signaling pathway is essential in gene transcription and calcium homeostasis, which was considered beneficial for osteogenesis [73]. Besides, ESWT was revealed to have a dose-dependent effect on the metabolism of mesenchymal stem cells (MSCs), which potentially improve bone regeneration and chondrogenesis [74]. However, the exact mechanism of ESWT is still unknown, and further studies are required for better clinical utilization.

This study also had some limitations. First, we only searched studies in English and Chinese; thus, some potential relative studies in other languages might have been missed. Second, unreported negative results and gray literature could result in publication bias. Third, very few studies compared ESWT with surgery, PRP, and corticosteroid intra-articular injections, traditional Chinese medicine, or kinesiotherapy; thus, the subgroup analysis and sensibility analysis could not be performed, and the outcome might be misleading. Besides, in this meta-analysis, focused ESWT was performed in 8 studies in the experiment group and radial ESWT was

administered in 19 studies, while the type of ESWT was unmentioned in the other 5 studies. As a result, it was difficult to perform subgroup analysis according to the different type of ESWT and analyze whether there was a difference between the focused ESWT and radial ESWT in the treatment of OA. Further studies could be carried out to improve this issue.

5. Conclusion

In conclusion, ESWT showed a significant effect in the treatment of OA in pain reduction or/and functional improvement compared with placebo, corticosteroid, HA, medication, ultrasound, moxibustion, fumigation, PRP, and kinesiotherapy. However, ESWT failed to show a statistically significant difference compared with manipulation and surgery. As a result, ESWT could be recommended in the treatment of OA as a noninvasive therapy with safety and effectiveness but the grade of recommendations needs to be discussed in a further study.

Disclosure

The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. An earlier version of this work has been presented in 22th ISMST International Congress.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Ye L designed the study with contributions from Chen L. Yang PL and Yang BX screened and collected the data. Liu H carried out the quality assessment. Chen L analyzed the data and wrote the paper with the help from Ye L and Yang PL.

Acknowledgments

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References

[1] S. Glyn-Jones, A. J. Palmer, R. Agricola et al., "Osteoarthritis," *Lancet*, vol. 386, no. 9991, pp. 376–387, 2015.

[2] M. Cross, E. Smith, D. Hoy et al., "The global burden of hip and knee osteoarthritis: estimates from the Global Burden of Disease 2010 study," *Annals of the Rheumatic Diseases*, vol. 73, no. 7, pp. 1323–1330, 2014.

[3] D. Pereira, E. Ramos, and J. Branco, "Osteoarthritis," *Acta Médica Portuguesa*, vol. 28, no. 1, pp. 99–106, 2015.

[4] A. M. Briggs, M. J. Cross, D. G. Hoy et al., "Musculoskeletal health conditions represent a global threat to healthy aging: a report for the 2015 World Health Organization world report on ageing and health," *Gerontologist*, vol. 56, Supplement 2, pp. S243–S255, 2016.

[5] J. N. Katz, "Tanezumab for painful osteoarthritis," *JAMA*, vol. 322, no. 1, pp. 30–32, 2019.

[6] J. Martel-Pelletier, A. J. Barr, F. M. Cicuttini et al., "Osteoarthritis," *Nature Reviews Disease Primers*, vol. 2, no. 1, article 16072, 2016.

[7] Q. Ji, P. Wang, and C. He, "Extracorporeal shockwave therapy as a novel and potential treatment for degenerative cartilage and bone disease: osteoarthritis. A qualitative analysis of the literature," *Progress in Biophysics and Molecular Biology*, vol. 121, no. 3, pp. 255–265, 2016.

[8] C. J. Wang, "Extracorporeal shockwave therapy in musculoskeletal disorders," *Journal of Orthopaedic Surgery and Research*, vol. 7, no. 1, p. 11, 2012.

[9] J. H. Cheng, C. J. Wang, S. H. Su, C. Y. Huang, and S. L. Hsu, "Next-generation sequencing identifies articular cartilage and subchondral bone miRNAs after ESWT on early osteoarthritis knee," *Oncotarget*, vol. 7, no. 51, pp. 84398–84407, 2016.

[10] N. Ochiai, S. Ohtori, T. Sasho et al., "Extracorporeal shock wave therapy improves motor dysfunction and pain originating from knee osteoarthritis in rats," *Osteoarthritis and Cartilage*, vol. 15, no. 9, pp. 1093–1096, 2007.

[11] A. Kubot, A. Grzegorzewski, M. Synder, W. Szymczak, and P. Kozłowski, "Radial extracorporeal shockwave therapy and ultrasound therapy in the treatment of tennis elbow syndrome," *Ortopedia Traumatologia Rehabilitacja*, vol. 19, no. 5, pp. 415–426, 2017.

[12] W. Schaden, R. Mittermayr, N. Haffner, D. Smolen, L. Gerdesmeyer, and C. J. Wang, "Extracorporeal shockwave therapy (ESWT) - First choice treatment of fracture nonunions?," *International Journal of Surgery*, vol. 24, no. Part B, pp. 179–183, 2015.

[13] J. Lou, S. Wang, S. Liu, and G. Xing, "Effectiveness of extracorporeal shock wave therapy without local anesthesia in patients with recalcitrant plantar fasciitis: a meta-analysis of randomized controlled trials," *American Journal of Physical Medicine & Rehabilitation*, vol. 96, no. 8, pp. 529–534, 2017.

[14] C. Carulli, F. Tonelli, M. Innocenti, B. Gambardella, F. Muncibì, and M. Innocenti, "Effectiveness of extracorporeal shockwave therapy in three major tendon diseases," *Journal of Orthopaedics and Traumatology*, vol. 17, no. 1, pp. 15–20, 2016.

[15] W. Y. Chou, J. H. Cheng, C. J. Wang, S. L. Hsu, J. H. Chen, and C. Y. Huang, "Shockwave targeting on subchondral bone is more suitable than articular cartilage for knee osteoarthritis," *International Journal of Medical Sciences*, vol. 16, no. 1, pp. 156–166, 2019.

[16] S. Kang, F. Gao, J. Han et al., "Extracorporeal shock wave treatment can normalize painful bone marrow edema in knee osteoarthritis: a comparative historical cohort study," *Medicine*, vol. 97, no. 5, article e9796, 2018.

[17] Y. C. Wang, H. T. Huang, P. J. Huang, Z. M. Liu, and C. L. Shih, "Efficacy and safety of extracorporeal shockwave therapy for treatment of knee osteoarthritis: a systematic review and meta-analysis," *Pain Medicine*, 2019.

[18] T. Li, J. Ma, T. Zhao, F. Gao, and W. Sun, "Application and efficacy of extracorporeal shockwave treatment for knee

osteoarthritis: a systematic review and meta-analysis," *Experimental and Therapeutic Medicine*, vol. 18, no. 4, pp. 2843–2850, 2019.

[19] C. D. Liao, J. Y. Tsauo, T. H. Liou, H. C. Chen, and S. W. Huang, "Clinical efficacy of extracorporeal shockwave therapy for knee osteoarthritis: a systematic review and meta-regression of randomized controlled trials," *Clinical Rehabilitation*, vol. 33, no. 9, pp. 1419–1430, 2019.

[20] J. J. Deeks, J. Higgins, D. G. Altman, and S. Green, *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]*, The Cochrane Collaboration, 2011, http://www.handbook.cochrane.org/.

[21] J. X. Cai, *The effects of extracorporeal shock wave therapy for knee osteoarthritis*, Fujian Medical University, 2018.

[22] T. W. Chen, C. W. Lin, C. L. Lee et al., "The efficacy of shock wave therapy in patients with knee osteoarthritis and popliteal cyamella," *The Kaohsiung Journal of Medical Sciences*, vol. 30, no. 7, pp. 362–370, 2014.

[23] S. J. Cho, J. R. Yang, H. S. Yang, and H. E. Yang, "Effects of extracorporeal shockwave therapy in chronic stroke patients with knee osteoarthritis: a pilot study," *Annals of Rehabilitation Medicine*, vol. 40, no. 5, pp. 862–870, 2016.

[24] Y. X. Dou, J. Yuan, and J. Y. Zhao, "Short-term effect analysis of extracorporeal shock wave on knee osteoarthritis," *Chinese Journal of Rehabilitation Medicine*, vol. 31, no. 8, pp. 917–919, 2016.

[25] L. Ediz and M. Ozgokce, "Effectiveness of extracorporeal shock wave therapy to treat primary medial knee osteoarthritis with and without bone marrow edema in elderly patients," *Turkish Journal of Geriatrics-Turk Geriatri Dergisi*, vol. 21, no. 3, pp. 394–401, 2018.

[26] A. E. Elerian, T. M. A. Ewidea, and N. Ali, "Effect of shock wave Therapyversus corticosteroid injection in management of knee osteoarthritis," *International Journal of Physiotherapy*, vol. 3, no. 2, pp. 246–251, 2016.

[27] F. Ioppolo, F. Saracino, R. S. Rizzo et al., "Comparison between extracorporeal shock wave therapy and intra-articular hyaluronic acid injections in the treatment of first carpometacarpal joint osteoarthritis," *Annals of Rehabilitation Medicine*, vol. 42, no. 1, pp. 92–100, 2018.

[28] J. H. Lee, S. Lee, S. Choi, Y. H. Choi, and K. Lee, "The effects of extracorporeal shock wave therapy on the pain and function of patients with degenerative knee arthritis," *Journal of Physical Therapy Science*, vol. 29, no. 3, pp. 536–538, 2017.

[29] J.-K. Lee, B.-Y. Lee, W.-Y. Shin, M. J. An, K. I. Jung, and S. R. Yoon, "Effect of extracorporeal shockwave therapy versus intra-articular injections of hyaluronic acid for the treatment of knee osteoarthritis," *Annals of Rehabilitation Medicine-Arm*, vol. 41, no. 5, pp. 828–835, 2017.

[30] B. Z. Liu, Z. Y. Zhong, G. H. Liu et al., "The effects of extracorporeal shock wave therapy on the lower limb function and articular cartilage of pa-tients with knee osteoarthritis," *Chinese Journal of Physical Medicine and Rehabilitation*, vol. 41, no. 7, pp. 494–498, 2019.

[31] M. Y. Liu, H. Li, Y. Q. Zhang et al., "Efficacy of extracorporeal shock wave therapy in elderly patients with knee osteoarthritis and its influence on inflammatory factors," *Hainan Medical Journal (Hai Nan Yi Xue)*, vol. 28, no. 24, pp. 4015–4017, 2017.

[32] W. F. Liu, "Effects of extracorporeal shock wave therapy on early to mid-term knee osteoarthritis," *China Medical Device Information*, vol. 25, no. 8, pp. 61-62, 2019.

[33] W. T. Liu, K. L. Xue, M. Tian, and F. Zhang, "Comparative study of pneumatic lithotripsy extracorporeal shock wave and acupotomelysis in the treatment of knee osteoarthritis," *The Journal of Cervicodynia and Lumbodynia*, vol. 38, no. 1, pp. 64–67, 2017.

[34] Y. Liu, *Efficacy of shockwave therapy in postmenopausal women with early metaphase knee osteoarthritis*, Hebei Medical University, 2016.

[35] Y. X. Liu, H. L. Zhou, L. L. Xu, and T. T. Li, "Effect of extracorporeal shockwave combined with rehabilitation measures on Coll 2-1 and COMP level in patients with early and middle stage knee osteoarthritis," *Orthopaedics*, vol. 9, no. 4, pp. 302–305, 2018.

[36] Z. C. Liu, J. Song, and Q. L. Zhang, "Extracorporeal shock wave therapy versus intra-articular injection of sodium hyaluronate for knee osteoarthritis," *Chinese Journal of Tissue Engineering Research*, vol. 23, no. 15, pp. 2297–2302, 2019.

[37] P. Lizis, W. Kobza, and G. Manko, "Extracorporeal shockwave therapy vs. kinesiotherapy for osteoarthritis of the knee: a pilot randomized controlled trial," *Journal of back and musculoskeletal rehabilitation*, vol. 30, no. 5, pp. 1121–1128, 2017.

[38] S. Qi, X. H. Li, X. Q. Wu, and X. B. Lu, "The effect of extracorporeal shock wave combined with thermal moxibustion on knee osteoarthritis," *Chinese Journal of Physical Medicine and Rehabilitation*, vol. 37, no. 2, pp. 120–122, 2015.

[39] W. Z. Su, Y. Lin, G. Wang et al., "Prospective clinical study on extracorporeal shock wave therapy combined with plateletrich plasma injection for knee osteoarthritis," *Chinese Journal of Reparative and Reconstructive Surgery*, vol. 33, no. 12, pp. 1–5, 2019.

[40] W. Z. Su, Y. J. Lin, G. W. Wang, and Z. Geng, "Therapeutic efficacy of extracorporeal shock wave therapy combined with sodium hyaluronate injection on knee osteoarthritis," *Chinese Journal of Anatomy and Clinics*, vol. 23, no. 5, pp. 418–421, 2018.

[41] L. L. Wang, Y. Dong, S. Liang et al., "et alClinical application of radial shock wave therapy in knee osteoarthritis," *The Journal of Cervicodynia And Lumbodynia*, vol. 37, no. 4, pp. 354-355, 2016.

[42] Y. Wei, *Clinical efficacy of extracorporeal shock wave combined with manipulation in the treatment of knee osteoarthritis*, Guangxi University of Chinese Medicine, 2018.

[43] T. Y. Wu, X. Zhao, and Y. Guo, "Evaluation of the effect of extracorporeal shock wave on early and middle stage osteoarthritis," *Psychological Doctor*, vol. 24, no. 27, pp. 121-122, 2018.

[44] W. Wu, L. Ye, B. J. Zheng et al., "Efficacy and safety of extracorporea I shock wave therapy for knee osteoarthritis," *Shanghai Medical Journal*, vol. 37, no. 8, pp. 669–672, 2014.

[45] B. Z. Xie, D. D. Li, N. Yin, and Z. W. Wang, "A clinical study on treating knee osteoarthritis in early and middle stage by fumigation with Pingle Xitongning plus shock wave," *Clinical Journal of Chinese Medicine*, vol. 11, no. 25, pp. 109–111, 2019.

[46] Z. W. Yang Qinxian, C. Cuiping, C. Zhe, and T. Yongsheng, "A clinical study on treating knee osteoarthritis by extracorporeal shock wave plus TCM medicine fumigation," *Clinical Journal of Chinese Medicine*, vol. 9, no. 35, pp. 81–83, 2017.

[47] T. Zhang, W. B. Liu, H. Li, and L. Xiao, "The clinical study of radial shock wave therapy in the treatment of knee osteoarthritis," *Medical Innovation of China*, vol. 14, no. 30, pp. 36–40, 2017.

[48] A. Q. Zhao, W. L. Xie, and Y. Wang, "Effect of extracorporeal shock wave on the level of chemerin in serum and synovia in patients with knee osteoarthritis," *Medical Journal of Southeast China*, vol. 18, no. 5, pp. 498–500, 2016.

[49] Z. Zhao, R. Jing, Z. Shi, B. Zhao, Q. Ai, and G. Xing, "Efficacy of extracorporeal shockwave therapy for knee osteoarthritis: a randomized controlled trial," *Journal of Surgical Research*, vol. 185, no. 2, pp. 661–666, 2013.

[50] L. Zheng, *Analysis of the short-term effect of the treatment on knee osteoarthritis by extracorporeal shock wave*, Wannan Medical College, 2016.

[51] Z. Zhong, B. Liu, G. Liu et al., "A randomized controlled trial on the effects of low-dose extracorporeal shockwave therapy in patients with knee osteoarthritis," *Archives of Physical Medicine and Rehabilitation*, vol. 100, no. 9, pp. 1695–1702, 2019.

[52] Z. Y. Zhong, G. H. Liu, W. Q. Gu et al., "Clinical curative effect of radial extracorporeal shock wave therapy combined with muscle strengthening exercise on mild to moderate knee osteoarthritis," *Geriatric Health Care*, vol. 24, no. 5, pp. 490–493, 2018.

[53] A. Akinci, M. Al Shaker, M. H. Chang et al., "Predictive factors and clinical biomarkers for treatment in patients with chronic pain caused by osteoarthritis with a central sensitisation component," *International Journal of Clinical Practice*, vol. 70, no. 1, pp. 31–44, 2016.

[54] S. Ashford and J. Williard, "Osteoarthritis: a review," *The Nurse Practitioner*, vol. 39, no. 5, pp. 1–8, 2014.

[55] A. Litwic, M. H. Edwards, E. M. Dennison, and C. Cooper, "Epidemiology and burden of osteoarthritis," *British Medical Bulletin*, vol. 105, pp. 185–199, 2013.

[56] T. E. McAlindon, R. R. Bannuru, M. C. Sullivan et al., "OARSI guidelines for the non-surgical management of knee osteoarthritis," *Osteoarthritis and Cartilage*, vol. 22, no. 3, pp. 363–388, 2014.

[57] S. M. Hussain, D. W. Neilly, S. Baliga, S. Patil, and R. Meek, "Knee osteoarthritis: a review of management options," *Scottish Medical Journal*, vol. 61, no. 1, pp. 7–16, 2016.

[58] C. Sostres, C. J. Gargallo, and A. Lanas, "Nonsteroidal anti-inflammatory drugs and upper and lower gastrointestinal mucosal damage," *Arthritis Research & Therapy*, vol. 15, Supplement 3, p. S3, 2013.

[59] E. M. Ilieva, M. Gonkova, I. Todorova, and R. Minchev, "New field of application of radial shock wave therapy - osteoarthritis," *Annals of Physical and Rehabilitation Medicine*, vol. 57, article e268, 2014.

[60] M. Imamura, S. Alamino, W. Hsing, F. Alfieri, C. Schmitz, and L. Battistella, "Radial extracorporeal shock wave therapy for disabling pain due to severe primary knee osteoarthritis," *Journal of rehabilitation medicine*, vol. 49, no. 1, pp. 54–62, 2017.

[61] J.-H. Kim, J.-Y. Kim, C.-M. Choi et al., "The dose-related effects of extracorporeal shock wave therapy for knee osteoarthritis," *Annals of Rehabilitation Medicine*, vol. 39, no. 4, pp. 616–623, 2015.

[62] J. Zwerver, C. Waugh, H. van der Worp, and A. Scott, "Can shockwave therapy improve tendon metabolism?," *Advances in Experimental Medicine and Biology*, vol. 920, pp. 275–281, 2016.

[63] J.-H. Cheng and C.-J. Wang, "Biological mechanism of shockwave in bone," *International Journal of Surgery*, vol. 24, no. Part B, pp. 143–146, 2015.

[64] C. J. Wang, J. H. Cheng, W. Y. Chou, S. L. Hsu, J. H. Chen, and C. Y. Huang, "Changes of articular cartilage and subchondral bone after extracorporeal shockwave therapy in osteoarthritis of the knee," *International Journal of Medical Sciences*, vol. 14, no. 3, pp. 213–223, 2017.

[65] Q. Ji and C. He, "Extracorporeal shockwave therapy promotes chondrogenesis in cartilage tissue engineering: a hypothesis based on previous evidence," *Medical Hypotheses*, vol. 91, pp. 9–15, 2016.

[66] C.-J. Wang, F.-S. Wang, K. D. Yang et al., "Shock wave therapy induces neovascularization at the tendon–bone junction: a study in rabbits," *Journal of Orthopaedic Research*, vol. 21, no. 6, pp. 984–989, 2003.

[67] F. S. Wang, C. J. Wang, Y. J. Chen et al., "Ras induction of superoxide activates ERK-dependent angiogenic transcription factor HIF-1alpha and VEGF-A expression in shock wave-stimulated osteoblasts," *The Journal of Biological Chemistry*, vol. 279, no. 11, pp. 10331–10337, 2004.

[68] L. Martini, G. Giavaresi, M. Fini et al., "Effect of extracorporeal shock wave therapy on osteoblastlike cells," *Clinical Orthopaedics and Related Research*, vol. 413, pp. 269–280, 2003.

[69] C. V. B. de Gusmão, N. A. Batista, V. T. V. Lemes et al., "Effect of Low-Intensity Pulsed Ultrasound Stimulation, Extracorporeal Shockwaves and Radial Pressure Waves on Akt, BMP-2, ERK-2, FAK and TGF-β1 During Bone Healing in Rat Tibial Defects," *Ultrasound in Medicine & Biology*, vol. 45, no. 8, pp. 2140–2161, 2019.

[70] E. Suzuki, H. Ochiai-Shino, H. Aoki et al., "Akt activation is required for TGF-β1-induced osteoblast differentiation of MC3T3-E1 pre-osteoblasts," *PLoS One*, vol. 9, no. 12, article e112566, 2014.

[71] C. J. Wang, K. D. Yang, J. Y. Ko, C. C. Huang, H. Y. Huang, and F. S. Wang, "The effects of shockwave on bone healing and systemic concentrations of nitric oxide (NO), TGF-beta1, VEGF and BMP-2 in long bone non-unions," *Nitric Oxide*, vol. 20, no. 4, pp. 298–303, 2009.

[72] S.-L. Hsu, J.-H. Cheng, C.-J. Wang, J. Y. Ko, and C. H. Hsu, "Extracorporeal shockwave therapy enhances expression of Pdia-3 which is a key factor of the 1α,25-dihydroxyvitamin D 3 rapid membrane signaling pathway in treatment of early osteoarthritis of the knee," *International Journal of Medical Sciences*, vol. 14, no. 12, pp. 1220–1230, 2017.

[73] J. Chen, C. R. Dosier, J. H. Park et al., "Mineralization of three-dimensional osteoblast cultures is enhanced by the interaction of 1α,25-dihydroxyvitamin D3 and BMP2 via two specific vitamin D receptors," *Journal of Tissue Engineering and Regenerative Medicine*, vol. 10, no. 1, pp. 40–51, 2016.

[74] H. Zhang, Z. L. Li, F. Yang et al., "Radial shockwave treatment promotes human mesenchymal stem cell self-renewal and enhances cartilage healing," *Stem Cell Research & Therapy*, vol. 9, no. 1, p. 54, 2018.

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Research Article

Efficacy of Combination Therapies on Neck Pain and Muscle Tenderness in Male Patients with Upper Trapezius Active Myofascial Trigger Points

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Myofascial pain syndrome, thought to be the main cause of neck pain and shoulder muscle tenderness in the working population, is characterized by myofascial trigger points (MTrPs). This study aimed to examine the immediate and short-term effect of the combination of two therapeutic techniques for improving neck pain and muscle tenderness in male patients with upper trapezius active MTrPs. This study was a pretest-posttest single-blinded randomized controlled trial. Sixty male subjects with mechanical neck pain due to upper trapezius active MTrPs were recruited and randomly allocated into group A, which received muscle energy technique (MET) and ischemic compression technique (ICT) along with conventional intervention; group B, which received all the interventions of group A except ICT; and group C, which received conventional treatment only. Baseline (Pr), immediate postintervention (Po), and 2-week follow-up (Fo) measurements were made for all variables. Pain intensity and pressure pain threshold (PPT) were assessed by a visual analog scale (VAS) and pressure threshold meter, respectively. All the three groups received their defined intervention plans only. Repeated-measures analysis of variance was used to perform intra- and intergroup analyses. Cohen's d test was used to assess the effect size of the applied interventions within the groups. The intergroup analysis revealed significant differences among groups A, B, and C in VAS and PPT at Po (VAS-Po: $F = 13.88$, $p = 0.0001$; PPT-Po: $F = 17.17$, $p = 0.0001$) and even after 2 weeks of follow-up (VAS-Fo: $F = 222.35$, $p = 0.0001$; PPT-Fo: $F = 147.70$, $p = 0.0001$). Cohen's d revealed a significant treatment effect size within all groups except group C (only significant for VAS-Po–VAS-Pr: mean difference = 1.33, $p < 0.05$, $d = 1.09$); however, it showed a maximum effect size in group A for its variables (VAS-Fo–VAS-Pr: mean difference = 5.27, $p = 0.01$, $d = 4.04$; PPT-Fo–PPT-Pr: mean difference = 2.14, $p < 0.01$, $d = 3.89$). Combination therapies (MET plus ICT) showed immediate and short-term (2-week follow-up) improvements in neck pain and muscle tenderness in male patients with upper trapezius active MTrPs.

1. Introduction

Working and other age groups are more prone to musculoskeletal disorders that can result in disability [1, 2]. Work-related or entertaining activities that yield repetitive stress on or microtears in a definite muscle or muscle group cause chronic tension in muscle fibers, leading to the formation of trigger points [3]. Impelling activities include holding a telephone receiver between the ear and shoulder to free arms; bouts of bending, sitting with improper back support, inadequate chair arm rest heights; and moving boxes using poor body mechanics [4]. Postural muscles such as the upper trapezius, pelvic girdle muscles, and quadratus lumborum are often affected [5].

A very common painful muscle disorder is caused by myofascial trigger point (MTrP). MTrP is characterized by the presence of a taut band, a hypersensitive painful focus that on compression produces referred sensation,

tenderness, motor dysfunction, and autonomic phenomena [6–8]. A trigger point is described as active or latent, depending on its reproduction of clinical symptoms rather than the presence of spontaneous pain [8]. The trigger point that upon compression, either partially or completely, reproduces a familiarized symptom experienced by the patient although it may not be present at the time of examination is considered as an active trigger point; however, the latent TrPs do not reproduce any familiarized clinical presentation experienced by the patients [8–10].

Furthermore, Sonographic methods including sonoelastography, MTrP area, and pulsatility index and mechanosensitivity have been introduced to differentiate between active (higher stiffness and lower PPT) and latent MTrPs [11]. No valid imaging or laboratory tests are available to confirm the presence of MTrPs rather than sonography and palpation methods (flat/pincer palpation) [11]. Palpation method is very common and readily identified by a trained examiner. The diagnosis is made by suspecting the possibility of myofascial pain syndrome (MPS) from the history and then confirming it by identifying the MTrP on a physical examination [10].

Simon [5] suggested that a therapeutic approach that effectively inactivates tender points should constructively impact the trigger points as well. Hence, the management lines have included the application of various electrical modalities, different types of exercises, and manual techniques to produce the immediate effect on reducing neck pain and desensitizing the MTrPs. These applications of hot packs (moist heat), ultrasonic/laser/microwaves/infrared radiation therapies, transcutaneous electrical nerve stimulation, stretching/strengthening exercises, manual techniques (muscle energy technique [MET]/ischemic compression technique [ICT]), and myofascial release techniques (strain-counterstrain [SCS]/integrated neuroinhibitory technique [INIT]) involved in lengthening of shortened or contracted muscle and strengthening of muscles aid the drainage of fluid or blood, improve the range of motion of a stiff joint, and accentuate the relaxation of the contractile component of the muscles [5, 12–15].

The ischemic compression technique involves the direct application of a sustained digital/mechanical pressure over the trigger point with enough strength for a specific time duration, to blockade the blood flow and relieve tension in the area of muscle involved [14, 15]. A widely accepted explanation for the working mechanism behind the therapeutic benefit of ischemic compression is the resurgence of local blood flow upon sudden release of digital pressure, most probably from the spinal reflex mechanism [14, 16]. In addition, the longitudinal elongation of contracted sarcomeres of taut band which results in reducing pain and increasing pressure pain threshold of MTrPs is achieved through the application of ICT as equally achieved by the application of transverse friction massage [5, 16, 17].

The muscle energy technique is an osteopathic treatment technique used to lengthen the soft-tissue tightness [13]. The effective working mechanism of MET follows the postisometric relaxation principle in lengthening the contracted sarcomeres within the taut band that desensitizes the hypersensitive TrPs and, thus, reduces the pain and muscle tenderness in patients with neck pain [13, 17, 18].

Previously, few systematic review studies recommended the application of ICT after dry needling therapy, ICT followed by sustained stretching, and ICT with dry cupping as the most effective treatment option to improve neck pain and inactivate the upper trapezius trigger points [16, 17, 19, 20]. Additionally, researchers advocated that clinical evidence also supports this assumption, especially when the positional release technique is combined with other approaches such as ICT and MET, which have good track records for trigger point deactivation [13]. Therefore, Iqbal et al. [21, 22] and other research associates [14, 15] worked on this assumptions and reported the beneficial effect of the combination of two manual techniques on managing neck pain and upper trapezius muscle tenderness in male patients with MTrPs [21, 22].

MET used alone or in combination with SCS was previously proven effective in immediate, short-term, and long-term management of neck pain caused by active MTrPs of the upper trapezius muscle [14, 15, 22, 23]. However, no studies to date have attempted to reveal the effectiveness of MET combined with ICT for short-term or complete resolution of neck pain and muscle tenderness due to upper trapezius active MTrPs. Therefore, the objective of this study was to determine the immediate and short-term effects of MET combined with ICT for improving neck pain and muscle tenderness in male patients with upper trapezius active MTrPs.

The hypothesis of this study was that the efficacy of MET would be greater when combined with ICT than when used alone to improve neck pain and muscle tenderness in male patients with upper trapezius active MTrPs.

2. Material and Methods

2.1. Participants. Sixty male subjects with neck pain and muscle aches over the shoulder girdle were screened for inclusion in the study (Shah Physiotherapy Center, Delhi). Those patients who met the inclusion criteria for clinically active palpable MTrPs in a unilateral upper trapezius muscle were recruited. The inclusion criteria were as follows: male subject diagnosed with nonspecific neck pain [24] and muscle tenderness over the upper trapezius muscle due to an active MTrP; age 19–38 years; and presence of a maximum of 1-2 active MTrPs in a unilateral upper trapezius muscle.

Patients were excluded when they were diagnosed with fibromyalgia syndrome according to the American College of Rheumatology criteria [25]; had active MTrPs in the bilateral upper trapezius muscles; had a history of whiplash injury or cervical spine surgery; were diagnosed with cervical radiculopathy or myelopathy determined by their primary healthcare physician; had accepted myofascial pain therapy within 1 month before the study; or showed poor cooperation.

2.2. Study Design. This study was a randomized controlled three-arm trial with concealed allocation using http://www.randamization.com to allocate the 60 male participants into

three groups. A convenience sampling was used to collect the sample.

2.3. Ethical Consideration. Ethical approval was provided by the institutional review board, rehabilitation research chair, King Saud University, Saudi Arabia. This study maintained the human rights, monitored the conduct of appropriate research ethics, and was conducted in accordance with the Declaration of Helsinki (1964). As the Shah Physiotherapy Center did not have any institutional review board, approval for collecting the data was taken from the head of the center and IRB approval was granted by our institution (King Saud University), with whom there was a collaboration agreement. Furthermore, the study was registered and made public on ClinicalTrials.gov PRS (ClinicalTrials.gov Identifier: NCT03840473). A written informed consent was obtained from those who voluntarily participated in this study.

2.4. Sample Size. The calculation for sample size to ensure the sufficient power was performed with local software (GPower V. 3.1.9.4). The PPT score with the power of 80% (F-test) and a level of significance value 0.05 (2-tailed) were used for estimating the sample size. With effect size of 0.42, 20 participants in each group were required (total sample = 60).

2.5. Outcomes. Outcomes were muscle tenderness, i.e., pressure pain threshold and pain intensity assessed by a pressure threshold meter, i.e., pressure algometer (Wagner force dial FDK 20) and a visual analog scale (VAS), respectively. The interclass correlation (0.75–0.89, $F = 42.55$, $p < 0.01$) ranged from good to excellent for the interexaminer reliability of the pressure algometer [26–28]. The VAS is a reliable and valid measurement tool for assessing pain intensity in the clinical setup/research area. The VAS is shown on a100-mm horizontal line marked with two notions on either side. The notion at one end reads "no pain (score 0)," while the other end reads "worst pain imaginable (score 100)." The participants were guided to indicate a visible single spot on this horizontal line expressing their present level of pain [29, 30]. The minimal detectable change (MDC) for PPT and VAS scores was found to be 0.413 kg/cm^2 and 0.08 cm respectively [31, 32].

2.6. Procedures. 74 out of 87 subjects were guided to read and sign an informed consent form. Furthermore, 9 subjects did not match the inclusion criteria and 5 subjects dropped out without any reason. 60 subjects who qualified for the inclusion and exclusion criteria were assigned randomly to any of the three groups determined by the online site <http://www.randamization.com>. Irrespective of lab test (not confirmatory test) and MRI test (confirmatory test but much expensive), we follow the standard exploration diagnostic criteria to identify and locate the active MTrPs as described by Simon DG (1999 and 2002), Gerwin RD (1997 and 2014), and Fernández-de-las-Peñas C (2018) in their studies. [4, 8, 10] We considered the following five points to identify and differentiate between active and latent MTrPs: presence of (a) a taut band within the muscle, (b) a hypersensitive tender focus in the taut band, (c) spontaneous pain, (d) local twitch response on snapping palpation, and (e) a referred sensation on palpation [4, 8, 10]. We considered the active MTrPs if they fulfill at least the first three points (a), (b), and (c) and the latent trigger points if they did not fulfill the last two points (d) and (e), thus included and excluded from the study, respectively [8, 10]. PPT and VAS scores were taken just before and 2 minutes after the applied intervention and after 2 weeks of follow-up. Data were collected and sent for analysis. Diagrammatic presentation of study procedures can be understood in Figure 1.

2.7. Measurements. The Wagner force dial FDK 20 was used as a pressure algometer to assess the PPT scores of the MTrPs as suggested by Fischer [26]. The trigger point with the lowest PPT value was chosen as a primary trigger point. The subjects were instructed to indicate the sensation of pressure they felt from changing from one of pressure to one of pain by saying "there"/"yes." Three repeated measurements were obtained by the same assistant, and the mean was used in the analysis. At least a 1-minute gap was added between the two repeated measurements as recommended by Fischer [26]. After taking preintervention data for the PPT, a second application of 2.5 kg/cm^2 of pressure was applied at the rate of 1 kg/cm^2 by the physiotherapist while the subjects were stated to rate their pain on the VAS to evaluate local pain evoked by the application of that amount of pressure [29, 30]. All collected data were sent for analysis.

2.8. Interventions. The interventions were delivered to all groups only one time. Group A received hot packs (75°C) for 20 minutes and active stretching exercises for upper trapezius muscle (slow, 5 repetitions per session, 10-second hold and 10-second relaxation between two repetitions) followed by ICT (90-second hold) and MET (5-second hold, 3-second relaxation by exhalation while reaching the new barrier). Group B received all the exercises of group A except ICT. Control group C received all the exercises of group B except MET. Active stretching exercises were done by all the participants under the supervision of physical therapist. This approach was standardized for all participants.

For the MET, the patient was in a supine position with the cervical spine in the opposite lateral flexion to the treating part so that the upper trapezius muscle fibers were in a lengthened position [22]. The moderate isometric contraction (approximately 75% of maximal) of the upper trapezius muscles was elicited for a period of 5 seconds followed by 3 seconds of relaxation while reaching the new barrier. The technique was repeated four times in each session. Each subject was placed on a full back supported chair without arm rests and completed the maneuver under the therapist's supervision for active stretching.

For the ICT, the patient was in the supine position with the cervical spine in opposite lateral flexion to the treating part so that the upper trapezius muscle fibers were kept in a

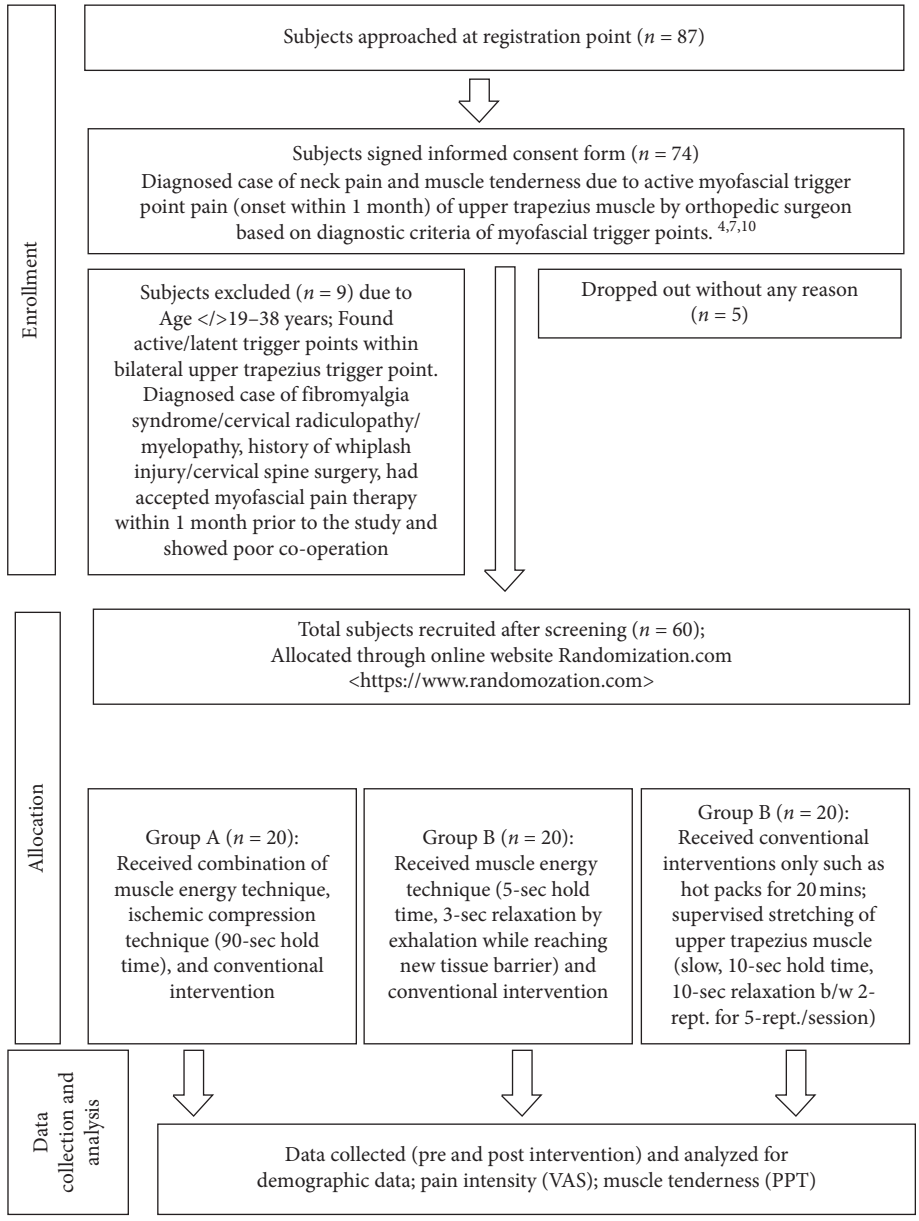

Figure 1: Flowchart of procedures (participant selection, allocation into groups, and data collection).

lengthened position [21, 26]. The physiotherapist applied gradually increasing pressure to the MTrPs until the subject perceived the first noticeable pain. At that moment, the pressure was maintained until the discomfort and/or pain eased by around 50% as perceived by the patient, at which time the pressure was increased until the discomfort appeared again. This process was maintained for 90 seconds.

2.9. Analysis. SPSS version 17.0 software was used for the statistical analyses. Analysis of variance (ANOVA) was used for the inter- and intragroup analyses. In addition, Cohen's d test was used to indicate the treatment difference/effect size between two means (comparison between Po-Pr, Fo-Pr, and Fo-Po) within the groups [33, 34]. The outcome measures were VAS and PPT scores to assess neck pain and muscle tenderness, respectively. The level of significance (α) was set at $p < 0.05$.

3. Results

The results of the statistical analysis for all variables are as follows. There was homogenous distribution of all male participants with respect to their age (between 25 and 38 years) among group A (mean = 32.47 years), group B (mean = 32.13 years), and group C (mean = 32.33 years). Baseline measurements for both neck pain (VAS-Pr) and muscle tenderness, i.e., pressure pain threshold (PPT-Pr), showed insignificant differences ($p > 0.05$) among all groups as described in Table 1.

ANOVA calculated significant differences (F-values and p value) between and within groups for VAS-Po ($F = 13.88$,

Table 1: Intergroup comparison of PPT (kg/cm^2) and VAS (cm) scores.

Variables	Group A mean ± SD	Group B mean ± SD	Group C mean ± SD	F-value	p value
VAS-Pr	6.20 ± 1.71	6.40 ± 1.47	6.33 ± 1.27	0.139	0.870
VAS-Po	3.20 ± 1.67	4.60 ± 1.27	5.00 ± 1.17	13.879	0.0001**
VAS-Fo	0.93 ± 0.69	2.47 ± 1.11	6.20 ± 1.13	222.348	0.0001**
PPT-Pr	1.71 ± 0.48	1.65 ± 0.47	1.67 ± 0.46	0.134	0.875
PPT-Po	2.67 ± 0.77	2.15 ± 0.48	1.81 ± 0.41	17.166	0.0001**
PPT-Fo	3.85 ± 0.63	2.52 ± 0.51	1.60 ± 0.36	147.700	0.0001**

*Significant at $p \leq 0.05$. **Highly significant at $p \leq 0.01$.

$p = 0.0001$), VAS-Fo ($F = 222.35$, $p = 0.0001$), PPT-Po ($F = 17.17$, $p = 0.0001$), and PPT-Fo ($F = 147.70$, $p = 0.0001$) with insignificant differences for VAS-Pr ($F = 0.14$, $p > 0.05$) and PPT-Pr ($F = 0.13$, $p > 0.05$) as described in Table 1.

Furthermore, post hoc (LSD) analysis compared the differences between the groups for all variables as given in Table 2. For VAS-Po, a significant difference was noted between group A and group B (mean difference = −1.40; $p = 0.0002$); group A and group C (mean difference=−1.80; $p = 0.0001$); and group B and group C (mean difference = −0.40; $p = 0.0210$). For VAS-Fo, a significant difference was found between group A and group B (mean difference = -1.53; $p = 0.0001$); group A and group C (mean difference = −5.27; $p = 0.0001$); and group B and group C (mean difference = −3.73; $p = 0.0001$). Similarly, for PPT-Po, a significant difference was detected between group A and group B (mean difference = 0.53; $p = 0.0007$); group A and group C (mean difference = 0.87; $p = 0.0001$); and group B and group C (mean difference = 0. 34; $p = 0.0250$). In addition, for PPT-Fo, a significant difference was revealed between group A and group B (mean difference = 1.33; $p = 0.0001$); group A and group C (mean difference = 2.25; $p = 0.0001$); and group B and group C (mean difference = 0. 92; $p = 0.0001$).

Cohen's d test was applied to assess the immediate and short-term treatment effect sizes within all the three groups for its variables VAS and PPT as follows. Effect size was understood as being large ($d = 0.8$), medium ($d = 0.5$), and small ($d = 0.2$).

3.1. Immediate Effects (Difference between Pre- and Post-intervention within Groups). On neck pain (VAS-Po—VAS-Pr), the treatment effect size was the largest in group A (mean difference = 3.00, $p < 0.01$, $d = 1.77$); larger in group B (mean difference = 1.80; $p < 0.01$; $d = 1.30$); and the smallest in group C (mean difference = 1.33, $p < 0.05$, $d = 1.09$). On muscle tenderness (PPT-Po – PPT-Pr), the treatment effect size was the largest in group A (mean difference = 0.96, $p < 0.01$, $d = 1.49$); larger in group B (mean difference = 0.49, $p < 0.01$, $d = 1.03$); and the smallest in group C (mean difference = 0.14, $p > 0.05$, $d = 0.32$) as described in Table 3.

3.2. Short-Term Effects (Difference between Preintervention and 2-Week Follow-Up). On neck pain (VAS-Fo—VAS-Pr), the treatment effect size was the largest in group A (mean difference=5.27, $p < 0.01$, $d = 4.04$); larger in group B (mean difference = 3.93, $p < 0.01$, $d = 3.02$); and the smallest in group C (mean difference = 0.13, $p > 0.05$, $d = 0.11$). Regarding muscle tenderness (PPT-Fo—PPT-Pr), the treatment effect size was the largest in group A (mean difference = 2.14, $p < 0.01$, $d = 3.89$); larger in group B (mean difference = 0.87, $p < 0.01$, $d = 1.76$); and the smallest in group C (mean difference = 0.07, $p > 0.05$, $d = 0.15$) as described in Table 3.

4. Discussion

This study was intended to determine the immediate and short-term effects of combination therapies on reducing neck pain and muscle tenderness in patients with upper trapezius active MTrPs. All participants in experimental groups A and B and control group C received their specified intervention plan. The results of intergroup revealed that experimental group A yielded the greatest improvement immediately after intervention ($F_{\text{VAS-Po}} = 13.879$, $p < 0.05$) as well as after the 2-week follow-up ($F_{\text{VAS-Fo}} = 222.348$, $p < 0.05$) for all variables. In addition, the intragroup results showed that all of the intervention plans yielded significant improvement immediately after intervention as well as after the 2-week follow-up except control group C for all variables excluding the mean differences between VAS-Pr and VAS-Po, which showed significant improvement (mean difference = 1.33, $p < 0.05$, $d = 1.09$).

The results of this study can be understood with the reports of previous studies declared by Kashyap et al. [23], Iqbal et al. [21, 22], Hong et al. [39], Martín-Pintado-Zugasti et al. [9], Benito-de-Pedro et al. [12], Nasb et al. [41], Hanten et al. [19], Chaitow [13], Fryer and Hodgson [3], Fernández-de-las-Peñas et al. [36], Cagnie et al. [16, 20], Capo-Juan et al. [17], and other researchers. The results achieved by these authors are similar to the results achieved in this study for the combination of two manual techniques (MET plus ICT) in the management of neck pain and muscle tenderness due to upper trapezius active MTrPs.

The concept of relief of neck pain and decreased muscle tenderness (trigger point sensitivity) by MET can be understood through its neurophysiological effect such as inhibitory Golgi tendon reflex and descending pathway of pain modulation theories, anti-inflammatory and vascular effects [13, 18, 35]. MET (isometric contraction of agonist muscles) induces inhibitory Golgi tendon reflex which results in the reflex relaxation of the antagonist muscles. At the same time, the mechanoreceptors available in the joint and muscles get activated which further leads to the excitation of sympathetic system via somatic afferent and activation of the

Table 2: Between-group analysis (LSD a posteriori test) of the variables PPT (kg/cm^2) and VAS (cm) scores.

Dependent variable	(*I*) group	(*J*) group	Mean difference (*I-J*)	Std. error	Sig.
VAS-Po	Group A	Group B	−1.40000-*	0.3588	0.0002
		Group C	−1.80000-*	0.3588	0.0001
	Group B	Group C	−0.40000-*	0.3588	0.0210
VAS-Fo	Group A	Group B	−1.53333-*	0.2569	0.0001
		Group C	−5.26667-*	0.2569	0.0001
	Group B	Group C	−3.73333-*	0.2569	0.0001
PPT-Po	Group A	Group B	0.52667*	0.1491	0.0007
		Group C	0.86667*	0.1491	0.0001
	Group B	Group C	0.34000*	0.1491	0.0250
PPT-Fo	Group A	Group B	1.33333*	0.1318	0.0001
		Group C	2.25333*	0.1318	0.0001
	Group B	Group C	0.92000*	0.1318	0.0001

Table 3: Treatment effect size (Cohen's *d*) within the group for PPT (kg/cm^2) and VAS (cm) scores.

Dependent variable	Group a			Group B			Group C		
	Mean difference	*p* value	Effect size (d^)	Mean difference	*p* value	Effect size (d^)	Mean difference	*p* value	Effect size (d^)
VAS (Po-Pr)	3.00	<0.01**	1.77	1.80	<0.01**	1.30	1.33	<0.05*	1.09
VAS (fo-pr)	5.27	<0.01**	4.04	3.93	<0.01**	3.02	0.13	>0.05	0.11
PPT (Po-Pr)	0.96	<0.01**	1.49	0.49	<0.01**	1.03	0.14	>0.05	0.32
PPT(Fo-pr)	2.14	<0.01**	3.89	0.87	<0.01**	1.76	0.07	>0.05	0.15

*Significant at $p \leq 0.05$. **Highly significant at $p \leq 0.01$. Treatment effect size (d): large if $d = 0.8$, medium if $d = 0.5$, small if $d = 0.2$[33].

periaqueductal gray matter (PEG) which regulate the descending pain modulation [35, 36]. Rhythmic muscle contraction in MET also affects the rate of lymphatic and blood flow that bring the changes in interstitial pressure and increase transcapillary blood flow. Vascular blood flow desensitizes the peripheral nociceptive chemical mediators such as cytokines. [18].

The effects of MET can be also explained through the concept of lengthening of muscle fibers, which would help dictate the length of the affected soft tissues [4, 5, 7]. Lewit and Simons revealed that muscle lengthening utilizing postisometric relaxation seems effective in decreasing the sensitivity of MTrPs pain without the use of vapocoolant spray [37]. Furthermore, there is evolving proof supporting the activation of agonist-antagonist inhibitory pathways with the application of manual intervention [36]. Hence, different mechanisms would probably act at the same time to reduce pain intensity and muscle tenderness due to active MTrPs. Recently, Faqih et al. (2019) conducted a study using MET in patients with postsurgical elbow stiffness and found that the application of MET immediately after postsurgical elbow brought a significant improvement in pain intensity (VAS scores), ROM, and functions (DASH scores) [35]. Kashyap et al. (2018) revealed that the MPR and the MET are equally effective in improving the VAS, PPT, NDI, and range of rotation scores among the participants with nonspecific neck pain due to MTrPs [23]. In addition, our findings have been supported by Iqbal and colleagues (2013), who worked on combination therapies including only male patients and reported that the positional release technique in combination with MET showed immediate and short-term effectiveness in reducing the intensity of neck pain (VAS scores) as well as improving muscle tenderness (PPT scores) and functional status of the neck (NDI scores) in male patients with upper trapezius active MTrPs [22].

The ICT can be described by the concept of the "barrier release" proposed by Lewit (1991), in which the therapist slowly applies pressure to the MTrPs until a conclusive increase in resistance is perceived, i.e., the barrier, which is usually sensed as not being painful by the subject [38]. Hong et al. (1993) proved that prime results in decreasing pain from MTrPs were found with compression techniques used on the deep soft tissue when matching conventional soft-tissue manipulation [39]. Furthermore, Martín-Pintado-Zugasti et al. (2015) revealed that the ICT is effective in reducing post-dry needling soreness intensity and duration when dealing with patients with latent MTrPs [9]. Benito-de-Pedro et al. (2019) conducted a study to assess the immediate effectiveness of both deep dry needling and ICT on PPT and skin temperature in subjects with the latent MTrPs of the triceps surae and reported that the ICT could be more effective in reducing the local mechanosensitivity immediately after the treatment of a latent MTrP [12]. Likewise, Cagnie et al. (2013 and 2015) revealed a significant improvement in the scores of VAS (neck and shoulder pain), PPT, ROM, and muscle strength when applying the ICT among office workers having MTrPs with moderately severe chronic pain. Further, reduction in VAS scores with no change in NDI scores was noticed at 6-month follow-up [16, 20]. Previously, Gemmell et al. (2008) found that ischemic compression is superior to sham ultrasound in immediately reducing pain intensity in patients with nonspecific neck pain and upper trapezius active trigger points [15]. Fryer and Hodgson (2005) have also concluded that ICT was better than the

sham myofascial technique at reducing muscle tenderness in latent MTrPs in the upper trapezius muscle [3].

Thus, the above-mentioned studies revealed that the application of ICT may induce analgesia and improve muscle tenderness (trigger point sensitivity) by the following mechanism. The pressure treatments may cause pain relief as a result of reactive hyperemia in the MTrPs region or act a spinal reflex mechanism for relieving muscle spasms [39]. Local pressure may align sarcomere length in the affected MTrPs and thus reduce pain, while deep pressure could offer effective stretching and mobilization of the taut bands [40]. Fryer and Hodgson (2005) already proved that local muscle tenderness due to MTrPs decreased only because of a change in tissue sensitivity rather than any unintentional release of pressure by the practitioner [3]. Hence, it can be concluded that ICT might be useful for decreasing neck pain (VAS) and improving muscle tenderness (PPT) in patients with upper trapezius active MTrPs.

In addition, combination therapy including ICT has proven to be more effective than the ICT alone, which supports the result of our study. Nasb et al. (2019) reported that the combination of ICT with dry cupping for 4 weeks has shown more effectiveness than either ICT or dry cupping alone in the improvement of PPT, NDI, and ROM scores significantly [41]. Hanten et al. (2000) examined the efficacy of a home program containing ischemic compression followed by sustained stretching over active MTrPs. The results of their study clearly revealed that the combination of these techniques was more effective in decreasing the muscle tenderness due to MTrPs [19]. Similarly, in a previous study (Iqbal et al. 2010) the short-term effect of ICT was also noted when applied in combination with strain-counterstrain in terms of pain relief, muscle tenderness, and functional status of the neck due to upper trapezius active MTrPs [21], thus supporting the findings of our study.

The improvement in the control group is attributed to the effects caused by stretching and hot pack use. Stretching of the affected muscle is believed to be an integral part of trigger point therapy. Jaeger and Reeves (1986), who stated the efficiency of spray and stretch at reducing pain intensity and increasing the pressure pain threshold, point out that vapocoolant spray could not bring anesthesia in the subcutaneous tissues or muscle because of the tissue depth. Therefore, they suggested that it is the stretch that reduced the pain sensitivity of the trigger points rather than the spray, thus reinforcing the idea that muscle lengthening is the process that offers pain relief [42]. Travell and Simons also argued that the stretch is the mechanism of relief in spray and stretch. They postulated that decreasing MTrPs pain utilizing spray and stretch is due to elongation of the muscle to its full normal length [7]. The patient's active or passive stretching exercises at home are more beneficial when performed during or soon after the application of moist heat [4]. Moist heat tends to relax the underlying muscles and diminish the tension in the trigger point, thus decreasing referred pain and local tenderness in response to pressure [5].

Because group A received both manual techniques such as MET and ICT, followed by conventional interventions such as active stretching and hot water fomentation, the higher benefit in pain relief and muscle tenderness (increased pain pressure threshold) may be credited to the above mechanism described and reinforced by different previous studies [12, 14, 15, 18–23, 35, 39–43]. However, MET alone and active stretching exercises were effective in group B but significantly less than in group A.

4.1. Limitations. This study included only male participants. We proposed to conduct a similar study among females through collaboration with female researchers and compare the results with current study. For this reason, the result of this study cannot be generalized for the female population of the same conditions. In addition, there was lack of advanced technology for measuring either the force of muscle contraction or amount of pressure required to stretch the muscle fibers/compress the trigger points to neutralize the MTrP pain. Moreover, only the immediate and short-term effect of combined manual therapies was assessed on unilateral upper trapezius MTrPs pain and muscle tenderness. Therefore, the above-mentioned shortcomings should be addressed by conducting a study on long-term effectiveness (12-week follow-up) of these combination techniques in bilateral upper trapezius MTrPs pain and muscle tenderness using advanced tools such as isokinetic machine and finger pressure algometer to execute an accurate and definitive amount of muscle contraction and application of pressure, respectively.

5. Conclusion

This study validated our hypothesis and concluded that MET plus ICT is more efficacious than MET alone in reducing neck pain and muscle tenderness in male patients with upper trapezius active MTrPs. Its immediate and short-term effects established this combination therapy as a prime treatment plan in the clinical setting to counteract the neck pain and muscle tenderness due to active MTrPs.

The clinical relevance of our findings to practice is that MET plus ICT is highly effective in dismissing MTrPs pain within a very brief period of time, is cost effective, is noninvasive, and achieves relief without causing much pain.

Abbreviations

MPS: Myofascial pain syndrome
MTrP: Myofascial trigger point
VAS: Visual analog scale
PPT: Pressure pain threshold
MET: Muscle energy technique
ICT: Ischemic compression technique

Data Availability

The dataset supporting the conclusions of this article is available through the corresponding author on reasonable request.

Conflicts of Interest

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Authors' Contributions

All authors contributed to the research design, data collection, data analysis, and manuscript formatting, drafting, and critical revision; gave final approval of the version to be published; and agreed to be held responsible for all facets of the work.

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References

[1] V. Occhionero, L. Korpinen, and F. Gobba, "Upper limb musculoskeletal disorders in healthcare personnel," *Ergonomics*, vol. 57, no. 8, pp. 1166–1191, 2014.

[2] S. Y. Wang, L. C. Liu, M. C. Lu, and M. Koo, "Comparisons of musculoskeletal disorders among ten different medical professions in Taiwan: a nationwide, population-based study," *PLoS One*, vol. 10, no. 4, Article ID e0123750, 2015.

[3] G. Fryer and L. Hodgson, "The effect of manual pressure release on myofascial trigger points in the upper trapezius muscle," *Journal of Bodywork and Movement Therapies*, vol. 9, no. 4, pp. 248–255, 2005.

[4] D. G. Simons, J. G. Travell, and L. S. Simons, *Travell & Simons' Myofascial Pain and Dysfunction: Upper Half of Body*, Lippincott Williams & Wilkins, Philadelphia, PA, USA, 1999.

[5] D. G. Simons, "Understanding effective treatments of myofascial trigger points," *Journal of Bodywork and Movement Therapies*, vol. 6, no. 2, pp. 81–88, 2002.

[6] C.-Z. Hong and T.-C. Hsueh, "Difference in pain relief after trigger point injections in myofascial pain patients with and without fibromyalgia," *Archives of Physical Medicine and Rehabilitation*, vol. 77, no. 11, pp. 1161–1166, 1996.

[7] R. D. Gerwin, S. Shannon, C. Z. Hong, D. Hubbard, and R. Gevirtz, "Interrater reliability in myofascial trigger point examination," *Pain*, vol. 69, no. 1-2, pp. 65–73, 1997.

[8] C. Fernández-de-las-Peñas and J. Dommerholt, "International consensus on diagnostic criteria and clinical considerations of myofascial trigger points: a Delphi study," *Pain Medicine*, vol. 19, no. 1, pp. 142–150, 2017.

[9] A. Martín-Pintado-Zugasti, D. Pecos-Martin, Áodrí Rodríguez-Fernández et al., "Ischemic compression after dry needling of a latent myofascial trigger point reduces postneedling soreness intensity and duration," *PM&R*, vol. 7, no. 10, pp. 1026–1034, 20151.

[10] R. D. Gerwin, "Diagnosis of myofascial pain syndrome," *Physical Medicine and Rehabilitation Clinics of North America*, vol. 25, no. 2, pp. 341–355, 2014.

[11] C. Calvo-Lobo, I. Diez-Vega, B. Martínez-Pascual et al., "Tensiomyography, sonoelastography, and mechanosensitivity differences between active, latent, and control low back myofascial trigger points: a cross-sectional study," *Medicine*, vol. 96, no. 10, 2017.

[12] M. Benito-de-Pedro, R. Becerro-de-Bengoa-Vallejo, M. E. Losa-Iglesias et al., "Effectiveness between dry needling and ischemic compression in the triceps surae latent myofascial trigger points of triathletes on pressure pain threshold and thermography: a single blinded randomized clinical trial," *Journal of Clinical Medicine*, vol. 8, no. 10, p. 1632, 2019.

[13] L. Chaitow, *Positional Release Techniques*, Churchill Livingstone, Elsevier, London, UK, 4th edition, 2015.

[14] C.-R. Hou, L.-C. Tsai, K.-F. Cheng, K.-C. Chung, and C.-Z. Hong, "Immediate effects of various physical therapeutic modalities on cervical myofascial pain and trigger-point sensitivity," *Archives of Physical Medicine and Rehabilitation*, vol. 83, no. 10, pp. 1406–1414, 2002.

[15] H. Gemmell, P. Miller, and H. Nordstrom, "Immediate effect of ischaemic compression and trigger point pressure release on neck pain and upper trapezius trigger points: a randomised controlled trial," *Clinical Chiropractic*, vol. 11, no. 1, pp. 30–36, 2008.

[16] B. Cagnie, B. Castelein, F. Pollie, L. Steelant, H. Verhoeyen, and A. Cools, "Evidence for the use of ischemic compression and dry needling in the management of trigger points of the upper trapezius in patients with neck pain," *American Journal of Physical Medicine & Rehabilitation*, vol. 94, no. 7, pp. 573–583, 2015.

[17] M. A. Capo-Juan, "Cervical myofascial pain syndrome. Narrative review of physiotherapeutic treatment," *An Sist Sanit Navar*, vol. 38, no. 1, pp. 105–115, 2015.

[18] G. Fryer, "Muscle energy technique: an evidence-informed approach," *International Journal of Osteopathic Medicine*, vol. 14, no. 1, pp. 3–9, 2011.

[19] W. P. Hanten, S. L. Olson, N. L. Butts, and A. L. Nowicki, "Effectiveness of a home program of ischemic pressure followed by sustained stretch for treatment of myofascial trigger points," *Physical Therapy*, vol. 80, no. 10, pp. 997–1003, 2000.

[20] B. Cagnie, V. Dewitte, I. Coppieters, J. Van Oosterwijck, A. Cools, and L. Danneels, "Effect of ischemic compression on trigger points in the neck and shoulder muscles in office workers: a cohort study," *Journal of Manipulative and Physiological Therapeutics*, vol. 36, no. 8, pp. 482–489, 2013.

[21] A. Iqbal, S. A. Khan, and M. Miraj, "Efficacy of ischaemic compression technique in combination with strain-counterstrain technique in managing upper trapezius myofascial trigger point pain," *The Indian Journal of Physiotherapy & Occupational Therapy*, vol. 4, no. 2, pp. 10–15, 2010.

[22] A. Iqbal, H. Ahmed, and A. Shaphe, "Efficacy of muscle energy technique in combination with strain-counterstrain technique on deactivation of trigger point pain," *Indian Journal of Physiotherapy and Occupational Therapy—An International Journal*, vol. 7, no. 3, pp. 118–123, 2013.

[23] R. Kashyap, A. Iqbal, and A. H. Alghadir, "Controlled intervention to compare the efficacies of manual pressure release and the muscle energy technique for treating mechanical neck pain due to upper trapezius trigger points," *Journal of Pain Research*, vol. 11, pp. 3151–3160, 2018.

[24] C. Fernández-de-las-Peñas, C. Alonso-Blanco, and J. C. Miangolarra, "Myofascial trigger points in subjects presenting with mechanical neck pain: a blinded, controlled study," *Manual Therapy*, vol. 12, no. 1, pp. 29–33, 2007.

[25] F. Wolfe, D. J. Clauw, M.-A. Fitzcharles et al., "The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity," *Arthritis Care & Research*, vol. 62, no. 5, pp. 600–610, 2010.

[26] A. A. Fischer, "Pressure algometry over normal muscles. Standard values, validity and reproducibility of pressure threshold," *Pain*, vol. 30, no. 1, pp. 115–126, 1987.

[27] J. A. Hogeweg, M. J. Langereis, A. T. Bernards, J. A. Faber, and P. J. Helders, "Algometry. Measuring pain threshold, method and characteristics in healthy subjects," *Scandinavian Journal of Rehabilitation Medicine*, vol. 24, no. 24, pp. 99–103, 1992.

[28] L. Vanderweeën, R. A. B. Oostendorp, P. Vaes, and W. Duquet, "Pressure algometry in manual therapy," *Manual Therapy*, vol. 1, no. 5, pp. 258–265, 1996.

[29] M. P. Jensen, J. A. Turner, J. M. Romano, and L. D. Fisher, "Comparative reliability and validity of chronic pain intensity measures," *Pain*, vol. 83, no. 2, pp. 157–162, 1999.

[30] G. A. Hawker, S. Mian, T. Kendzerska, and M. French, "Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF)," *Arthritis Care & Research*, vol. 63, no. 11, pp. S240–S252, 2011.

[31] T. K. Koo, J.-Y. Guo, and C. M. Brown, "Test-retest reliability, repeatability, and sensitivity of an automated deformation-controlled indentation on pressure pain threshold measurement," *Journal of Manipulative and Physiological Therapeutics*, vol. 36, no. 2, pp. 84–90, 2013.

[32] A. Alghadir, S. Anwer, A. Iqbal, and Z. Iqbal, "Test–retest reliability, validity, and minimum detectable change of visual analog, numerical rating, and verbal rating scales for measurement of osteoarthritic knee pain," *Journal of Pain Research*, vol. 11, pp. 851–856, 2018.

[33] J. Cohen, *Statistical Power Analysis for the Behavioral Sciences*, Routledge, Abingdon, UK, 2nd edition, 1988.

[34] J. Cohen, "Statistical power analysis," *Current Directions in Psychological Science*, vol. 1, no. 3, pp. 98–101, 1992.

[35] A. I. Faqih, N. Bedekar, A. Shyam, and P. Sancheti, "Effects of muscle energy technique on pain, range of motion and function in patients with post-surgical elbow stiffness: a randomized controlled trial," *Hong Kong Physiotherapy Journal*, vol. 39, no. 1, pp. 25–33, 2019.

[36] C. Fernández de las Peñas, M. Sohrbeck Campo, J. Fernández Carnero, and J. C. Miangolarra Page, "Manual therapies in the myofascial trigger point treatment: a systematic review," *Journal of Bodywork and Movement Therapies*, vol. 9, no. 1, pp. 27–34, 2005.

[37] K. Lewit and D. G. Simons, "Myofascial pain: relief by post-isometric relaxation," *Archives of Physical Medicine and Rehabilitation*, vol. 65, no. 65, pp. 452–456, 1984.

[38] K. Lewit, *Manipulative Therapy in Rehabilitation of the Locomotor System*, Butterworth Heinemann, Oxford, UK, Second edition, 1991.

[39] C.-Z. Hong, Y.-C. Chen, C. H. Pon, and J. Yu, "Immediate effects of various physical medicine modalities on pain threshold of an active myofascial trigger point," *Journal of Musculoskeletal Pain*, vol. 1, no. 2, pp. 37–53, 1993.

[40] A. Blikstad and H. Gemmell, "Immediate effect of activator trigger point therapy and myofascial band therapy on non-specific neck pain in patients with upper trapezius trigger points compared to sham ultrasound: a randomised controlled trial," *Clinical Chiropractic*, vol. 11, no. 1, pp. 23–29, 2008.

[41] M. Nasb, X. Qun, C. R. Withanage, X. Lingfeng, and C. Hong, "Dry cupping, ischemic compression, or their combination for the treatment of trigger points: a pilot randomized trial," *The Journal of Alternative and Complementary Medicine*, vol. 26, no. 1, 2019.

[42] B. Jaeger and J. L. Reeves, "Quantification of changes in myofascial trigger point sensitivity with the pressure algometer following passive stretch," *Pain*, vol. 27, no. 2, pp. 203–210, 1986.

[43] S. Zamani, F. Okhovatian, S. Naimi, and A. Akbarzadeh, "The immediate effect of a combination of pressure release and cervical mobilization techniques on the active range of motion in the latent trigger points of upper trapezius muscle in young adult females," *Austin Physical Medicine*, vol. 1, no. 1, p. 1002, 2017.

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Clinical Study

Effect of Tai Chi Training on Plantar Loads during Walking in Individuals with Knee Osteoarthritis

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Tai Chi is an available method for the treatment of knee osteoarthritis (KOA). The impacts of Tai Chi on plantar loads of individuals with KOA are not fully understood. 46 participants with knee osteoarthritis were randomly assigned into the Tai Chi group ($n = 23$) or the control group ($n = 23$). The Tai Chi group attended a 6-month Tai Chi program, and the control group participated in a wellness education program. Novel Pedar-X system was used to collect the peak pressure (PP) and maximum force (MF) during walking before and 6 months after the intervention. Significant higher peak pressure and maximum force were observed in the 4th and 5th metatarsophalangeal joints in the Tai Chi group. However, there were significant declines in the peak pressure of the whole foot and the 2nd and 3rd metatarsophalangeal joints and maximum force of the heel in the control group. These results suggested that individuals with KOA might change the pattern of plantar loads during walking through Tai Chi, and plantar loads would be useful as a parameter to assess the effect of Tai Chi on knee osteoarthritis. This trial is registered with Clinical Trials: CHiCTR-TRC-13003264.

1. Introduction

Knee osteoarthritis (KOA) is a chronic musculoskeletal disorder resulting in pain, disability, and decreased quality of life [1, 2]. More than 70% of population aged 65 years or older suffers from symptomatic KOA [3]. The overall costs spent on treating KOA cause a large economic burden on individuals [4]. Females are more likely to suffer from KOA than males [5, 6].

Nonpharmacological and nonsurgical interventions can reduce pain and improve physical function in patients with knee OA [7]. Some previous studies show the effectiveness of some interventions such as traditional Chinese medicine (auriculotherapy, acupuncture) and whole body vibration [8], orthotic devises [9], and electrical stimulation [10]. In addition, a systematic review of guidelines for the management of osteoarthritis proposes that exercise is a key factor for treating OA [11].

Exercise and physical therapies are recommended for nonpharmacological management of KOA [12–14]. Thus, selecting an appropriate form of exercise and physical therapies for females with KOA is vital in treating such condition.

The feet are the only segment of the human body that contacts the external environment directly during walking. Foot plantar load is the pressure field that acts between the support surface and the foot during walking [15]. The typical applications of plantar loads are injury prevention [16], footwear design [17], and sport performance [18]. Some studies [19, 20] had revealed that the ankle may play a compensatory role in individuals with KOA to relieve the pain or discomfort during walking, and loading patterns in the feet were related to KOA [21]. Zhang et al. [22] found that peak pressure and maximum force were significantly different from KOA females in midfoot and forefoot when compared with normal females. Rosland et al. [23] also reveal that maximum force in plantar distribution in individuals with KOA was associated with pain intensity, function, specific pain mechanisms, and radiological findings. Therefore, the management of plantar loads should be a part in the treatment of KOA.

Tai Chi, which is low impact and aerobic, is a form of mind–body therapy [24]. Given that Tai Chi includes many fundamental postures that flow smoothly from one to another [25], it can be an appropriate therapy for old-aged people. Tai Chi is an effective management for individuals

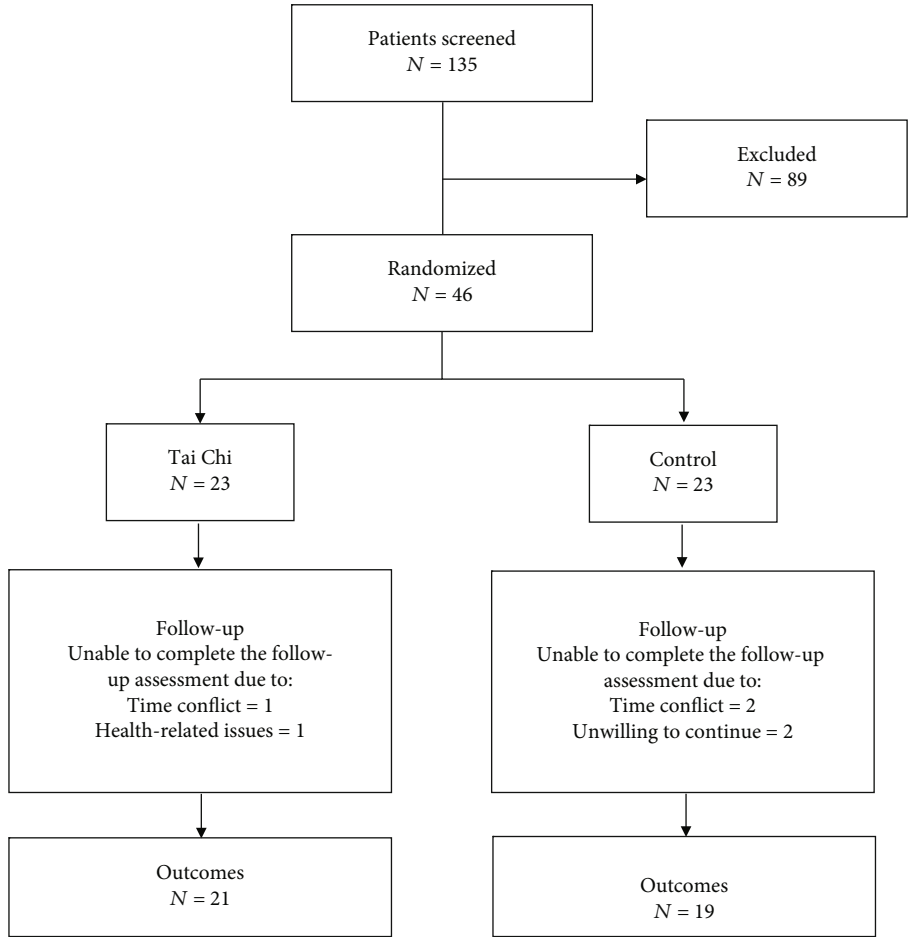

Figure 1: Flowchart explaining assignment of the participants to the Tai Chi and control groups.

with KOA because it can reduce pain and promote muscle endurance [26], motor control, and postural stability [12].

However, most previous biomechanical studies [27, 28] of Tai Chi only focus on pain, physical function, kinematics, and kinetics of the knee joint for KOA, rarely considering plantar loads. Hence, the present study is aimed at investigating the effect of Tai Chi on plantar loads in individuals with KOA after a 6-month Tai Chi exercise program. We hypothesized that participants receiving Tai Chi will show larger plantar loads than participants treated with wellness education.

2. Materials and Methods

2.1. Trial Design. The study was a single-blind randomized trial that investigated the effects of 6-month Tai Chi exercise on plantar loads among individuals with KOA. The Chinese Clinical Trial Registry was CHiCTR-TRC-13003264, and the data of registration was 27/05/2013. The study was approved by the Ethics Committee of Shanghai University of Sport, and the approval document number was 2013-001.

2.2. Participant. Female individuals aged 60–90 years who met the American College of Rheumatology criteria were recruited from three local communities in Yangpu District, Shanghai. The American College of Rheumatology criteria to make a definite diagnosis of KOA is that individuals show pain in the knee plus any three of the following six factors: (1) age more than 50 y, (2) less than 30 min of morning stiffness, (3) presence of crepitus on active motion, (4) bony overgrowth, (5) bony tenderness, and (6) no palpable warmth of synovium [29].

The recruitment began in April 2013, and the baseline assessments were completed in June. The participants with mild to moderate KOA diagnosed by X-ray, pain symptoms for at least 12 weeks, and available for Tai Chi training or health education were included in the study [30]. Participants with surgery planned in the next 6 months, uncontrolled hypertension, cardiovascular diseases, and other illnesses that may affect their walking were excluded. Then, eligible participants were randomly assigned to either the Tai Chi group or the control group by computer. These two groups were blinded with each other. This study had obtained the patients' written informed consents to publish experimental results. The flow diagram of the trial is shown in Figure 1. All work was completed at the Shanghai University of Sport and the Shanghai Shangti Orthopedic Hospital.

2.3. Sample Size. The study was aimed at assessing the efficacy of Tai Chi intervention on plantar loads for women with knee OA. Participation by 17 participants per group

(34 total) would provide 80% power to detect an effect size of 0.8 using a two-sided t-test with alpha = 0.05. Anticipating a 20% dropout rate, 20 participants should be enrolled for each group.

2.4. Interventions. The Tai Chi exercise, which was taught to the participants, was described in a previous study [30]. There were five Tai Chi movements, named brushing knee and twist steps, playing the lute, stepping back to repulse monkey, grasping sparrow's tail, and waving hands like clouds. In the first four weeks of the Tai Chi intervention, the participant was taught Tai Chi for two times per week. Each session included a 10-minute warm-up, learning new movements for 20 minutes, reviewing the learnt movements for 20 minutes, and 10-minute cooling down. In subsequent weeks, the Tai Chi program included a 10-minute warm-up, a 45-minute Tai Chi exercise, and cooling down for 5 minutes. The warm-up and cooling down sections included smooth breathing and gentle stretching of upper limb joints, lower limbs joints, and the trunk. Individuals should have no resistance to move their bodies after the warm-up and become relaxed after the cooling down. Two Tai Chi masters who had 15-year training experience were responsible for the instruction of Tai Chi exercise, and they were blinded to the randomization. The control group participated in a wellness education program. In the first session, research staff explained the aim of the program and procedures of the intervention. A variety of health professionals provided information which included diet and nutrition and mental and physical education (recognizing and dealing with stress and depression) in the following sessions; each session lasted for 60 minutes and was performed once a week for 6 months. This approach was successfully used in other studies [25, 31]. All subjects were encouraged to maintain their usual medication and ways of life.

2.5. Instrument and Measures. Peak pressure (PP) and maximum force (MF) were measured using the Pedar-X system (Novel GmbH, Munich Germany), sampling at 50 Hz. With the aid of the Trublu calibration device, all insoles of the Pedar-X system were calibrated before plantar loading assessment. Participants were required to walk on a 15 m walkway under a stable and comfortable speed, and five trials were recorded at baseline. All plantar loading data were processed with the Novel Multimask Evaluation software (Novel GmbH, Munich, Germany). The plantar foot was divided into seven regions in accordance with plantar anatomy, namely, heel (M1), midfoot (M2), the first metatarsophalangeal joint (M3), the 2nd and 3rd metatarsophalangeal joints (M4), the 4th and 5th metatarsophalangeal joints (M5), hallux (M6), and lessor toes (M7) with a mask (Figure 2) [32]. The data collectors were blind to the result of the random allocation sequence and were unclear about the aim of the study. The baseline data were collected in one week before the formal intervention, and the follow-up assessment was completed in one week after 6-month intervention.

2.6. Statistical Analysis. Independent t-test was used to analyse the differences among the characteristics (age, height, weight, and BMI), PP, and MF, and chi-square distribution was applied to compare the proportions of severity of knee at baseline of the Tai Chi group and the control group. The Shapiro–Wilk test was used for normal distribution to ensure that data distribution did not differ significantly from normal, and homoscedasticity was verified using Levene's test. A two-way ANOVA with repeated measure was used to examine the effects of interventions on plantar loads, including PP and MF of the whole foot and each region. Changes in outcome variables for participants in the Tai Chi and control groups were also determined with paired-samples t test, respectively. Analyses were performed using SPSS 20.0 software, and the significance level was set at 0.05.

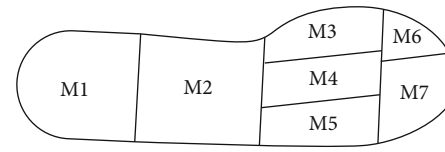

Figure 2: Foot mask. The foot was divided into 7 regions: heel (M1), midfoot (M2), the first metatarsophalangeal joint (M3), the 2nd and 3rd metatarsophalangeal joints (M4), the 4th and 5th metatarsophalangeal joints (M5), hallux (M6), and lessor toes (M7).

Table 1: Participants' characteristics at baseline.

Variable	Tai Chi ($n = 23$)	Control ($n = 23$)	P value
Age (y)	64.6 ± 3.4	64.54 ± 3.4	0.512
Body weight (kg)	58.7 ± 8.3	62.8 ± 9.2	0.191
Height (cm)	154.8 ± 7.6	155.8 ± 4.8	0.689
BMI (kg/m^2)	24.5 ± 3.1	25.9 ± 3.6	0.242
Kellgren-Lawrence grade, n (%)			
1	7 (30)	6 (26)	
2	12 (52)	14 (61)	
3	4 (17)	3 (13)	

Data reported as mean ± standard deviation (SD). There were no significant differences between groups ($P > 0.05$).

3. Results

As shown in Figure 1, a total of 135 elders were recruited, and 89 elders were excluded. Among these individuals who completed the screening, 46 participants were randomly assigned into one of the two groups. Forty subjects completed the follow-up assessment (87%). Two participants in the Tai Chi group did not complete the study, due to time conflict and health-related issues, respectively. Four participants in the control group withdrew from the study, due to time conflict ($n = 2$) and unwillingness ($n = 2$). The characteristics of these subjects are listed in Table 1. No significant differences in demographic characteristics of participants were found between the Tai Chi group (age, 64.6 ± 3.4 years; body height, 154.8 ± 7.6 cm; body weight, 58.7 ± 8.3 kg; and BMI, 24.5 ± 3.kg/m21) and the control group (age, 64.5 ± 3.4 years; body height, 155.8 ± 4.8 cm; body weight, 62.8 ± 9.2 kg; and BMI, 25.9 ± 3.6 kg/m^2) at the baseline. The PP

Table 2: The peak pressure of the Tai Chi group and the control group at the baseline and follow-up assessment.

Region	Tai Chi		Control		Between-group	Within-group	Interaction
	Baseline	Follow-up	Baseline	Follow-up			
Total foot	345.81 ± 67.26	363.77 ± 88.77	354.14 ± 79.88	305.33 ± 79.88	0.261	0.278	**0.019**
M1	276.67 ± 60.64	298.52 ± 95.62	291.03 ± 65.74	244.28 ± 40.45	0.370	0.252	**0.006**
M2	173.26 ± 33.69	170.22 ± 34.06	176.91 ± 42.94	172.11 ± 24.43	0.144	0.270	0.091
M3	230.61 ± 67.96	246.45 ± 75.75	212.14 ± 81.24	200.03 ± 53.09	0.148	0.869	0.225
M4	280.46 ± 61.84	312.12 ± 70.61	319.19 ± 102.61	248.44 ± 50.01	0.573	0.151	**0.001**
M5	180.01 ± 55.45	214.12 ± 50.29	160.67 ± 47.87	158.01 ± 36.68	0.102	**0.012**	0.058
M6	242.55 ± 89.34	239.09 ± 69.18	230.36 ± 87.07	216.61 ± 44.06	0.452	0.518	0.698
M7	190.39 ± 53.41	179.39 ± 54.68	185.81 ± 52.11	158.28 ± 38.72	0.411	0.133	0.344

Values were means ± standard deviation (SD); significant differences ($P < 0.05$) are highlighted in bold. M1: heel; M2: midfoot; M3: the first metatarsophalangeal joint; M4: the 2nd and 3rd metatarsophalangeal joints; M5: 5th metatarsophalangeal joints; M6: hallux; M7: lessor toes.

Table 3: The maximum force of the Tai Chi group and the control group at the baseline and follow-up assessment.

Region	Tai Chi		Control		Between-group	Within-group	Interaction
	Baseline	Follow-up	Baseline	Follow-up			
Total foot	115.81 ± 15.73	119.29 ± 12.33	124.12 ± 17.89	114.65 ± 9.15	0.591	0.423	0.091
M1	70.05 ± 13.63	71.78 ± 13.54	68.88 ± 11.81	61.62 ± 7.53	0.143	0.171	**0.030**
M2	28.17 ± 6.77	27.51 ± 6.82	33.02 ± 5.07	28.89 ± 4.06	0.103	0.113	0.066
M3	22.81 ± 7.22	23.89 ± 8.32	18.31 ± 7.76	18.48 ± 7.82	0.073	0.257	0.417
M4	36.61 ± 7.62	40.41 ± 8.64	37.74 ± 10.51	34.68 ± 6.35	0.368	0.814	**0.034**
M5	15.84 ± 5.04	19.44 ± 5.82	14.11 ± 4.32	14.85 ± 4.62	0.071	**0.031**	0.190
M6	17.99 ± 6.67	18.49 ± 7.44	16.22 ± 6.71	15.64 ± 3.76	0.243	0.976	0.652
M7	25.24 ± 8.55	21.79 ± 8.18	21.88 ± 7.63	18.59 ± 4.57	0.169	0.109	0.947

Values were means ± standard deviation (SD); significant differences ($P < 0.05$) are highlighted in bold. M1: heel; M2: midfoot; M3: the first metatarsophalangeal joint; M4: the 2nd and 3rd metatarsophalangeal joints; M5: 5th metatarsophalangeal joints; M6: hallux; M7: lessor toes.

and MF showed no differences between the Tai Chi group and the control group at baseline. Participants were also well-balanced between groups about scores of radiographic severity (Kellgren-Lawrence grade). Tables 2 and 3 illustrate the comparison for PP and MF of the Tai Chi group and the control group at the baseline and follow-up assessment.

3.1. Peak Pressure. There were statistically significant group × time interactions in total foot ($F = 5.66$, df = 1, $P = 0.02$), M1 ($F = 10.35$, df = 1, $P = 0.01$), and M4 ($F = 14.90$, df = 1, $P = 0.01$). Individuals receiving Tai Chi experienced no improvement in PP in total foot ($P = 0.37$), M1 ($P = 0.14$), and M4 ($P = 0.08$) between baseline and follow-up assessment. By contrast, those who received health program showed lower PP in total foot ($P = 0.03$), M1 ($P = 0.01$), and M4 ($P = 0.01$) at follow-up assessment. The statistically significant main effect of the within-group only showed in M5 ($F = 7.08$, df = 1, $P = 0.01$), which meant a greater PP in M5 after Tai Chi intervention.

3.2. Maximum Force. The ANOVA revealed significant group × time interactions for changes in M1 ($F = 5.21$, df = 1, $P = 0.03$) and M4 ($F = 4.91$, df = 1, $P = 0.03$). Individuals in the Tai Chi group also experienced no improvement in MF in M1 ($P = 0.55$) and M4 ($P = 0.08$) between baseline and follow-up assessment. By contrast, those who received health program showed lower MF in M1 ($P = 0.02$) at follow-up assessment except M4 ($P = 0.21$). The statistically significant main effect of the within-group only showed in M5 ($F = 5.11$, df = 1, $P = 0.03$), which meant a greater MF in M5 receiving Tai Chi intervention.

4. Discussion

Although Tai Chi exercise demands low posture [33], the ground contact loads of Tai Chi movements, such as Tai Chi gait [34] and push hand [35], are equal to the body weight of participants because these movements are gentle and fluid [33]. The present study investigated the effectiveness of Tai Chi in plantar loading for KOA individuals during walking after a 6-month intervention period. Results suggested that individuals in the Tai Chi group experienced larger PP and MF in 5th metatarsophalangeal joints and the control group had lower MF under heel and lower PP under total foot and the 2nd and 3rd metatarsophalangeal joints.

Our study showed that although a significant group × time interaction for the PP of the total region of foot was observed, there was no higher PP in the Tai Chi group and a lower PP in the control group. The significant change of whole foot PP of the control group in the present study was

possibly due to that lower muscle strength in lower limbs. An experiment about the knee kinetics of individuals with KOA confirmed that they experience a significantly lower knee extensor moment than persons with no KOA [36]. Tai Chi practitioners had better isokinetic knee muscle strength than healthy participants [37]. Several studies also measured the kinematics of Tai Chi gait and normal gait and proved that Tai Chi gait exerts a large joint motion in ankle dorsiflexion, plantar flexion, knee flexion, and hip flexion [33, 38]. Meanwhile, an 8-week Tai Chi training could improve muscle strength of all lower limbs for community-dwelling participants aged 65 [39]. Therefore, Tai Chi intervention in our study would keep the muscle strength and PP for the total region.

Our study suggested that individuals receiving health program experienced lower MF, particularly on the rear foot, than individuals receiving Tai Chi exercise. Abnormally lower pressure on the heel for KOA participants is related to insufficient knee extension of individuals during the heel-contact phase than those of healthy elder persons [40]. A previous experiment about the knee kinetics of individuals with KOA confirmed that they experience a significantly lower knee extensor moment than persons with no KOA [36]. Furthermore, individuals with symptomatic KOA show significantly small knee range of motion during gait [41]. These changes in heel in our study implied that individuals in the Tai Chi group may maintain the biomechanics in the knee during walking after 6-month intervention because the program uses double-stance, weight-bearing, or single-stance weight-bearing movements from knee flexion to knee extension. The plantar loads of the control group were lower during the heel-contact phase than those at the baseline in our study, which demonstrated that individuals obtained low extension of the knee during walking.

In this study, the MF and PP were more significantly higher under M5 in the Tai Chi group and a lower PP in M4 was observed in the control group during walking. These changes might be related to the movement of Tai Chi. A previous study showed foot loads were mainly located in the anterior-medial areas in Tai Chi movements [32]. Moreover, most of the loads during the toe-off phase of gait are concentrated on metatarsal areas [42, 43] and increased forefoot load indicated an increased plantar flexion moment during walking [44]. A previous study also investigated the influence of regular Tai Chi practice on the muscle strength of the lower extremities in older people, and results demonstrated that the Tai Chi group generates more torque in their ankle dorsiflexion than the control group [45]. Meanwhile, the forefoot maintains the balance and cutaneous feedback during one-leg stance with eye open or closed [46]. The high plantar loading in the forefoot indicates a strategy so that elderly can maintain balance [47]. These findings may support the idea that Tai Chi can improve balance during walking, which is in agreement with those of previous studies demonstrating that Tai Chi reduces the risk of falling in older adult population [48, 49].

Although some studies implied that education program can provide benefits to cognitive ability and pain [50], the plantar loads in the control group of the present study showed a small decline after 6-month wellness education in our study. This decline might be related to intervention duration and frequency.

The current study also showed several potential limitations. First, the duration of Tai Chi might be not enough to show significant changes in all foot regions. Second, adding the individual weight may be considerably rigorous, although the weight in the current study showed no significant differences.

5. Conclusion

This study showed that these participants with KOA showed greater plantar loads in forefoot after 6-month Tai Chi intervention and Tai Chi could prevent the decrease of plantar loads during walking. Therefore, plantar load assessment would be a useful tool to assess the effect of Tai Chi on knee osteoarthritis.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Acknowledgments

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References

[1] C. Wang, M. D. Iversen, T. McAlindon et al., "Assessing the comparative effectiveness of tai chi versus physical therapy for knee osteoarthritis: design and rationale for a randomized trial," *BMC Complementary and Alternative Medicine*, vol. 14, no. 1, p. 333, 2014.

[2] T. Vos, A. D. Flaxman, M. Naghavi et al., "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010," *The Lancet*, vol. 380, no. 9859, pp. 2163–2196, 2012.

[3] M. C. Corti and C. Rigon, "Epidemiology of osteoarthritis: prevalence, risk factors and functional impact," *Aging Clinical and Experimental Research*, vol. 15, no. 5, pp. 359–363, 2003.

[4] S. Gupta, G. A. Hawker, A. Laporte, R. Croxford, and P. C. Coyte, "The economic burden of disabling hip and knee osteoarthritis (OA) from the perspective of individuals living with this condition," *Rheumatology*, vol. 44, no. 12, pp. 1531–1537, 2005.

[5] M. I. O'Connor, "Sex differences in osteoarthritis of the hip and knee," *The Journal of the American Academy of Orthopaedic Surgeons*, vol. 15, Supplement 1, pp. S22–S25, 2007.

[6] A. Prashansanie Hettihewa, N. S. Gunawardena, I. Atukorala, F. Hassan, I. N. Lekamge, and D. J. Hunter, "Prevalence of knee osteoarthritis in a suburban, Srilankan, adult female population: a population-based study," *International Journal of Rheumatic Diseases*, vol. 21, no. 2, pp. 394–401, 2018.

[7] R. M. Ferreira, J. A. Duarte, and R. S. Goncalves, "Non-pharmacological and non-surgical interventions to manage patients with knee osteoarthritis: an umbrella review," *Acta Reumatológica Portuguesa*, vol. 43, no. 3, pp. 182–200, 2018.

[8] S. B. S. Neto, E. M. Marconi, C. R. Kutter et al., "Beneficial effects of whole body mechanical vibration alone or combined with auriculotherapy in the pain and in flexion of knee of individuals with knee osteoarthritis," *Acupuncture & Electro-Therapeutics Research*, vol. 42, no. 3, pp. 185–201, 2017.

[9] C. Gohal, A. Shanmugaraj, P. Tate et al., "Effectiveness of valgus offloading knee braces in the treatment of medial compartment knee osteoarthritis: a systematic review," *Sports Health: A Multidisciplinary Approach*, vol. 10, no. 6, pp. 500–514, 2018.

[10] O. Melo Mde, K. D. Pompeo, G. A. Brodt, B. M. Baroni, D. P. da Silva Junior, and M. A. Vaz, "Effects of neuromuscular electrical stimulation and low-level laser therapy on the muscle architecture and functional capacity in elderly patients with knee osteoarthritis: a randomized controlled trial," *Clinical Rehabilitation*, vol. 29, no. 6, pp. 570–580, 2015.

[11] A. E. Nelson, K. D. Allen, Y. M. Golightly, A. P. Goode, and J. M. Jordan, "A systematic review of recommendations and guidelines for the management of osteoarthritis: the chronic osteoarthritis management initiative of the U.S. bone and joint initiative," *Seminars in Arthritis and Rheumatism*, vol. 43, no. 6, pp. 701–712, 2014.

[12] E. Ghandali, S. T. Moghadam, M. R. Hadian, G. Olyaei, S. Jalaie, and E. Sajjadi, "The effect of tai chi exercises on postural stability and control in older patients with knee osteoarthritis," *Journal of Bodywork and Movement Therapies*, vol. 21, no. 3, pp. 594–598, 2017.

[13] G. H. Goncalves, F. A. Sendin, P. R. M. da Silva Serrao et al., "Ankle strength impairments associated with knee osteoarthritis," *Clinical Biomechanics*, vol. 46, pp. 33–39, 2017.

[14] S. Anwer, A. Alghadir, and J. M. Brismee, "Effect of home exercise program in patients with knee osteoarthritis: a systematic review and meta-analysis," *Journal of Geriatric Physical Therapy*, vol. 39, no. 1, pp. 38–48, 2016.

[15] A. H. Razak, A. Zayegh, R. K. Begg, and Y. Wahab, "Foot plantar pressure measurement system: a review," *Sensors*, vol. 12, no. 7, pp. 9884–9912, 2012.

[16] W. Li, S. Xu, Y. Liu, Y. Zhou, L. Qu, and X. Yang, "Application of static characteristics of plantar pressure distribution in the assessment of knee joint injury," *Zhongguo Yi Liao Qi Xie Za Zhi*, vol. 42, no. 6, pp. 395–399, 2018.

[17] F. Fourchet, N. A. Maffiuletti, F. Agosti, A. Patrizi, and A. Sartorio, "Impact of rocker sole footwear on plantar pressure distribution during standing and walking in adult obese women," *Disability and Rehabilitation*, vol. 25, pp. 1–4, 2018.

[18] Z. Wei, Z. Zhang, J. Jiang, Y. Zhang, and L. Wang, "Comparison of plantar loads among runners with different strike patterns," *Journal of Sports Sciences*, vol. 37, no. 18, pp. 2152–2158, 2019.

[19] T. Fukaya, H. Mutsuzaki, T. Okubo, K. Mori, and Y. Wadano, "Relationships between the center of pressure and the movements of the ankle and knee joints during the stance phase in patients with severe medial knee osteoarthritis," *The Knee*, vol. 23, no. 4, pp. 631–636, 2016.

[20] C. H. Fantini Pagani, S. Willwacher, R. Benker, and G. P. Brüggemann, "Effect of an ankle-foot orthosis on knee joint mechanics: a novel conservative treatment for knee osteoarthritis," *Prosthetics and Orthotics International*, vol. 38, no. 6, pp. 481–491, 2014.

[21] R. H. Lidtke, C. Muehleman, M. Kwasny, and J. A. Block, "Foot center of pressure and medial knee osteoarthritis," *Journal of the American Podiatric Medical Association*, vol. 100, no. 3, pp. 178–184, 2010.

[22] Z. Zhang, L. Wang, K. Hu, and Y. Liu, "Characteristics of plantar loads during walking in patients with knee osteoarthritis," *Medical Science Monitor*, vol. 23, pp. 5714–5719, 2017.

[23] T. Rosland, L. S. Gregersen, T. N. Eskehave, U. G. Kersting, and L. Arendt-Nielsen, "Pain sensitization and degenerative changes are associated with aberrant plantar loading in patients with painful knee osteoarthritis," *Scandinavian Journal of Rheumatology*, vol. 44, no. 1, pp. 61–69, 2015.

[24] R. Shengelia, S. J. Parker, M. Ballin, T. George, and M. C. Reid, "Complementary therapies for osteoarthritis: are they effective?," *Pain Management Nursing*, vol. 14, no. 4, pp. E274–E288, 2013.

[25] C. Wang, C. H. Schmid, P. L. Hibberd et al., "Tai chi for treating knee osteoarthritis: designing a long-term follow up randomized controlled trial," *BMC Musculoskeletal Disorders*, vol. 9, no. 1, p. 108, 2008.

[26] T. Field, "Knee osteoarthritis pain in the elderly can be reduced by massage therapy, yoga and tai chi: a review," *Complementary Therapies in Clinical Practice*, vol. 22, pp. 87–92, 2016.

[27] Q. G. Zhu, L. Y. Huang, X. Wu et al., "Effects of Tai Ji Quan training on gait kinematics in older Chinese women with knee osteoarthritis: a randomized controlled trial," *Journal of Sport and Health Science*, vol. 5, no. 3, pp. 297–303, 2016.

[28] C. L. Shen, C. R. James, M. C. Chyu et al., "Effects of tai chi on gait kinematics, physical function, and pain in elderly with knee osteoarthritis–a pilot study," *The American Journal of Chinese Medicine*, vol. 36, no. 2, pp. 219–232, 2008.

[29] A. K. Singh, M. Kalaivani, A. Krishnan, P. K. Aggarwal, and S. Kumar Gupta, "Prevalence of osteoarthritis of knee among elderly persons in urban slums using American College of Rheumatology (ACR) criteria," *Journal of Clinical and Diagnostic Research*, vol. 8, pp. 9–11, 2014.

[30] X. Q. Wang, L. Y. Huang, Y. Liu et al., "Effects of tai chi program on neuromuscular function for patients with knee osteoarthritis: study protocol for a randomized controlled trial," *Trials*, vol. 14, no. 1, p. 375, 2013.

[31] P. F. Tsai, J. Y. Chang, C. Beck, Y. F. Kuo, and F. J. Keefe, "A pilot cluster-randomized trial of a 20-week tai chi program in elders with cognitive impairment and osteoarthritic knee: effects on pain and other health outcomes," *Journal of Pain and Symptom Management*, vol. 45, no. 4, pp. 660–669, 2013.

[32] D. W. Mao, J. X. Li, and Y. Hong, "The duration and plantar pressure distribution during one-leg stance in tai chi exercise," *Clinical Biomechanics*, vol. 21, no. 6, pp. 640–645, 2006.

[33] N. Y. Law and J. X. Li, "The temporospatial and kinematic characteristics of typical tai chi movements: repulse monkey and wave-hand in cloud," *Research in Sports Medicine*, vol. 22, no. 2, pp. 111–123, 2014.

[34] G. Wu and J. Hitt, "Ground contact characteristics of tai chi gait," *Gait & Posture*, vol. 22, no. 1, pp. 32–39, 2005.

[35] Y. T. Chang, J. H. Chang, and C. F. Huang, "Ground reaction force characteristics of tai chi push hand," *Journal of Sports Sciences*, vol. 32, no. 18, pp. 1698–1703, 2014.

[36] K. R. Kaufman, C. Hughes, B. F. Morrey, M. Morrey, and K. N. An, "Gait characteristics of patients with knee osteoarthritis," *Journal of Biomechanics*, vol. 34, no. 7, pp. 907–915, 2001.

[37] X. Lu, C. W. Hui-Chan, and W. W. Tsang, "Tai chi, arterial compliance, and muscle strength in older adults," *European Journal of Preventive Cardiology*, vol. 20, no. 4, pp. 613–619, 2013.

[38] G. Wu, W. Liu, J. Hitt, and D. Millon, "Spatial, temporal and muscle action patterns of tai chi gait," *Journal of Electromyography and Kinesiology*, vol. 14, no. 3, pp. 343–354, 2004.

[39] I. W. Penn, W. H. Sung, C. H. Lin, E. Chuang, T. Y. Chuang, and P. H. Lin, "Effects of individualized tai-chi on balance and lower-limb strength in older adults," *BMC Geriatrics*, vol. 19, no. 1, p. 235, 2019.

[40] I. Saito, K. Okada, T. Nishi et al., "Foot pressure pattern and its correlation with knee range of motion limitations for individuals with medial knee osteoarthritis," *Archives of Physical Medicine and Rehabilitation*, vol. 94, no. 12, pp. 2502–2508, 2013.

[41] S. P. Messier, R. F. Loeser, J. L. Hoover, E. L. Semble, and C. M. Wise, "Osteoarthritis of the knee: effects on gait, strength, and flexibility," *Archives of Physical Medicine and Rehabilitation*, vol. 73, no. 1, pp. 29–36, 1992.

[42] W. L. Hsi, J. H. Kang, and X. X. Lee, "Optimum position of metatarsal pad in metatarsalgia for pressure relief," *American Journal of Physical Medicine & Rehabilitation*, vol. 84, no. 7, pp. 514–520, 2005.

[43] J. H. Kang, M. D. Chen, S. C. Chen, and W. L. Hsi, "Correlations between subjective treatment responses and plantar pressure parameters of metatarsal pad treatment in metatarsalgia patients: a prospective study," *BMC Musculoskeletal Disorders*, vol. 7, no. 1, p. 95, 2006.

[44] T. Melai, N. C. Schaper, T. H. Ijzerman et al., "Increased forefoot loading is associated with an increased plantar flexion moment," *Human Movement Science*, vol. 32, no. 4, pp. 785–793, 2013.

[45] D. Q. Xu, Y. Hong, and J. X. Li, "Tai chi exercise and muscle strength and endurance in older people," *Medicine and Sport Science*, vol. 52, pp. 20–29, 2008.

[46] P. F. Meyer, L. I. Oddsson, and C. J. De Luca, "The role of plantar cutaneous sensation in unperturbed stance," *Experimental Brain Research*, vol. 156, no. 4, pp. 505–512, 2004.

[47] A. S. Machado, G. D. Bombach, J. Duysens, and F. P. Carpes, "Differences in foot sensitivity and plantar pressure between young adults and elderly," *Archives of Gerontology and Geriatrics*, vol. 63, pp. 67–71, 2016.

[48] M. P. Gallant, M. Tartaglia, S. Hardman, and K. Burke, "Using tai chi to reduce fall risk factors among older adults: an evaluation of a community-based implementation," *Journal of Applied Gerontology*, vol. 38, no. 7, pp. 983–998, 2017.

[49] R. Lomas-Vega, E. Obrero-Gaitan, F. J. Molina-Ortega, and R. Del-Pino-Casado, "Tai chi for risk of falls. A meta-analysis," *Journal of the American Geriatrics Society*, vol. 65, no. 9, pp. 2037–2043, 2017.

[50] P. F. Tsai, J. Y. Chang, C. Beck, Y. F. Kuo, F. J. Keefe, and K. Rosengren, "A supplemental report to a randomized cluster trial of a 20-week sun-style tai chi for osteoarthritic knee pain in elders with cognitive impairment," *Complementary Therapies in Medicine*, vol. 23, no. 4, pp. 570–576, 2015.

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Clinical Study

The Impact of Auricular Vagus Nerve Stimulation on Pain and Life Quality in Patients with Fibromyalgia Syndrome

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The purpose of this study is to evaluate the impact of auricular vagus nerve stimulation, applied in conjunction with an exercise treatment program, on pain and life quality in patients with fibromyalgia syndrome (FMS). To achieve the study objectives, 60 female patients between the ages 18 and 50, with diagnosed FMS according to the American College of Rheumatology (ACR) 2010 diagnostic criteria, were randomly divided into 2 groups of 30. The first group was assigned 20 sessions of a home-based exercise program, while the second group was assigned 20 sessions of auricular vagus nerve stimulation and 20 sessions of a home-based exercise program. Patients were assessed before and after the treatments using the Visual Analog Scale (VAS) for pain, Beck Depression Scale for depression, Beck Anxiety Scale for anxiety, Fibromyalgia Impact Questionnaire (FIQ) for functional evaluation, and Short Form-36 (SF-36) for life quality. In this randomized controlled trial, comparisons within the groups revealed that both groups had statistically significant improvements in pain, depression, anxiety, functionality, and life quality scores ($p < 0.05$), while comparisons across the groups revealed that the group experiencing the vagus nerve stimulation had no statistically significant differences between the baseline scores, except for those of SF-36's subparameters of physical function, social functionality, and pain. In fact, comparisons across the groups after the interventions revealed that the group experiencing the vagus nerve stimulation had better scores but not statistically significant. From analysis of this data, we observed that vagus nerve stimulation in FMS treatment did not give additional benefit together with exercise, except for three subparameters of SF-36. It was identified that further studies which separately investigate the effects of vagus nerve stimulation and exercise on FMS with longer follow-up periods and an increased number of patients are needed.

1. Introduction

Fibromyalgia syndrome (FMS) is a syndrome characterized by chronic widespread pain that continues for a minimum of 3 months and pain felt upon 11 out of 9 pairs of identified sore points. It is often accompanied by systemic symptoms such as fatigue, sleep disorders, cognitive dysfunction, and depression [1, 2]. Moreover, headache, dysmenorrhea, irritable bowel syndrome, restless leg syndrome, chest pain, jaw pain, stomach ache, sensitive skin, mitral valve prolapses, sicca symptoms, Raynaud phenomenon, and female urethral syndrome accompany the clinical picture in many patients with FMS [2, 3]. This syndrome, the etiology of which is unknown, is commonly seen in women, and the age of onset is usually 30–50 [4]. Its prevalence among the general population is reported to be between 2.9 and 4.7% percent [5]. While it is often seen in the adult population, it can also be observed in childhood or later age [6]. Recent research studies show that various anomalies in genetic structure, autonomic nervous system (ANS), neurotransmitters, hypothalamic-hypophyseal-adrenal axe hormones, oxidative stress, pain modulation centers, central sensitization, and muscular structure occur in FMS [7]. The etiology of FMS is still not fully understood; nonetheless, the data reveals that this syndrome may stem from dysfunctionality in ANS [8]. Sympathetic nervous system (SNS) dominance is widespread in FMS, chronic fatigue, irritable bowel syndrome, and interstitial cystitis [9]. A highly peripheral sympathetic tone causes

regional ischemia, which in turn causes widespread pain. Therapeutic interventions that result in vasodilatation (e.g., exercise) and appropriate autonomic changes are proven to be effective for reducing pain levels [10].

The "great and perfect protector" of the body, the vagus nerve, includes a neuro-endocrine-immune network that ensures homeostasis. The vagus nerve, which has reciprocal neural connections with more than one region of the brain, serves a control center that combines sensitive information and provides appropriate feedback responses. Recent studies show that the vagus nerve also encompasses inflammation, mood, and pain regulation. All of these can be modulated with vagus nerve stimulation. Vagus nerve stimulation can generate a neuromodulating effect to activate other natural protective paths to improve health [11]. The development of vagus nerve stimulation began in the 19th century. A number of new electrical stimulation devices have now been developed. Noninvasive transcutaneal devices stimulate the vagus nerve through the auricular branch or from the carotid. Moreover, they are used in the treatment of various disorders, such as epilepsy, pain, and headache [12]. Recent preclinical studies have shown that vagus nerve stimulation heavily modulates pain in humans and is quite effective. The use of a medical device allows the auricular branch of the vagus nerve to be stimulated without surgical intervention. Consequently, it has been found that the threshold of pain is elevated and mechanical pain sensitivity is reduced [13].

As a result of these completed studies, there is a possibility that FMS is a disease, which occurs through ANS impairment. Vagus nerve stimulation could be used as an additional treatment method to improve the ANS impairment. However, as there are no studies that investigate vagus nerve stimulation in FMS, this study is designed and executed.

2. Material and Method

Our study, in which we investigated the impact of auricular vagus nerve stimulation on pain and life quality in patients with FMS, was conducted in Beykoz Public Hospital's Department of Physiotherapy and Rehabilitation. A total of 60 female patients within the age range 18–50, with diagnosed FMS by a physiatrist according to 2010 ACR criteria, were included in this study. We include only females to make groups homogenous and ended the age range at 50 to avoid comorbid illnesses seen in elderly people and also menopause. Pregnant, perimenopausal, and postmenopausal women are not included; also those experiencing any comorbid illnesses like neurological deficits, diabetes, neuropathic disorders, chronic inflammation, immune deficiency, cardiac disorders, and current vitamin D intake were excluded from the study. In addition, those who started using new drugs in the last month and during the study were not included. Patients who experienced vasovagal syncope in their past could not participate in the study.

Ethics committee approval was awarded by the Ethics Committee of Beykoz State Hospital Clinical Research prior to the commencement of the study. Written consent forms were obtained from all patients to demonstrate their consent to being included in the study. Patients were assessed twice during the study, first before treatment and then after treatment. Before the assessment, data was obtained from patients relating to age, height, weight, occupation, level of education, marital status, regular medication, general health complaints, and the duration of these complaints. All responses were recorded. Patients were also asked to not participate in any other treatments during the study, in order to prevent any external influences on the data and study parameters.

Patients are diagnosed with FSM, in accordance with the ACR 2010 Diagnostic Criteria. A total of 60 patients are included in the study. Patients were randomly divided into two groups: an exercise (control) group and an exercise and vagus stimulation (treatment) group. Randomization was carried out by random number assignment. The exercise group began with 30 patients, and the exercise and vagus stimulation group began with 30 patients. By the end of the study, there were 25 patients in the exercise group and 27 patients in the exercise and vagus stimulation group. Five patients in the exercise group were excluded as they had not completed the exercise program. Three patients in the exercise and vagus stimulation group failed to complete the study, and they missed treatment sessions. There was no blinding in the study.

The exercise group was assigned a program, which consisted of strengthening, stretching, isometric, and posture exercises, targeting the body and upper and lower extremities. That program was home-based, and the program was requested to be completed. Patients were asked to attend weekly face-to-face sessions with a total of 4 of these sessions in the study duration.

Patients in the exercise and vagus stimulation group received auricular vagus nerve stimulation at Beykoz Public Hospital's Department of Physical Therapy and Rehabilitation on 5 weekdays for 4 weeks, making up a total of 20 sessions with each session taking 30 minutes. Patients were admitted to the treatment as day visitors. Vagus nerve stimulation is carried out with a TENS device, which has specially designed surface electrodes in the shape of earphones, the size of which can be selected according to ear size. Electrodes were placed to correspond with the inner and rear surfaces of the tragus and the concha for both ears (Figure 1). The application is carried out, for 30 minutes, using a biphasic, asymmetrical waveform with a pulse duration that is less than 500 microseconds and a frequency of 10 hertz. Amplitude is adjusted according to the sensory threshold level. Patients in this group were also assigned the same home-based exercise program assigned to the patients in the exercise group with application of the program 5 days a week with 2 sets per day, and each set involved 10 repetitions of every exercise. Patients were asked to attend weekly face-to-face sessions with a total of 4 of these sessions in the study duration.

Measurements were performed twice, before and after the treatments. Patients were asked to complete the Turkish version of the Fibromyalgia Impact Questionnaire (FIQ), consisting of 21 questions, displaying the extent to which pain impacts the daily activities, social lives, moods, and professional lives of the patients during the previous week. This scale was developed by Burchardt et al. to gauge the

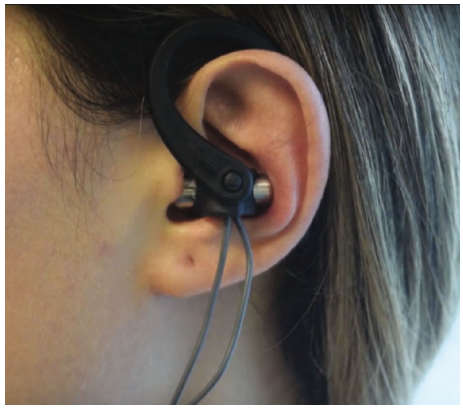

Figure 1: Electrode placing of the auricular vagus nerve stimulation.

functional condition of patients with FM, while its specific validity and reliability adaptation for Turkey was carried out by Sarmer et al. [14].

Pain intensity was evaluated within the context of this study using the Visual Analog Scale (VAS). Patients were asked to select the corresponding interval for their own intensity of pain on a table of 0-100 mm with the explanation that 0 refers to no pain and 100 is excruciating pain [15].

Life quality of patients was evaluated using the SF-36 life quality scale. The Turkish validity and reliability of this scale was carried out by Koçyiğit et al. Investigating life quality regarding overall health, this questionnaire contains 36 questions in 8 different categories [16, 17].

The level of depression of patients was evaluated using the Beck Depression Scale. The Turkish validity and reliability of this scale was carried out by Hisli in 1988. It is a questionnaire that consists of 21 questions with 4 items, and each item is awarded between 0 and 3 points [18].

The level of anxiety of patients was evaluated using the Beck Anxiety Scale. This scale was developed by Beck et al., and its Turkish validity and reliability studies were conducted by Ulusoy et al. in 1998 [19].

2.1. Statistical Analysis. The presentation of variables acquired within the scope of the study such as sex, level of education, and occupation includes numbers (n) and percentage values.

The Shapiro-Wilk test is used to determine whether the variables in the study are congruent with the normal distribution. Interquartile range (IQR) values for the variables without normal distribution and average ± SD (Standard Deviation) values for the variables with normal distribution are provided in the descriptive statistics.

In the comparison of measurement values before and after the treatment, results of t-test for the variables with normal distribution and of Wilcoxon-Signed Rank test for the variables without normal distribution are provided.

In the comparison of the treatment group and control group after the treatment, results of t-test for variables with normal distribution and of Mann–Whitney U test for variables without normal distribution are provided.

Chi-square and likelihood ratio chi-square tests were used to assess the relationship between patient and control group complaints, accompanying diseases, duration of pain, and daily sports activities.

IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) and MS-Excel 2007 were used for statistical analyses and calculations. The level for statistical significance was accepted to be $p < 0.05$.

3. Findings

The average age of the individuals in the control group is 38.60 ± 9.34 years, while the individuals in the treatment group have an average age of 39.44 ± 8.28 years, and all the respondents are female ($n = 52$). There is no statistically significant difference between the average ages of the individuals in the control group and the treatment group ($t = 0.346$, $p = 0.731$). The individuals in the control group have an average height of 1.64 ± 0.07 meters, while those in the treatment group have 1.60 ± 0.06 meters. A statistically significant difference between the average height of the control group and that of the treatment group is found ($t = 2{,}035$, $p = 0.047$). The average weight of those in the control group is 69.32 ± 13.86 kg and those in the treatment group have an average weight of 66.78 ± 12.67 kg, and no statistically significant differences were found between groups with respect to weight ($t = 0.691$, $p = 0.493$).

Within the control group, 84.0% ($n = 21$) of the individuals are married and 16.0% ($n = 14$) are single. Among them, 48.0% are housewives and 24.0% are teachers. 72.0% of the respondents complained from pain only. The remaining 28.0%, however, expressed complaints of numbness, weakness, and fatigue, alongside pain. 80.0% of respondents stated that they do not undertake any daily sporting activities, whereas 20.0% stated they take daily walks (Table 1).

Within the individuals in the treatment group, 66.7% ($n = 18$) are married and 22.2% ($n = 6$) are single (Table 2). In this group, 51.9% are housewives and 14.8% are nurses. Pain-only complaints were reported from 66.7% of the patients. The remaining 33.7%, however, expressed complaints such as numbness, weakness, and fatigue, in addition to pain. Similarly, 59.3% of patients stated that they undertake no daily sporting activities and 22.2% reported walking.

The average score from the Beck Depression Scale before the exercise is 16.76 ± 10.63, while the average score after the exercise is detected to be 11.92 ± 7.06 in the control group (Table 3). A statistically significant difference between the average scores from the Beck Depression Scale before and after the exercise is identified ($t = 4.132$, $p < 0.001$). Similarly, the median score from the Beck Anxiety Scale before the exercise was 20.00 (IQR = 16.5) while the median score after the exercise was 13.00 (IQR = 11.00). There is a statistically significant difference between the median scores from the Beck Anxiety Scale before and after the treatment ($Z = 3.636$, $p < 0.001$).

The average score acquired from the Fibromyalgia Impact Questionnaire before the exercise is 54.48 ± 18.81 and the average score from the same questionnaire after the exercise is 41.93 ± 18.15. A statistically significant difference between the scores from the Fibromyalgia

Table 1: Descriptive statistics of identified variables for the control group ($n = 25$).

		n (%)			n (%)
Marital status	Married	21 (84.0)	Occupation	Housewife	12 (48.0)
	Single	14 (16.0)		Canteen employee	1 (4.0)
Level of education	Elementary school	7 (28.0)		Accountant	1 (4.0)
	Junior high school	4 (16.0)		Student	2 (8.0)
	High school	3 (12.0)		Teacher	6 (24.0)
	University	11 (44.0)		Professional cook	1 (4.0)
Complaints	Pain	18 (72.0)		Insurance professional	1 (4.0)
	Pain, numbness	1 (4.0)		Cleaning staff	1 (4.0)
	Pain, numbness, weakness	1 (4.0)	Accompanying diseases/conditions	Asthma	1 (4.0)
	Pain, numbness, fatigue	1 (4.0)		Herniated disc	2 (8.0)
	Pain, fatigue	4 (16.0)		Herniated disc (neck, lower back)	1 (4.0)
Daily sporting act.	None	20 (80.0)		High blood pressure	2 (8.0)
	Walking	5 (20.0)		None	19 (76.0)
Duration of pain	≤1 year	12 (48.0)			
	1-8 years	7 (28.0)			
	≥8 years	6 (24.0)			

Table 2: Descriptive statistics of identified variables for the treatment group ($n = 27$).

		n (%)			n (%)
Marital status	Married	18 (66.7)	Occupation	Retired	1 (3.7)
	Single	6 (22.2)		Housewife	14 (51.9)
	Other	3 (11.1)		Financial officer	1 (3.7)
Level of education	Elementary school	9 (33.3)		Nurse	4 (14.8)
	Junior high school	1 (3.7)		Mechanical engineer	1 (3.7)
	High school	9 (33.3)		Accountant	2 (7.4)
	University	7 (26.0)		Student	1 (3.7)
	Master's/PhD	1 (3.7)		Secretary	1 (3.7)
Complaints	Pain	18 (66.7)		Textile	2 (7.4)
	Pain, weakness	1 (3.7)		Allergic asthma	1 (3.7)
	Pain, numbness	2 (7.4)		Anxiety	1 (3.7)
	Pain, numbness, fatigue	1 (3.7)		Herniated disc	3 (11.1)
	Pain, burning	2 (7.4)		Straightening of cervical lordosis	2 (7.4)
	Pain, fatigue	1 (3.7)	Accompanying diseases/conditions	Goiter	1 (3.7)
	Pain, fatigue, insomnia	2 (7.4)		Hypoglycemia	1 (3.7)
Daily sporting act.	Stretching ex.	1 (3.7)		Reflux	1 (3.7)
	Pilates	2 (7.4)		High blood pressure	1 (3.7)
	Pilates, fitness	1 (3.7)		None	16 (59.3)
	Pilates, walking	1 (3.7)	Duration of pain	≤1 year	8 (29.6)
	Walking	6 (22.2)		1-8 years	9 (33.3)
	None	16 (59.3)		≥8 years	10 (37.1)

Impact Questionnaire before and after the exercise is determined ($t = 5.763$, $p < 0.001$). The average score of the VAS Pain Scale before the exercise is 5.67 ± 2.10, while the average score after the exercise is 3.45 ± 1.73. There is a statistically significant difference between the average scores from the VAS Pain Scale, collected before and after the exercise ($t = 7.097$, $p < 0.001$).

An examination of the scores from the SF-36 Scale reveals that the median score before the exercise under the Physical Function subscale was 70.00 (IQR = 17.50) and the median score after the exercise was 85.00 (IQR = 22.50). A statistically significant difference is identified between the median scores, acquired before and after the exercise ($Z = 3.619$, $p < 0.001$). In the Physical Role Difficulty

Table 3: Comparison of measurement values in the control group before and after the exercise.

	Before treatment Average ± SD interquartile (IQR)	After treatment Average ± SD interquartile (IQR)	t, Z	p
Beck Depression Scale	16.76 ± 10.63	11.92 ± 7.06	4.132*	**<0.001**
Beck Anxiety Scale	20.00 (16.50)	13.00 (11.00)	3.636	**<0.001**
Fibromyalgia Impact Questionnaire	54.48 ± 18.81	41.93 ± 18.15	5.763*	**<0.001**
VAS	5.67 ± 2.10	3.45 ± 1.73	7.097*	**<0.001**
SF 36 Scale				
Physical Function	70.00 (17.50)	85.00 (22.50)	3.619	**<0.001**
Physical Role Difficulty	25.00 (50.00)	50.00 (50.00)	3.225	**0.001**
Emotional Role Difficulty	33.33 (66.67)	66.67 (33.33)	2.336	**0.019**
Energy/Liveliness/Vitality	40.00 (37.50)	50.00 (20.00)	3.791	**<0.001**
Mental Health	50.24 ± 19.26	62.40 ± 16.93	3.919*	**0.001**
Social Functionality	62.50 (25.00)	75.00 (18.75)	3.824	**<0.001**
General Health Perception	42.60 ± 21.51	52.20 ± 15.46	4.129	**<0.001**
Pain	41.10 ± 21.06	59.50 ± 15.28	5.451*	**<0.001**

*t-test results are provided.

subscale, the median score before the exercise was 25.00 (IQR = 50.00) and median score after the exercise was 50.00 (IQR = 50.00). A statistically significant difference was identified between the scores, acquired before and after the exercise ($Z = 3.225$, $p < 0.001$). In the Emotional Role Difficulty subscale, the median score before the exercise was 33.3 (IQR = 66.67) and the median score after the exercise was 66.67 (IQR = 33.33). A statistically significant difference was identified between the scores, acquired before and after the exercise ($Z = 2.336$, $p = 0.019$). In the Energy/Liveliness/-Vitality subscale, the median score before the exercise was 40.00 (IQR = 37.50) and the median score after the exercise was 50.00 (IQR = 20.00). A statistically significant difference was identified between the scores, acquired before and after the exercise ($Z = 3.791$, $p < 0.001$). In the Mental Health subscale, the average score before the exercise was 50.24 ± 19.26 and the average score after the exercise was 62.40 ± 16.93. There is a statistically significant difference between average scores: scores before the exercise and scores after the exercise ($t = 3.919$, $p = 0.001$). In the Social Functionality subscale, the median score before the exercise was 62.50 (IQR = 25.00) and the median score after the exercise was 75.00 (IQR = 18.75). A statistically significant difference was identified between the medians scores, acquired before and after the exercise ($Z = 3.824$, $p < 0.001$). In the General Health Perception subscale, the average score before the exercise was 42.60 ± 21.51 and the average score after the exercise was 52.20 ± 15.46. There is a statistically significant difference between the average scores, before the exercise and after the exercise ($t = 4.129$, $p < 0.001$). In the Pain subscale, the average score before the exercise was 41.10 ± 21.06 and the average score after the exercise was 59.50 ± 15.28. A statistically significant difference between the average scores before and after the exercise is also determined ($t = 5.451$, $p < 0.001$).

The median of the scores collected using the Beck Depression Scale before the treatment was 16.00 (IQR = 12.00), while the median of the scores from after the treatment was 8.00 (IQR = 12.00). A statistically significant difference was identified between medians of scores, collected using the Beck Depression Scale before and after the treatment ($Z = 3.660$, $p < 0.001$) (Table 4). Similarly, the median score before the treatment collected using the Beck Anxiety Scale was 18.00 (IQR = 13.00) while the median score after the treatment was 13.00 (IQR = 13.00). A statistically significant difference between median scores before and after the treatment as per Beck Anxiety Scale is also identified ($Z = 3.692$, $p < 0.001$).

The average of the before treatment scores, obtained using the FIQ, was 61.98 ± 18.45, and the average of the after treatment score was 37.27 ± 19.48. A statistically significant difference between the average scores acquired using the FIQ before and after treatment was determined ($t = 5.883$, $p < 0.001$). The average before treatment scores, collected using the VAS Pain Scale, was 6.17 ± 2.58, and the average after treatment score was 2.56 ± 1.91. There is a statistically significant difference between the before and after treatment score averages as per VAS Pain Scale ($t = 5.859$, $p < 0.001$).

An examination of the scores from the SF 36 Scale shows that in the Physical Function subscale, median of the before treatment scores was 65.00 (IQR = 25.00) and median of the after treatment scores was 80.00 (IQR = 25.00). There is a statistically significant difference between the median scores, acquired before and after treatment ($Z = 4.024$, $p < 0.001$). In the Physical Role Difficulty, the median of the before treatment scores was 00.00 (IQR = 50.00) and the median of the after treatment scores was 75.00 (IQR = 75.00). There is a statistically significant difference between the medians scores, acquired before and after treatment ($Z = 3.116$, $p = 0.002$). In the Emotional Role Difficulty subscale, the median of the before treatment scores was 0.00 (IQR = 66.67) and the median of the after treatment scores was 100.00 (IQR = 66.67). There is a statistically

Table 4: Comparison of measurement values in the treatment group before and after the treatment.

	Before treatment Average ± SD interquartile (IQR)	After treatment Average ± SD interquartile (IQR)	t, Z	p
Beck Depression Scale	16.00 (12.00)	8.00 (12.00)	3.660	**<0.001**
Beck Anxiety Scale	18.00 (13.00)	13.00 (13.00)	3.692	**<0.001**
Fibromyalgia Impact Questionnaire	61.98 ± 18.45	37.27 ± 19.48	5.883*	**<0.001**
VAS	6.17 ± 2.58	2.56 ± 1.91	5.859*	**<0.001**
SF 36 Scale				
Physical Function	65.00 (25.00)	80.00 (25.00)	4.024	**<0.001**
Physical Role Difficulty	0.00 (50.00)	75.00 (75.00)	3.116	**0.002**
Emotional Role Difficulty	0.00 (66.67)	100.00 (66.67)	2.764	**0.006**
Energy/Liveliness/Vitality	28.70 ± 21.64	57.59 ± 22.97	5.153*	**<0.001**
Mental Health	46.37 ± 19.09	65.33 ± 20.66	4.265*	**0.001**
Social Functionality	47.22 ± 26.02	69.91 ± 22.80	3.583*	**0.001**
General Health Perception	33.89 ± 19.38	56.85 ± 21.45	6.126	**<0.001**
Pain	27.87 ± 21.54	58.05 ± 18.80	6.741*	**<0.001**

*t-test results are provided.

significant difference between the medians scores, acquired before and after treatment ($Z = 2.764$, $p = 0.006$). In the Energy/Liveliness/Vitality subscale, the average of the before treatment scores was 28.70 ± 21.64 and the average of the after treatment score was 57.59 ± 22.97. A statistically significant difference between the score averages from before and after treatment is identified ($Z = 5.153$, $p < 0.001$). In the Mental Health subscale, the average of the before treatment scores was 46.37 ± 19.09 and the average of the after treatment scores was 65.33 ± 20.66. A statistically significant difference between the score averages from before and after treatment is identified ($t = 4.265$, $p = 0.001$). In the Social Functionality subscale, the average of the before treatment scores was 47.22 ± 26.02 and the average of the after treatment scores was 69.91 ± 22.80. A statistically significant difference between the score averages from before and after treatment is identified ($t = 3.583$, $p = 0.001$). In the General Health Perception subscale, the average of the before treatment scores was 33.89 ± 19.38 and the average of the after treatment score was 56.85 ± 21.45. A statistically significant difference between the score averages from before and after treatment is identified ($t = 6.126$, $p < 0.001$). In the Pain subscale, the average of the before treatment scores was 27.87 ± 21.54 and the average of the after treatment score was 58.05 ± 18.80. A statistically significant difference between the score averages from before and after treatment is identified ($t = 6.741$, $p < 0.001$).

In reviewing the scores, acquired using the SF 36 Scale, a significant difference between the scores of the treatment group and the control group occurs, with respect to the Physical Function subscale ($Z = 2.281$, $p = 0.023$). The median of the scores of the control group from the Physical Function subscale was 70.00 (IQR = 17.50), and the median of the scores of the treatment group was 65.00 (IQR = 25.00). There was no statistically significant difference between the medians of the scores from subscales of Physical Role Difficulty, Emotional Role Difficulty, and Energy/Liveliness/Vitality (respectively: $Z = 0.908$, $p = 0.364$; $Z = 0.520$, $p = 0.603$; and $Z = 1.444$, $p = 0.149$). Similarly, the treatment group and the control group did not reveal any statistically significant differences with respect to their average scores from the Mental Health and General Health Perception subscales (respectively: $t = 0.727$, $p = 0.471$; $Z = 0.536$, $p = 0.131$). Finally, a statistically significant difference between the average of scores from the subscales of Social Functionality and Pain is determined (respectively: $t = 2.386$, $p = 0.021$; $t = 2.363$, $p = 0.0.18$) (Table 5).

In reviewing the scores after the intervention, the treatment group and the control group did not reveal any statistically significant differences (Table 6).

4. Discussion and Conclusion

Multiple controlled studies, investigating both pharmacological and nonpharmacological FMS treatments, have been carried out during the past 40 years [20]. Studies found out that the treatment protocols involve methods that approach FMS as a systemic disorder, rather than a regional or multifocal skeletal disorder. Approaches that combine pharmacological and nonpharmacological treatment methods, considering the severity of symptoms, variety, and functional conditions of the patient, are required in order to gain maximum benefit from the treatment [21]. In our study, we aimed to see exercise and vagus nerve stimulation effects on FMS.

A new method, associated with FMS treatment, is the noninvasive stimulation of the vagus nerve, for which research is still ongoing. While the impact mechanism of the vagus nerve stimulation is not yet fully understood, studies on humans reveal that it affected many regions of the brain subcortical and cortical levels [22]. However, there are many unknowns about this procedure.

Table 5: Comparison of control group and treatment group before intervention.

	Control Average ± SD interquartile (IQR)	Treatment Average ± SD interquartile (IQR)	t, Z	p
Beck Depression Scale	16.76 ± 10.63	17.63 ± 8.43	0.328	0.744
Beck Anxiety Scale	20.00 (16.50)	18.00 (13.00)	0.284	0.776
Fibromyalgia Impact Questionnaire	54.48 ± 18.81	61.98 ± 18.45	1.450	0.153
VAS	5.67 ± 2.10	6.17 ± 2.58	0.756	0.453
SF 36 Scale				
Physical Function	70.00 (17.50)	65.00 (25.00)	2.281	**0.023**
Physical Role Difficulty	25.00 (50.00)	0.00 (50.00)	0.908	0.364
Emotional Role Difficulty	33.33 (66.67)	0.00 (66.67)	0.520	0.603
Energy/Liveliness/Vitality	40.00 (37.50)	25.00 (35.00)	1.444	0.149
Mental Health	50.24 ± 19.26	46.37 ± 19.09	0.727	0.471
Social Functionality	62.00 ± 18.21	47.22 ± 26.02	2.386	**0.021**
General Health Perception	42.60 ± 21.51	33.89 ± 19.38	1.536	0.131
Pain	45.00 (35.00)	22.50 (32.50)	2.363	**0.018**

*t-test results are provided.

Table 6: Comparison of control group and treatment group after intervention.

	Control Average ± SD interquartile (IQR)	Treatment Average ± SD interquartile (IQR)	t, Z	p
Beck Depression Scale	13.00 (12.00)	8.00 (12.00)	1.357	0.175
Beck Anxiety Scale	13.00 (11.00)	13.00 (13.00)	0.513	0.608
Fibromyalgia Impact Questionnaire	41.93 ± 18.15	37.27 ± 19.48	0.890*	0.378
VAS	3.45 ± 1.73	2.56 ± 1.91	1.766*	0.084
SF 36 Scale				
Physical Function	85.00 (22.50)	80.00 (25.00)	1.383	0.167
Physical Role Difficulty	50.00 (50.00)	75.00 (75.00)	0.680	0.496
Emotional Role Difficulty	66.67 (33.33)	100.00 (66.67)	1.299	0.194
Energy/Liveliness/Vitality	51.60 ± 19.46	57.59 ± 22.97	1.011*	0.317
Mental Health	62.40 ± 16.93	65.33 ± 20.66	0.557*	0.580
Social Functionality	75.00 (18.75)	75.00 (37.50)	0.580	0.562
General Health Perception	52.20 ± 15.46	56.85 ± 21.45	0.508*	0.614
Pain	59.50 ± 15.28	58.06 ± 18.80	0.303*	0.763

*t-test results are provided.

The best location and parameters of stimulation for the auricular vagus nerve have not been revealed yet. The current knowledge lacks a clear consensus on the sites that are most suitable for stimulation of the auricular branch of the vagus nerve. When the studies up to today are evaluated, it can be said that the concha and inner tragus appear to be good locations for vagal neuromodulation [23]. We used a new design ear set to stimulate both parts of the auricular vagus bilaterally.

Since the underlying causes of FMS include ANS dysfunction and mostly sympathetic nervous system hyperactivity, we focused on vagus nerve stimulation, in addition to exercise treatment that would impact ANS. For this reason, the control group set up was only assigned an exercise treatment program whereas the treatment group received vagus nerve stimulation alongside the exercise treatment program. All patients were asked to complete VAS, FIQ, SF-36, Beck Depression, and Beck Anxiety Questionnaires before and after treatment in order to evaluate the efficiency of the treatment. One of the shortcomings in our study is to not evaluate the ANS activity by heart rate variability or other methods despite FMS being associated with ANS dysfunction.

There is a myriad of studies in the literature investigating the efficiency of exercise in FMS treatment; however, there is no fully completed study on the usage of vagus nerve stimulation on FMS treatment.

A systematic review by Brosseau et al. focuses on the importance of aerobic exercise in FMS treatment, stating that aerobic exercise stimulates the endogenous analgesic system and generates beneficial impacts by improving deep sleep state and life quality [24].

Wennemer et al. studied exercise training with FMS patients during an 8-week multidisciplinary treatment program. Within this study, the exercise training involves flexibility, strengthening, stretching, Tai Chi, resting, and aerobic exercise. Researchers reported that this multidisciplinary treatment program impacted physical functionality and functional capacity, which is evaluated with a 6-minute walking test [25].

In another study, conducted with 27 patients with diagnosed FMS, the effects of callisthenic exercise training, conventional strengthening exercises, and stretching exercises were compared. Patients were divided into two groups. The callisthenic exercise program was assigned to the first group, and strengthening, stretching, and posture exercises, involving neck and back muscles, were assigned to the second group. Patients were asked to complete the assigned exercises 3 days a week for an 8-week period. The number of sore points, level of physical functionality, life quality, flexibility, and grip strength were evaluated before and after the exercises. The results demonstrated that both groups displayed significant improvement [4].

Another study, conducted at Dokuz Eylül University, divided 32 patients with diagnosed FMS according to ACR criteria into two groups. The first group completed stretching, strengthening, and posture exercises, and the second group completed postisometric relaxation, remedial exercises, and active mobilization exercises 3 times a week for 3 weeks. Patients were evaluated before and after the treatment, and both groups revealed statistically significant improvement [26]. Researches about efficacy of exercise on FMS show that it should be preferred for treatment.

The control group in our study revealed similar outcomes as those in the literature. Patients were evaluated before and after treatment, and the results demonstrated that exercise had a statistically significant impact on depression, anxiety, pain, physical function, physical role difficulty, emotional role difficulty, energy/liveliness/vitality, mental health, social functionality, and general health perception.

The studies illustrated that transcutaneous vagus nerve stimulation, which is a noninvasive stimulation method through the auricular branch of the vagus nerve, generates hopeful results in the treatment of a major depressive disorder. Involving 17 patients and 21 patients in the control group, a study by Fang et al. included 4 weeks of vagus nerve stimulation. Findings before and after the treatment were evaluated with the Hamilton Depression Assessment Scale. Scores revealed significant improvement as a result of the 4-week treatment program [27].

In another study, conducted to determine the potential impact of transcutaneous stimulation of the periodic path of the vagus nerve on pain, 38 healthy volunteers were assigned tonic thermoanalgesic paradigms that show a constant pain component. Volunteers were later measured using a quantitative sense test by a trained experimenter, according to standard protocols and standard equipment. Each subject participated in two experimental sessions on different days and in randomized orders with active vagus nerve stimulation or pseudo stimulation. As a result of the active vagus nerve stimulation, it was observed that mechanic and compression pain thresholds increased and mechanic pain sensibility decreased. The study, therefore, suggests that active vagus nerve stimulation significantly decreases pain classifications, compared to the control group, and caused no other side effects on cardiac and respiratory activities [13].

In a study that evaluates the efficiency of transcutaneous stimulation of the auricular branch of the vagus nerve for chronic migraine treatment, 46 patients with chronic migraines were randomized to receive 25 Hz. or 1 Hz. stimulation of the sensory vagal region in the left ear for 4 hours a day for a 3-month period. In total, 40 out of the original 46 patients completed the study. As a result, the headache days of the patients in the 1 Hz. group experienced a significantly larger drop, in comparison with those in the 25 Hz. group. Overall, 29.4% of the patients in the 1 Hz. group experienced a reduction greater than 50% while patients in the 25 Hz. group experienced a reduction of 13.3%. Pain assessment scores also revealed significant improvement in both groups without any group distinctions. No side effects were encountered in this treatment [28].

Bauer et al. conducted a randomized double-blind controlled study that measures the efficiency of transcutaneous vagus nerve stimulation for 20 weeks in drug-resistant epilepsy patients. The purpose of the study was to illustrate the potential improvements to health as a result of 20 weeks of transcutaneous vagus nerve stimulation compared to the control group, which was under drug therapy in terms of decreasing seizure frequency. At the end of the treatment, no statistically significant drop in the average number of seizures between the groups was observed; yet, a significant decrease in the seizure frequency of patients was, in fact, found [29]. All these studies related with depression, pain, epilepsy, and migraine give clues about the central neuromodulatory effects of auricular vagus nerve stimulation.

With the exception of our study, there are currently no other completed studies investigating the use of vagus nerve stimulation for fibromyalgia. However, there is an ongoing study which is estimated for completion. In this study, 20 patients between the ages of 20 and 60, with diagnosed FMS according to 2010 ACR diagnostic criteria, are randomly divided into two groups. The control group receives pharmacological physical therapy methods, while the treatment group receives Percutaneous Electrical Neural Region Stimulation through the auditory canal. The neurostimulation system that is implemented in the ear for five days is changed once a week for four weeks. The assessment methods are implemented two weeks prior to treatment commences and two weeks after the treatment is completed. This study began in 2017 and is ongoing [30].

Additionally, in a study that investigates the efficiency of exercise in the treatment of sleep apnea, which is a disease that stems from ANS dysfunctions, 74 patients between the ages of 40 and 80 were divided into two groups and treatment

group participated in an exercise program for 9 months. The control group did not do any kind of exercise. Cardiac autonomic functions of the patients were then measured using the method of heart rate variability. Patients in the exercise treatment group also revealed statistically significant improvements [31].

An examination of the literature shows that various evaluations have been carried out to investigate the efficiency of exercise treatment and vagus nerve stimulation in major depressive disorders, epilepsy, migraines, chronic pain, sleep apnea, and many other diseases that manifest through ANS dysfunctions. Since ANS dysfunction is included in the etiology of FMS and due to a lack of completed studies on the efficiency of vagus nerve stimulation for this condition, we carried out this study, aiming to illustrate the efficiency of auricular vagus nerve stimulation in FMS patients for pain and life quality. We assessed 60 patients in the study; however, only 52 were able to complete the full program. We divided patients into two groups; 27 received home-based exercise programs along with auricular vagus nerve stimulation (treatment group), while the control group was prescribed only the home-based exercise programs. The questionnaires showed that both groups yielded significant improvements in all findings at the end of 20 sessions. An examination of the relationship between groups before and after the treatment showed that the treatment group had better results; however, the SF-36 Questionnaire only revealed statistically significant differences in physical function, social functionality, and pain subparameters. We do not have sufficient data to prove the superiority of vagus nerve stimulation compared to exercise only because statistically detailed calculation of the intergroup relations is quite challenging and limited time was available. We did not encounter any side effects due to vagus nerve stimulation, and it was well tolerated by the patients.

The impact of exercise treatment on FMS is clearly demonstrated in our study, the result of which is in line with the previous studies found in the literature. Employment of vagus nerve stimulation, in addition to exercise treatment in FMS, improves the efficiency of treatment. Aside from the parameters we assessed in our study, vagus nerve stimulation may provide additional contributions to the exercise treatment itself. Vagus nerve stimulation could be an option for patients who cannot exercise. Therefore, further studies with more participants are required in order to further evaluate the impact of exercise and vagus nerve stimulation on FMS.

Data Availability

The [DATA TYPE] data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] D. S. Ozcan, O. Oken, M. Aras, and B. F. Koseoglu, "Vitamin D levels in women with fibromyalgia and relationship between pain, depression and sleep," *Türkiye Fiziksel Tıp ve Rehabilitasyon Dergisi*, vol. 60, no. 4, pp. 329–334, 2014.

[2] Ş. Aslan, S. Başaran, R. Çeliker et al., *Fiziksel Tıp ve Rehabilitasyonda Yeni Ufuklar Fibromiyalji*, Güneş Tıp Kitabevi, 2012.

[3] G. Gürer and Ö. F. Şendur, *Corelations of Clinical Features and Findings in Fibromyalgia Patients, Adnan Menderes Üniversitesi Tıp Fakültesi Fiziksel Tıp Ve*, Rehabilitasyon AD, Aydın, 2006.

[4] Ö. Yürük and Z. Gültekin, "Fibromiyalji sendromu olan kadınlarda iki farklı egzersiz programının karşılaştırılması," *Fizyoterapi Rehabilitasyon*, vol. 19, no. 1, 2008.

[5] Ş. Doğan, S. Ay, and D. Evcik, "Current approaches in the treatment of fibromyalgia," *Yeni Tıp Dergisi*, vol. 28, no. 2, 2011.

[6] A. Gür, "Etiopathogenesis in fibromyalgia," *Türkiye Fiziksel Tıp ve Rehabilitasyon Dergisi, Türkiye Fiziksel Tıp ve Rehabilitasyon Dergisi*, vol. 54, no. 1, 2008.

[7] S. Toprak Celenay, B. Anaforoglu Kulunkoglu, M. E. Yasa et al., "A comparison of the effects of exercises plus connective tissue massage to exercises alone in women with fibromyalgia syndrome: a randomized controlled trial," *Rheumatology International*, vol. 37, no. 11, pp. 1799–1806, 2017.

[8] J. D. Kingsley, "Autonomic dysfunction in women with fibromyalgia," *Arthritis Research and Therapy*, vol. 14, no. 1, p. 103, 2012.

[9] L.-A. Martínez-Martínez, T. Mora, A. Vargas, M. Fuentes-Iniestra, and M. Martínez-Lavín, "Sympathetic nervous system dysfunction in fibromyalgia chronic fatigue syndrome, irritable bowel syndrome and interstitial cystitis," *Journal of Clinical Rheumatology*, vol. 20, no. 3, pp. 146–150, 2014.

[10] P. Kulshreshtha, R. Gupta, R. K. Yadav, R. L. Bijlani, and K. K. Deepak, "A comprehensive study of autonomic dysfunction in the fibromyalgia patients," *Clinical Autonomic Research*, vol. 22, no. 3, pp. 117–122, 2012.

[11] H. Yuan and S. D. Silberstein, "Vagus nerve and vagus nerve stimulation, a comprehensive review: part I," *Headache*, vol. 56, no. 1, pp. 71–78, 2016.

[12] H. Yuan and S. D. Silberstein, "Vagus nerve and vagus nerve stimulation, a comprehensive review: part II," *Headache*, vol. 56, no. 2, pp. 259–266, 2016.

[13] V. Busch, F. Zeman, A. Heckel, F. Menne, J. Ellrich, and P. Eichhammer, "The effect of transcutaneous vagus nerve stimulation on pain perception - An experimental study," *Brain Stimulation*, vol. 6, no. 2, pp. 202–209, 2013.

[14] S. Sarmer, S. Ergin, and G. Yavuzer, "The validity and reliability of the turkish version of the fibromyalgia impact questionnaire," *Rheumatology International*, vol. 20, no. 1, pp. 9–12, 2000.

[15] D. D. Price, P. A. McGrath, A. Rafii, and B. Buckingham, "The validation of visual analogue scales as ratio scale measures for chronic and experimental pain," *Pain*, vol. 17, no. 1, pp. 45–56, 1983.

[16] Y. Demiral, G. Ergor, B. Unal et al., "Normative data and discriminative properties of short form 36 (SF-36) in turkish urban population," *BMC Public Health*, vol. 6, no. 1, 2006.

[17] H. Koçyiğit, Ö. Aydemir, G. Fişek, N. Ölmez, and A. Memiş, "Kısa form-36'nın Türkçe versiyonunun güvenilirliği ve geçerliliği," *İlaç ve Tedavi Dergisi*, vol. 12, 1999.

[18] N. Hisli, "A validation study of Beck depression inventory [in Turkish]," *Turkish Journal of Psychology*, vol. 6, pp. 118–126, 1988.

[19] M. Ulusoy, N. Şahin, and H. Erkmen, "Turkish version of the beck anxiety inventory: psychometric properties," *Journal of Cognitive Psychotherapy*, vol. 12, p. 2, 1998.

[20] N. Özkan, "Complementary approach in fibromyalgia syndrome," *Journal of Complementary Medicine, Regulation and Neural Therapy*, vol. 11, p. 1, 2017.

[21] D. Sindel, İ. Saral, and S. Esmaeilzadeh, "Management approaches in fibromyalgia syndrome," *Türkiye Fiziksel Tıp ve Rehabilitasyon Dergisi*, vol. 58, 2012.

[22] V. Buturak and B. Bakar, "İlaç tedavisine dirençli depresyonda bir alternatif tedavi yöntemi: vagal sinir uyarımı," *Journal of Mood Disorders*, vol. 4, no. 4, 2014.

[23] M. F. Butt, A. Albusoda, A. D. Farmer, and Q. Aziz, "The anatomical basis for transcutaneous auricular vagus nerve stimulation," *Journal of Anatomy*, 2019.

[24] L. Brosseau, G. A. Wells, P. Tugwell et al., "Ottawa panel evidence-based clinical practice guidelines for aerobic fitness exercises in the management of fibromyalgia: part 1," *Physical Therapy*, vol. 88, no. 7, pp. 857–871, 2008.

[25] H. K. Wennemer, J. Borg-Stein, L. Gomba et al., "Functionally oriented rehabilitation program for patients with fibromyalgia," *American Journal of Physical Medicine & Rehabilitation.*, vol. 85, no. 8, pp. 659–666, 2006.

[26] A. Genç and E. Sağıroğlu, "Comparison of two different exercise programs in fibromiyalgia treatment," *Turkish Journal of Physical Medicine and Rehabilitation*, vol. 13, no. 2, pp. 90–95, 2002.

[27] J. Fang, N. Egorova, P. Rong et al., "Early cortical biomarkers of longitudinal transcutaneous vagus nerve stimulation treatment success in depression," *NeuroImage: Clinical*, vol. 14, pp. 105–111, 2017.

[28] A. Straube, J. Ellrich, O. Eren, B. Blum, and R. Ruscheweyh, "Treatment of chronic migraine with transcutaneous stimulation of the auricular branch of the vagal nerve (auricular t-VNS): a randomized, monocentric clinical trial," *The Journal of Headache and Pain*, vol. 16, 2015.

[29] H. M. Hamer and S. Bauer, "Lessons learned from transcutaneous vagus nerve stimulation (tVNS)," *Epilepsy Research*, vol. 153, pp. 83-84, 2019.

[30] M. Gebre, A. Woodbury, V. Napadow et al., "Functional magnetic resonance imaging evaluation of auricular percutaneous electrical neural field stimulation for fibromyalgia: protocol for a feasibility study," *JMIR Research Protocols*, vol. 7, no. 2, p. e39, 2018.

[31] M. Berger, J. Raffin, V. Pichot et al., "Effect of exercise training on heart rate variability in patients with obstructive sleep apnea: a randomized controlled trial," *Scandinavian Journal of Medicine & Science in Sports.*, vol. 29, 2019.

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Research Article

Beneficial Effects of Pulsed Electromagnetic Field during Cast Immobilization in Patients with Distal Radius Fracture

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To assess whether pulsed electromagnetic field therapy during cast immobilization of distal radius fractures has beneficial effects on pain and limb function, the study included 52 patients (mean age 60.8 ± 15.0 years) with distal radius fractures treated with cast immobilization. Patients were allocated to a pulsed electromagnetic field group ($n = 27$) or a control group ($n = 25$). Pain; forearm and arm circumference; range of motion; disabilities of the arm, shoulder, and hand score; and touch sensation were evaluated on the day of the plaster cast dressing and 3 and 6 weeks after. In comparison to the control group, the pulsed electromagnetic field group reported significant changes after 3 and 6 weeks of treatment: lower pain levels ($p = 0.0052$; $p < 0.0001$, respectively), greater mobility of upper-limb joints, improvement in exteroceptive sensation, and reduction in disability of the upper limb (disabilities of the arm, shoulder, and hand) ($p = 0.0003$; $p < 0.0001$, respectively). Our results suggest that early addition of pulsed electromagnetic field treatment, during cast immobilization of distal radius fractures, has beneficial effects on the pain, exteroceptive sensation, range of motion, and daily functioning of patients.

1. Introduction

A distal radius fracture (DRF), also known as Colles' fracture, is one of the most common fractures [1] in people aged over 40 years [2].

The therapeutic procedure for DRFs consists of the repositioning of the fracture and cast immobilization. In some cases, surgery is performed. An important element of treatment is the rehabilitation intervention aimed at restoring the strength and function of the limb and helping prevent complications. However, a meta-analysis indicated that insufficient evidence is available to determine the best form of rehabilitation [1].

Early introduction of treatment in patients with DRFs aims to decrease pain and improve hand function. Collins [3] emphasized that DRF treatment needs to be implemented when the forearm is still immobilized to maximize functional recovery. During this period, joint mobilization exercises are often ignored, resulting in the reduction of range of joint motion (ROM), muscle atrophy, and pain [4]. Romanowski and Lisiewicz-Bręborowicz [5] reported the importance of paying attention to the joints, which are not covered with cast, in the early stage of physiotherapy. Metacarpophalangeal joints are particularly important because they are prone to contractures and pain. Performing finger joint motions and global motions is, therefore, advisable. Because of the cast weight, drawing the patient's attention to humeral joint motion, which is often neglected in the period of forearm cast immobilization, is important. However, it is a common practice to refer patients to rehabilitation only after cast removal [6–8]. The aim of physiotherapy is to strengthen the muscles, extend the joint ROM, and reduce edema [2].

Pulsed electromagnetic fields (PEMF) have been used for many years to support fracture healing [9]. A meta-analysis suggested that stimulation of the electromagnetic field may have some benefits in the treatment of bone nonunion or delayed union. However, the mechanisms of action at cellular and molecular levels have not been fully explained [9, 10].

In addition, PEMF therapy has shown other beneficial effects, including reduction of acute and chronic pain associated with connective tissue (tendon, ligaments, bone, and cartilage) injury as well as edema and inflammation control and wound healing [11].

Various strategies for the use of PEMF can be found in the literature. The studies mainly involve patients with tibia fractures [12–14]. Most studies describe starting PEMF treatment only when a nonunion is diagnosed: immediately after diagnosis of delayed union, about 16 weeks after the fracture, or at a late stage of delayed union, more than 6 months after the fracture [13, 14]. Griffin et al. [13] concluded that introduction of electromagnetic field stimulation for the treatment of delayed union and nonunion of long-bone fractures to current practice requires further investigation. Few studies describe the administration of this treatment during the acute stage of the fracture [15]. A single study investigated the clinical effectiveness of 10 PEMF treatments applied from day 7 after a Colles' fracture in postmenopausal women [16]. However, in this study, the authors did not assess how the therapy affected functioning of these patients in everyday life.

Therefore, this study aimed to determine the effect of PEMF therapy, started a day after injury and cast immobilization, on pain, edema, limb range of motion, exteroceptive sensation, and daily functioning in patients with DRFs.

2. Methods

2.1. Participants. The study included 52 consecutive patients (45 women and 7 men; mean age 60.8 ± 15.0) who were admitted to the casualty department after a distal radius fracture based on the AO classification (Arbeitsgemeinschaft für Osteosynthesefragen) developed by Müller et al. [17], type A and B according to the OTA (Orthopaedic Trauma Association) [18]. On the admission day, they were treated with reduction and cast immobilization after clinical and radiographic examination.

The inclusion criteria for the study were as follows: distal end radius fracture type A or B according to the AO classification, cast immobilization treatment, no limitation of wrist and hand function before injury, no contraindication to PEMF, and patient's consent. The exclusion criteria were multiple-organ injury; reports of previous DRF; and concurrent diseases influencing DRF recovery, such as diabetes, hyperthyroidism, psychiatric illness, and inflammatory osteoarthritis.

2.2. Ethical Considerations. This study was approved by the Research Ethics Committee at Poznań University of Medical Sciences (protocol number: 957/11). All procedures performed in the study were in accordance with the principles of the 1964 Declaration of Helsinki. Each participant was informed about the study and signed the informed consent statement.

2.3. Procedures. The study participants were allocated to one of the two groups: the PEMF group, consisting of 27 patients, and the control non-PEMF group, consisting of 25 patients.

The PEMF therapy device was produced by ASTAR ABR (Bielsko-Biała, Poland). The patient's hand, wrist, and distal forearm were placed inside a concentric coil applicator 345 mm in diameter and 440 mm in height generating a magnetic field intensity of 6–10 mT and a frequency of 25–30 Hz. Each treatment lasted 30 min. The magnetic field applied was initially generated for 1 s with a break. The length of the break in the first treatment was 3 s and was reduced by 0.5 s in each consecutive application. As from the seventh treatment, the magnetic field applied was generated with a constant amplitude throughout the treatment. For 10 days, the patients received the treatment once a day at the same time in the morning, with a break over the weekend, and then three times a week. Altogether, the patients received 22 treatments over six weeks [19].

On the day following the injury and cast immobilization, both the PEMF and control groups started rehabilitation that consisted of active shoulder, elbow, and finger mobilization exercises three times a day (all joints without immobilization). All participants were given instructions for home exercises to be performed under the supervision of a physiotherapist.

All patients participating in the study underwent conservative treatment without the need for surgery and the need for extension of the period of plaster immobilization beyond 6 weeks.

2.4. Outcome Measures

2.4.1. Pain. The visual Analogue Scale (VAS) was used to assess pain severity. The results were obtained by measuring the distance (0 to 100 mm) from the beginning of the scale to the position selected by the patient, where "0" is "no pain" and "100" is "the worst possible pain" [20].

2.4.2. Limb Circumference. Shoulder and forearm circumferences of both injured and uninjured limbs were measured with a tape measure. To assess edema, the measurement was taken at the proximal end of the radius (above the cast) and mid-shaft of the humeral bone at the deltoid tuberosity. The mean of the measurements of both limbs formed the outcome.

2.4.3. Range of Joint Motion. The range of joint motion was measured using a goniometric method according to the rules of the International Standard Orthopaedic Measurement using the Sagittal Frontal Transverse Rotation system to an accuracy of 1°[21]. The range of motion of all joints without

immobilization was measured three times. Mean measurement of both limbs formed the outcome. In joints that were not immobilized, the range of joint motion stayed within acceptable limits. The range of motion of the wrist was measured after cast removal and assessed in comparison to the uninjured limb.

2.4.4. Grip Strength. Grip strength was measured using a Jamar dynamometer (Poland), and the results are expressed in kilograms (kg). The participant was seated comfortably in a chair, the shoulder was adducted and neutrally rotated, and the elbow was flexed at 90°, with the forearm and wrist in neutral positions. The participant was instructed to grip the dynamometer handle as hard as possible for 5 s [22]. Global grip strength was measured after cast removal and assessed in comparison to the uninjured limb.

2.4.5. Touch Sensation. Two-point discrimination sense perception was measured using a standardized Dellon's discriminator (two-point discrimination test) with a preset distance between individual filaments as measurement points. The shortest distance was estimated at which two-point discrimination occurred (proper distance of 2–5 mm on a digital pulp) [23]. At the beginning of the examination, the patient was informed about the procedure. The examination was carried out statically in a patient whose eyes were closed. This manner of examination is believed to enable the evaluation of innervation density of slowly adapting touch sense receptors. The pads of fingers II and V were tested with one or two filaments. In the test, the patient was asked if they discriminated one or two points. When the pressure was sufficient, the skin around the pressure spot turned delicately white. Smaller distances, in mm, between the filaments resulted in the patient's improved ability to discriminate [24].

The WEST hand monofilament test (Weinstein Enhanced Sensory Test) (Bioinstruments, Connecticut, USA) was performed to assess the skin's sensitivity to touch, with the use of five individual fibers of standardized diameter, rigidity, and weight and with pressures of 0.07 g, 0.2 g, 4 g, and 200 g. The patient was sitting with eyes closed. Thumb and fingers II and V were examined, starting with the heaviest monofilament. The examination consisted of touching the given spot three times. It was considered successful when the patient could feel the touch at least one time [25]. Data analysis was categorized 1–5, with 1 (smallest force) standing for normal touch sensation. Larger figures indicate higher impairment of skin sensation [26].

2.4.6. Disabilities of the Upper Limb. The DASH (disabilities of the arm, shoulder, and hand) questionnaire was used to assess the disability of the upper limb. In this questionnaire, the upper limb is considered a functional unity. Partial dysfunction of a limb impaired general function of a limb as well as everyday life and social activity of the patient. The basic version of the thirty-point questionnaire was used in this examination [27, 28].

The measurements were evaluated on the day of immobilization, then after 3 weeks, and on the day of the cast removal. All evaluations were carried out by the same researcher.

2.5. Statistical Analysis. Descriptive data were presented as median values and standard deviations. The normality distribution was tested using the Shapiro–Wilk test. Most variables in both groups were not distributed normally. To assess differences between the two groups, the Mann–Whitney U test was used. To assess the differences in the examination dates, the ANOVA Friedman's test was employed with the post-hoc comparison. The calculations were performed using StatSoft STATISTICA 10.0 software. A p value < 0.05 was considered significant.

3. Results

Patient demographics (Table 1) were comparable between the two groups.

Before the therapy, no significant difference was observed between the groups with regard to age, pain (VAS), circumference of the forearm and shoulder, and the range of motion (shoulder flexion, extension, abduction, and elbow flexion) (Tables 1 and 2).

Three and six weeks after the zero examination, significant pain ($p < 0.01$) and circumference of the forearm ($p < 0.01$) were reduced, whereas the range of motion significantly increased (shoulder flexion ($p < 0.01$), extension ($p < 0.01$), abduction ($p < 0.01$), and elbow flexion ($p < 0.01$)) in both groups.

Pain reduction was significantly higher during examination in the PEMF group in comparison to that in the control group (three weeks $p = 0.0052$, six weeks $p < 0.0001$). No significant difference was noted between the two groups with regard to the circumference of the forearm and shoulder. The range of motion was significantly higher in the PEMF group in comparison to that in the control group: shoulder flexion (three weeks, $p = 0.0280$; six weeks, $p = 0.0034$), extension (three weeks, $p = 0.0004$; six weeks, $p = 0.0004$), and abduction (three weeks, $p = 0.0015$; six weeks, $p = 0.0002$) (Table 2).

Wrist mobility and global grip strength were evaluated only after cast removal at week six. In comparison to the control group, the PEMF group had significantly higher mean values for palmar and dorsal wrist flexion in the fractured limb ($p = 0.003$ and $p = 0.001$, respectively) and higher grip strength in the fractured and unfractured hand ($p = 0.0344$ and $p = 0.0012$, respectively) (Table 3).

Prior to therapy, no significant difference was found between the two groups with regard to the exteroceptive sensation measured with the WEST hand monofilaments and Dellon's discriminator.

After three weeks, a significantly greater improvement in exteroceptive sensation measured with Dellon's discriminator was observed in the PEMF group in comparison to that in the

Table 1: Baseline characteristics of the investigated groups.

	PEMF group $N = 27$	Control group $N = 25$	p between groups
Gender (female/male)	22/5	23/2	
Age (years)	58.1 (18.2)	63.6 (10.4)	0.5275
Broken limb (right/left)	9/18	12/13	

PEMF: pulsed electromagnetic fields.

Table 2: Differences in the evaluation of pain, circumference, and range of motion between the PEMF and control groups during the study.

		PEMF group ($n = 27$)	Control group ($n = 25$)	p between groups
Pain VAS (mm)	Before	6.2 ± 2.00	7.1 ± 1.88	0.0956
	After 3 weeks	2.1 ± 1.41	3.5 ± 1.71	0.0052
	p value I *vs.* II	$p < 0.01$	$p < 0.01$	
	After 6 weeks	0.2 ± 0.42	2.7 ± 2.15	<0.0001
	p value I *vs.* III	$p < 0.01$	$p < 0.01$	
Circumference of forearm (cm)	Before	25.8 ± 2.46	25.9 ± 1.89	0.9198
	After 3 weeks	24.7 ± 2.39	24.2 ± 1.94	0.5097
	p value I *vs.* II	$p < 0.01$	$p < 0.01$	
	After 6 weeks	23.9 ± 2.31	22.9 ± 1.95	0.1285
	p value I *vs.* III	$p < 0.01$	$p < 0.01$	
Circumference of shoulder (cm)	Before	28.1 ± 2.54	28.9 ± 3.51	0.4582
	After 3 weeks	26.9 ± 2.52	27.6 ± 3.34	0.5097
	p value I *vs.* II	$p < 0.01$	$p < 0.01$	
	After 6 weeks	26.4 ± 2.36	26.8 ± 3.41	0.7486
	p value I *vs.* III	$p < 0.01$	$p < 0.01$	
Range of motion (°) shoulder flexion	Before	151.8 ± 18.96	146.4 ± 17.32	0.1331
	After 3 weeks	162.1 ± 12.78	156.6 ± 13.87	0.0280
	p value I *vs.* II	$p < 0.01$	$p < 0.01$	
	After 6 weeks	167.5 ± 6.42	162.0 ± 9.43	0.0034
	p value I *vs.* III			
Shoulder extension	Before	39.6 ± 5.23	37.8 ± 6.03	0.1935
	After 3 weeks	47.7 ± 3.11	42.6 ± 5.19	0.0004
	p value I *vs.* II	$p < 0.01$	$p < 0.01$	
	After 6 weeks	49.7 ± 0.81	45.8 ± 4.29	0.0004
	p value I *vs.* III	$p < 0.01$	$p < 0.01$	
Shoulder abduction	Before	149.9 ± 18.21	142.3 ± 14.12	0.0727
	After 3 weeks	164.5 ± 8.19	153.6 ± 12.7	0.0015
	p value I *vs.* II	$p < 0.01$	$p < 0.01$	
	After 6 weeks	168.4 ± 3.72	159.5 ± 10.01	0.0002
	p value I *vs.* III	$p < 0.01$	$p < 0.01$	
Elbow flexion	Before	116.1 ± 14.10	111.2 ± 8.55	0.2198
	After 3 weeks	129.8 ± 14.10	122.8 ± 7.43	0.0115
	p value I *vs.* II	$p < 0.01$	$p < 0.01$	
	After 6 weeks	141.6 ± 7.19	132.1 ± 8.24	0.0001
	p value I *vs.* III	$p < 0.01$	$p < 0.01$	

PEMF: pulsed electromagnetic fields; VAS : Visual Analogue Scale.

Table 3: Differences in wrist mobility and global grip strength between the PEMF and control groups after therapy.

	PEMF group ($n = 27$)	Control group ($n = 25$)	p between groups
Range of wrist dorsal flexion (°)			
Broken limb	26 ± 10.60	15 ± 6.85	0.0001
Unaffected limb	50 ± 0.0	50 ± 0.0	0.9927
Range of palmar flexion (°)			
Broken limb	29.5 ± 9.17	19.8 ± 5.79	0.0003
Unaffected limb	60 ± 0.0	60 ± 0.0	0.9927
Global grip strength (kg)			
Broken limb	4.5 ± 3.14	2.2 ± 1.52	0.0012
Unaffected limb	25.4 ± 10.72	19.4 ± 7.04	0.0344

PEMF: pulsed electromagnetic fields.

control group ($p = 0.0098$). After six weeks, the exteroceptive sensation measured with the monofilaments and Dellon's discriminator was significantly better in the PEMF group in comparison to that in the control group ($p = 0.0013$; $p = 0.0018$, respectively) (Table 4).

The upper-limb disability evaluation (DASH) showed significant differences between the two groups in the first examination ($p = 0.0499$). A significantly greater decrease in limb disability was recorded in the PEMF group in comparison to that in the control group after three ($p < 0.0001$) and six weeks of therapy ($p < 0.0001$) (Table 5).

4. Discussion

In comparison to the control group, the PEMF group showed a significantly higher reduction in pain, increased mobility of the upper-limb joint, improvement in exteroceptive sensation, and reduction in the upper-limb disability, assessed by the DASH questionnaire, after 3 and 6 weeks of treatment. In this study, the duration of casting was six weeks, and prolonging this duration was not necessary in any patient.

The study originally aimed to investigate the effects of the PEMF treatment, applied immediately after the fracture diagnosis and casting, on pain and limb function. In most published studies, except one [16], PEMF therapy was performed only after a nonunion had been diagnosed, more than three months after injury, with the bone union formation being primarily examined [14].

In a prospective randomized controlled study of long-bone fractures, Shi et al. [14] demonstrated that patients who received PEMF treatment between 16 weeks and 6 months of delayed union had a significantly increased rate of union and an overall reduction in the healing period compared to that achieved in those who received PEMF treatment after 6 months or more of delayed union. Griffin et al. [13] confirmed that the results of the conducted studies indicate the potential beneficial effect of magnetic fields on delayed union or nonunion. Meanwhile, they suggest further research for final conclusions.

Similarly, Hannemann et al. [15] concluded that the results of randomized studies on acute fractures are not enough to state that the beneficial effect of PEMF on bone growth stimulation also influences the reduction of nonunion cases. However, their systematic review and meta-analysis suggested possible beneficial PEMF effects, taking radiological and clinical union into consideration. Significant radiological union was observed in cases of acute inoperable fractures of the upper limb.

It should be noted that a DRF can lead to pain, edema, movement restrictions in joints, and functional impairment. Exercise and other physical interventions (also PEMF therapy for this purpose) are used to prevent complications and speed up recovery [1].

Several studies reported that the PEMF therapy has beneficial effects on both acute and chronic pain [29, 30].

The results of the present study confirmed the pain relief effect of magnetotherapy. Significantly lower pain levels were reported in PEMF patients after three and six weeks of therapy, referring to the initial examination, in comparison to the patients who were not exposed to magnetic field therapy. Our research results are in agreement with the observations reported by Lazović et al. [16] Their randomized study included 60 female patients with distal end radius fractures, divided into two groups. One group received 10 applications of 30-minute PEMF treatments, and the other was a control group. Each patient was taught and given instructions for a home-exercise program consisting of active shoulder, elbow, and finger exercises. The pain assessment values achieved in PEMF patients were lower, but not statistically significant [16].

In their systematic review of randomized studies, Andrade et al. [11] confirmed that the PEMF treatment causes pain relief and functional improvement in patients with low back pain. Hence, they reported the PEMF treatment as a potential alternative to pharmacological pain treatment.

In our research, significant edema reduction was reported in both groups, which is believed to be of primary importance in obtaining hand function [2]. Contrary to other studies [16, 29], we did not confirm a significant improvement in the PEMF group compared to control group. Similar to our research, Lazović et al. [16] applied PEMF to DRF patients during cast immobilization. In the research group, significant edema reduction was noted in comparison to that in the control group. Cheing et al. [31] achieved interesting results in their study. After cast removal, patients were randomized into four research groups, each receiving a combination of treatments, including ice packs, alternating magnetic fields, and simulated magnetotherapy. Results showed that the most significant reduction in edema was achieved by a combination of ice and magnetotherapy.

In our research, the beneficial effect of alternating magnetic fields on the increase in shoulder and elbow range of motion was observed. This can be explained by greater pain reduction in PEMF patients. Pain leads to increased muscular tension. Moreover, severe pain may have a negative impact on patients' psyche and, consequently, discourage them from participating in rehabilitation. The beneficial effect of PEMF on pain and function in musculoskeletal disorders has been confirmed in other studies [32].

Taking into consideration the wrist joint range of motion, the mean values for palmar and dorsal wrist flexion after fraction were significantly higher in the PEMF group in comparison to that in the control group. Significant differences were also noted in grip strength, which was measured after the period of cast immobilization.

Cheing et al. [31] noted a greater extended range of wrist flexion in patients who received magnetotherapy (either with or without ice) after cast removal. Similarly, Lazović et al. [16] found a statistically significant increase in palmar and dorsal wrist flexion in comparison to that in the control group.

Evaluation of exteroceptive sensation is vital for the assessment of hand function. Melchior et al. [33] demonstrated the relationship between upper-limb function and

Table 4: Differences in the evaluation of exteroceptive sensation between the PEMF and control groups during the study.

Exteroceptive sensation		PEMF group ($n = 27$)	Control group ($n = 25$)	p between groups
Monofilaments (g)	Before	2.1 ± 0.72	2.2 ± 0.41	0.7555
	After 3 weeks	1.7 ± 0.55	1.9 ± 0.49	0.1585
	p value I *vs.* II	n.s.	n.s.	
	After 6 weeks	1.0 ± 0.19	1.6 ± 0.51	0.0013
	p value I *vs.* III	$p < 0.01$	$p < 0.01$	
Dellon's discriminator (mm)	Before	2.4 ± 0.74	2.6 ± 0.65	0.3051
	After 3 weeks	1.7 ± 0.66	2.3 ± 0.75	0.0098
	p value I *vs.* II	$p < 0.05$	n.s.	
	After 6 weeks	1.2 ± 0.42	1.8 ± 0.52	0.0018
	p value I *vs.* III	$p < 0.01$	0.01	

PEMF: pulsed electromagnetic fields.

Table 5: Upper-limb disability evaluation (DASH) in both groups during the study.

Disabilities of the upper limb		PEMF group ($n = 27$)	Control group ($n = 25$)	p between groups
DASH questionnaire [score]	Before	67.6 ± 13.16	75 ± 17.06	0.0499
	After 3 weeks	45.9 ± 15.39	66.7 ± 19.39	0.0003
	p value I *vs.* II	<0.0001	<0.0001	
	After 6 weeks	29.1 ± 13.97	60.1 ± 20.29	<0.0001
	p value I *vs.* III	<0.0001	<0.0001	

PEMF: pulsed electromagnetic fields; DASH: disabilities of the arm, shoulder, and hand.

exteroceptive sensation, measured with Semmes-Weinstein monofilaments. Accessible literature provides individual studies about the effect of magnetotherapy on sensory threshold changes. Witkoś et al. [34] demonstrated a significant increase in sensory sensitivity in patients who received a single application of magnetotherapy in comparison to that in the control group.

In our own research, a significant increase in exteroceptive sensation, evaluated with Dellon's discriminator and monofilaments, was observed after six weeks in both groups. However, it was more significant in the PEMF group than in the control group. Notably, the weakening in touch sensation may have been as a result of soft tissue injury and pain that accompanied the fraction.

The authors of other studies point out further consequences of the fracture: functional impairment and loss of independence [1]. Therefore, DRF is not only a common clinical problem, but also a social and an economical one [35]. It entails high costs concerning treatment, rehabilitation, or absence from work. Therefore, it has been investigated for years which rehabilitation intervention is necessary to optimise functional recovery to achieve the activities required for daily living [1]. We were also interested in this aspect of rehabilitation with PEMF use.

The DASH questionnaire was used for assessment of upper-limb disability. It is considered one of the best clinical measures of the upper-limb disability assessment [36]. Its usefulness has been mentioned by many researchers [37–39]. Our results showed a decreased disability in subjective assessments after early physiotherapy. At the same time, a significantly lower disability index was recorded in the PEMF group than that in the control group after three and six weeks of therapy. A similar observation of the beneficial effect of early physiotherapy on hand function (DASH) after a displaced DRF was noted by Wilcke and Abbaszadegan [40].

The limitation of this study was the small number of patients included. However, 52 patients were examined three times by the same researcher, and all of them completed the examination. Our research did not only focus on the monitoring of symptoms associated with the pathology, but, more importantly, it evaluated the effect of the therapy on patients' daily functioning. The effect of PEMF treatment on fracture healing has not been studied.

In conclusion, this finding suggests that the early addition of PEMF treatment during cast immobilization for DRFs has some beneficial effect, particularly on the pain and function of the broken limb, and improves daily functioning. Final conclusions, however, await further well-conducted randomized controlled trials, in line with the principles of evidence-based medicine in this field.

Data Availability

The data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of Interest

The authors declare that they have no conflicts of interest regarding the publication of this paper.

Authors' Contributions

Krzyżańska and Straburzyńska-Lupa contributed equally to this work.

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References

[1] H. H. G. Handoll and J. Elliott, "Rehabilitation for distal radial fractures in adults," *Cochrane Cochrane Database of Systematic Reviews*, vol. 25, no. 9, Article ID CD003324, 2015.

[2] Y. Dionyssiotis, I. A. Dontas, D. Economopoulos, and G. P. Lyritis, "Rehabilitation after falls and fractures," *Journal of Musculoskeletal and Neuronal Interactions*, vol. 8, no. 3, pp. 244–250, 2008.

[3] D. C. Collins, "Management and rehabilitation of distal radius fractures," *The Orthopedic Clinics of North America*, vol. 24, no. 2, pp. 365–378, 1993.

[4] T. Einsiedel, D. Herzig, G. Grön, J. Mayer, C. Becker, and F. Gebhard, "Mentales Training beeinflusst Bewegungseinschränkung des ruhiggestellten Handgelenks—eine prospektive Experimentalstudie," *Zeitschrift für Orthopädie und Unfallchirurgie*, vol. 149, no. 3, pp. 288–295, 2011.

[5] L. Romanowski and E. Lisiewicz-Bręborowicz, "Przedramię i ręka," in *Fizjoterapia W Ortopedii*, J. Adamczyk, D. Białoszewski, and G. Benke, Eds., pp. 228–231, Wydawnictwo Lekarskie PZWL, Warszawa, Poland, 2014.

[6] J. S. Maciel, N. F. Taylor, and C. McIlveen, "A randomised clinical trial of activity-focussed physiotherapy on patients with distal radius fractures," *Archives of Orthopaedic and Trauma Surgery*, vol. 125, no. 8, pp. 515–520, 2005.

[7] O. M. Christensen, A. Kunov, F. F. Hansen, T. C. Christiansen, and M. Krasheninnikoff, "Occupational therapy and Colles' fractures," *International Orthopaedics*, vol. 25, no. 1, pp. 43–45, 2001.

[8] G. V. Oskarsson, A. Hjall, and P. Aaser, "Physiotherapy: an overestimated factor in after—treatment of fractures in the distal radius?" *Archives of Orthopaedic and Trauma Surgery*, vol. 116, no. 6-7, pp. 373–375, 1997.

[9] C. Daish, R. Blanchard, K. Fox, P. Pivonka, and E. Pirogova, "The application of pulsed electromagnetic fields (PEMFs) for bone fracture repair: past and perspective findings," *Annals of Biomedical Engineering*, vol. 46, no. 4, pp. 525–542, 2018.

[10] B. Chalidis, N. Sachinis, A. Assiotis, G. Maccauro, and F. Graziani, "Stimulation of bone formation and fracture healing with pulsed electromagnetic fields: biologic responses and clinical implications," *International Journal of Immunopathology and Pharmacology*, vol. 24, no. 1_suppl2, pp. 17–20, 2011.

[11] R. Andrade, H. Duarte, R. Pereira et al., "Pulsed electromagnetic field therapy effectiveness in low back pain: a systematic review of randomized controlled trials," *Porto Biomedical Journal*, vol. 1, no. 5, pp. 156–163, 2016.

[12] A. Assiotis, N. P. Sachinis, and B. E. Chalidis, "Pulsed electromagnetic fields for the treatment of tibial delayed unions and nonunions. A prospective clinical study and review of the literature," *Journal of Orthopaedic Surgery and Research*, vol. 7, no. 1, p. 24, 2012.

[13] X. L. Griffin, M. L. Costa, N. Parsons, and N. Smith, "Electromagnetic field stimulation for treating delayed union or non-union of long bone fractures in adults," *Cochrane Database of Systematic Reviews*, vol. 13, no. 4, Article ID CD008471, 2011.

[14] H.-F. Shi, J. Xiong, Y.-X. Chen et al., "Early application of pulsed electromagnetic field in the treatment of postoperative delayed union of long-bone fractures: a prospective randomized controlled study," *BMC Musculoskeletal Disorders*, vol. 14, no. 1, p. 35, 2013.

[15] P. F. W. Hannemann, E. H. H. Mommers, J. P. M. Schots, P. R. G. Brink, and M. Poeze, "The effects of low-intensity pulsed ultrasound and pulsed electromagnetic fields bone growth stimulation in acute fractures: a systematic review and meta-analysis of randomized controlled trials," *Archives of Orthopaedic and Trauma Surgery*, vol. 134, no. 8, pp. 1093–1106, 2014.

[16] M. Lazović, M. Kocić, L. Dimitrijević, I. Stanković, M. Spalević, and T. Cirić, "Pulsed electromagnetic field during cast immobilization in postmenopausal women with Colles' fracture," *Srpski Arhiv Za Celokupno Lekarstvo*, vol. 140, no. 9-10, pp. 619–624, 2012.

[17] M. E. N. Müller, S. Nazarian, and P. Koch, *Classification AO des Fractures: Tome I: les os Longs*, Springer-Verlag, Berlin, Germany, Part 2, 1st edition, 1987.

[18] J. L. Marsh, "OTA fracture classification," *Journal of Orthopaedic Trauma*, vol. 23, no. 8, p. 551, 2009.

[19] A. Straburzyńska-Lupa and G. Straburzyński, *Fizjoterapia Z Elementami Klinicznymi. Tom I. Wyd. 1*, Wydawnictwo Lekarskie PZWL, Warszawa, Poland, 2008.

[20] S. L. Collins, R. A. Moore, and H. J. McQuay, "The visual analogue pain intensity scale: what is moderate pain in millimetres?" *Pain*, vol. 72, no. 1, pp. 95–97, 1997.

[21] R. D. Lea and J. J. Gerhardt, "Range-of-motion measurements," *The Journal of Bone & Joint Surgery*, vol. 77, no. 5, pp. 784–798, 1995.

[22] C. S. Edgren, R. G. Radwin, and C. B. Irwin, "Grip force vectors for varying handle diameters and hand sizes," *Human Factors: The Journal of the Human Factors and Ergonomics Society*, vol. 46, no. 2, pp. 244–251, 2004.

[23] W. R. Hepp and H. U. Debrunner, *Diagnostyka W Ortopedii. Wyd. 1*, Wydawnictwo Lekarskie PZWL, Warszawa, Poland, 2008.

[24] G. Lundborg and B. Rosén, "The two-point discrimination test—time for a re-appraisal?" *Journal of Hand Surgery*, vol. 29, no. 5, pp. 418–422, 2004.

[25] J. A. Bell-Krotoski, E. E. Fess, J. H. Figarola, and D. Hiltz, "Threshold detection and Semmes-Weinstein monofilaments," *Journal of Hand Therapy*, vol. 8, no. 2, pp. 155–162, 1995.

[26] V. A. Hill, T. Fisher, A. A. Schmid, J. Crabtree, and S. J. Page, "Relationship between touch sensation of the affected hand and performance of valued activities in individuals with chronic stroke," *Topics in Stroke Rehabilitation*, vol. 21, no. 4, pp. 339–346, 2014.

[27] N. M. Alotaibi, "The cross-cultural adaptation of the disability of arm, shoulder and hand (DASH): a systematic review," *Occupational Therapy International*, vol. 15, no. 3, pp. 178–190, 2008.

[28] D. Golicki, M. Krzysiak, and P. Strzelczyk, "Translation and cultural adaptation of the polish version of the disabilities of the arm, shoulder and hand (DASH) and QuickDASH questionnaires," *Ortopedia Traumatologia Rehabilitacja*, vol. 16, no. 4, pp. 387–395, 2014.

[29] P. Hedén and A. A. Pilla, "Effects of pulsed electromagnetic fields on postoperative pain: a double-blind randomized pilot study in breast augmentation patients," *Aesthetic Plastic Surgery*, vol. 32, no. 4, pp. 660–666, 2008.

[30] A. W. Thomas, K. Graham, F. S. Prato et al., "A randomized, double-blind, placebo-controlled clinical trial using a low-frequency magnetic field in the treatment of musculoskeletal chronic pain," *Pain Research and Management*, vol. 12, no. 4, pp. 249–258, 2007.

[31] G. Cheing, J. Wan, and S. Kai Lo, "Ice and pulsed electromagnetic field to reduce pain and swelling after distal radius fractures," *Journal of Rehabilitation Medicine*, vol. 37, no. 6, pp. 372–377, 2005.

[32] A. Straburzyńska-Lupa, W. Romanowski, A. Romanowska, and Z. Świetlik, "Ocena subiektywnego odczucia bólu i sprawności ruchowej u pacjentek z chorobą zwyrodnieniową stawów leczonych magnetoterapią i kinezyterapią," *Fizjoterapia Polska*, vol. 4, no. 2, pp. 151–156, 2004.

[33] H. Melchior, J.-J. Vatine, and P. L. Weiss, "Is there a relationship between light touch-pressure sensation and functional hand ability?" *Disability and Rehabilitation*, vol. 29, no. 7, pp. 567–575, 2007.

[34] J. Witkoś, J. Nowotny, A. Rudzińska, and K. Bąk, "Zmiany progu czucia pod wpływem pulsującego pola magnetycznego o niskim natężeniu," *Fizjoterapia*, vol. 15, no. 1, pp. 17–22, 2007.

[35] A. Skorupińska, M. Tora, and S. Bojarska-Hurnik, "Classification and elements of distal radius fractures treatment," *Fizjoterapia*, vol. 23, no. 3, pp. 40–46, 2015.

[36] S. D. M. Bot, C. B. Terwee, D. A. Van Der Windt, L. M. Bouter, J. Dekker, and H. C. De Vet, "Clinimetric evaluation of shoulder disability questionnaires: a systematic review of the literature," *Annals of the Rheumatic Diseases*, vol. 63, no. 4, pp. 335–341, 2004.

[37] A. Abramo, P. Kopylov, and M. Tägil, "Evaluation of a treatment protocol in distal radius fractures," *Acta Orthopaedica*, vol. 79, no. 3, pp. 376–385, 2008.

[38] N. Schott and H. Korbus, "Preventing functional loss during immobilization after osteoporotic wrist fractures in elderly patients: a randomized clinical trial," *BMC Musculoskeletal Disorders*, vol. 15, no. 1, p. 287, 2014.

[39] K. A. Egol, R. Karia, R. K. Zingman, S. Lee, and N. Paksima, "Hand stiffness following distal radius fractures. Who gets it and is it a functional problem?" *Bulletin of The Hospital for Joint Disease (2013)*, vol. 72, no. 4, pp. 288–293, 2014.

[40] M. K. T. Wilcke, H. Abbaszadegan, and P. Y. Adolphson, "Patient-perceived outcome after displaced distal radius fractures," *Journal of Hand Therapy*, vol. 20, no. 4, pp. 290–299, 2007.

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Research Article

Effects of 12-Week Exercise Program on Enzyme Activity of Serum Matrix Metalloproteinase-9 and Tissue Inhibitor of Metalloproteinase-1 in Female Patients with Postmenopausal Osteoporosis: A Randomized Control Study

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Background. Osteoporosis is a disease characterized by decreased bone density and destruction of bone microarchitecture. Indicators for altered bone homeostasis are changes in the serum level of matrix metalloproteinases (MMPs) and their tissue inhibitors (TIMPs). The purpose of the current study was to evaluate the effect of a 12-week exercise program on enzyme activity of serum MMP-9 and TIMP-1 in postmenopausal osteoporotic patients. *Materials and methods*. Participants were randomized in two groups: exercise (EG) ($N = 37$) and control (CG) ($N = 31$). The exercise group completed a 12-week supervised exercise program, while the control group did not take part in any physical activity. Enzyme activities of serum MMP-9 and TIMP-1 were detected by gelatin zymography and ELISA in both groups, respectively. *Results*. Significant differences between pretreatment and posttreatment enzyme activities of serum MMP-9 ($p = 0.009$), TIMP-1 ($p \leq 0.001$), and MMP-9/TIMP-1 ratio ($p \leq 0.001$) were detected in the exercise group. Exercises decreased the activity of serum MMP-9 and increased the activity of TIMP-1, while the enzyme activities of MMP-9 (0.583) and TIMP-1 (0.210) have not been significantly changed in CG. Patients from the exercise group had better treatment. *Conclusion*. Our results suggest that a 12-week exercise program has an influence on enzyme activity of serum MMP-9, revealing a possible role of MMPs in initiating training-specific adaptation. Although measurements of circulating MMP-9 and TIMP-1 allowed us to detect effects of exercise, as of today, they have no real role in the diagnosis of osteoporosis and/or follow-up of osteoporotic patient's response to treatment. MMP-9 might be used as an important prognostic marker for the evaluation of patient's response to exercise. Larger-randomized controlled studies need to be performed to expand this area of knowledge. This trial is registered with trial registration number: NCT03816449).

1. Introduction

Osteoporosis is a chronic, progressive, and systemic metabolic bone disease characterized by low bone mineral density and microarchitectural changes of bone tissue leading to an increased tendency to fractures [1, 2]. Because of its multifactorial dimension, identifying the factors that are involved in osteoclast and osteoclast differentiation is as important as their dynamic changes, depending on the use of appropriate therapy [1].

Matrix metalloproteinases (MMPs) are a family of zinc dependent, proteolytic enzymes, responsible for extracellular matrix (ECM) degradation and cleavage of its structural components such as collagen and gelatin, thus having a

crucial role in the process of ECM remodeling [3]. This process is important not only in bone formation but also in bone resorption, happening under physiological as well as pathological conditions, the latest arising mainly from altered MMP expression and activity causing abnormalities of the ECM remodeling [3, 4]. MMP expression and activity are very complex mechanism, regulated at different levels, including gene transcription, translation, secretion of the inactive proenzyme and proenzyme activation and inactivation via signaling from cytokines, growth and endocrine factors, integrins, and diverse ECM proteins [5, 6]. One of the principle modes of MMPs' regulation is through specific inhibition by direct binding to ECM secreted, tissue inhibitors of metalloproteinases, TIMPs (21–29 kDa) [7]. The association between MMP-1, MMP-2, MMP-3, MMP-9, and MMP-13 with the pathogenesis of osteoporosis has been demonstrated in different studies [5, 8, 9]. These are essential proteolytic enzymes responsible for early bone resorption because they degrade the collagen layer of the bone surface before demineralization begins [5, 8]. The complexity of the treatment of osteoporosis is reflected in the application of pharmacological and nonpharmacological therapy. According to the recommendations of the National Osteoporosis Foundation (NOF) bisphosphonates are still gold standard [1]. Nonpharmacological preventive measures include a modification of daily changes in physical activity, such as increasing weight-bearing exercises and muscle-strengthening exercise [1, 2]. Those exercises have an impact on slowing or stopping the loss of bone mass, improving balance, and reducing the risk of fall and fractures [1, 10, 11]. Weight-bearing exercise and resistance training might have an influence on osteogenesis only if the mechanical stress of long bones is strong enough [12]. This mechanical stress causes endogenous changes that interfere with bone remodeling, while the mechanical signal is being converted in biochemical signals that regulate bone activity mechanism [1, 2, 10–12].

Even if we assume that antiresorptive medicaments, together with the regular exercise program, are able to protect bone tissue to a similar extent [7], their mechanisms of action are most probably different. They may act on both organic and inorganic components, on both osteoblasts and the osteoclasts, and in both quantitative (protection of the bone) and qualitative sense (adequate primary and secondary mineralization, the formation of a normal organic matrix with suitable collagen fibers, etc.). The closer mechanism of these protective possibilities has to be clarified.

The serum MMP-9 concentration was observed to be negatively correlated with BMD (bone mineral density) and is considered as a biochemical marker of bone resorption and remodeling [13, 14] and an important marker in the early diagnosis of osteoporosis [8].

In bone tissue MMP-9 high specific degrading activity for denatured collagens in the ECM is highly expressed in osteoclasts, with a potential role in implantation and bone-resorbing activity of osteoclasts [5, 6, 15]. TIMP-1 is expressed from osteoblasts and osteocytes, and the activity of MMP-9 is likely to be inhibited by TIMP-1 [5]. Besides numerous experiments, a pathophysiologic understanding of MMP regulation focused on their mechanism of activation or suppression to date still remains partially resolved.

There is limited data of MMP-9 and TIMP-1 response on exercise. To our knowledge, there is no published data on enzyme activity of serum MMP-9 and TIMP-1 in postmenopausal women with osteoporosis involved in a 12-week exercise program performed with moderate intensity. In accordance with the current knowledge about the role of MMP-9 in bone remodeling and osteoporosis [3–5, 7, 16], we assumed that the serum level of MMP-9 could serve as an important marker for early assessment of treatment response. During this study, the enzyme activity of serum MMP-9, TIMP-1, as well as MMP-9/TIMP-1 ratio were observed in patients with postmenopausal osteoporosis, before and after prescribing to a 12-week exercise program [1, 2, 10–12, 17]. Therefore the aim of the study was to evaluate the enzyme activity of serum MMP-9 and TIMP-1 at baseline and after the 12-week period of supervised exercise program. MMP-9 activation was characterized by substrate gel electrophoresis (gelatin zymography) [18–20], while TIMP-1 by enzyme-linked immunosorbent assay (ELISA).

This study of a moderately sized, carefully defined group with well-constructed analysis sought to validate the effectiveness of a specifically designed exercise program on postmenopausal osteoporotic patient rehabilitation based on a careful evaluation of enzyme activity of serum MMP-9 and TIMP-1 at baseline and after the 12-week period.

2. Materials and Methods

2.1. Patient Population and Treatment. Of the 108 patients who were screened for eligibility, 74 female patients were invited for participation. Of these, 72 potential participants were recruited for the study, of whom 70 showed up at the first visit and were randomized. The eligible consecutively recruited participants were randomly assigned in two groups in 1 : 1 ratio. In total, 37 patients in the exercise group (EG/aged 64.27 ± 5.61) and 31 in the control group (CG/aged 64.39 ± 4.50) accomplished the 3 months measurements and were included in the intent-to-treat analysis (Figure 1). Before starting the intervention, 70 female patients with postmenopausal osteoporosis started with regular medicamentous (bisphosphonate) therapy for osteoporosis according to the NOF recommendations [1]. Precisely, patients from both groups (EG and CG) have been treated with alendronate therapy and this treatment have not been changed during the study. Participants were highly motivated so there was high compliance (about 97%, 70 participants started the intervention, but two of them dropped off due to some personal reasons (one from the experimental, one from the control group); 68 of them completed the intervention period and were taken to final evaluation).

Standard recruiting criteria were as follows: (1) having postmenopausal osteoporosis diagnosed by central osteodensitometry (DEXA BMD, Osteosys: H2AY-002A, Seoul, Korea) according to T-score value at the lumbar spine and femoral neck (≤ -2, 5) [1, 2] at the Institute of

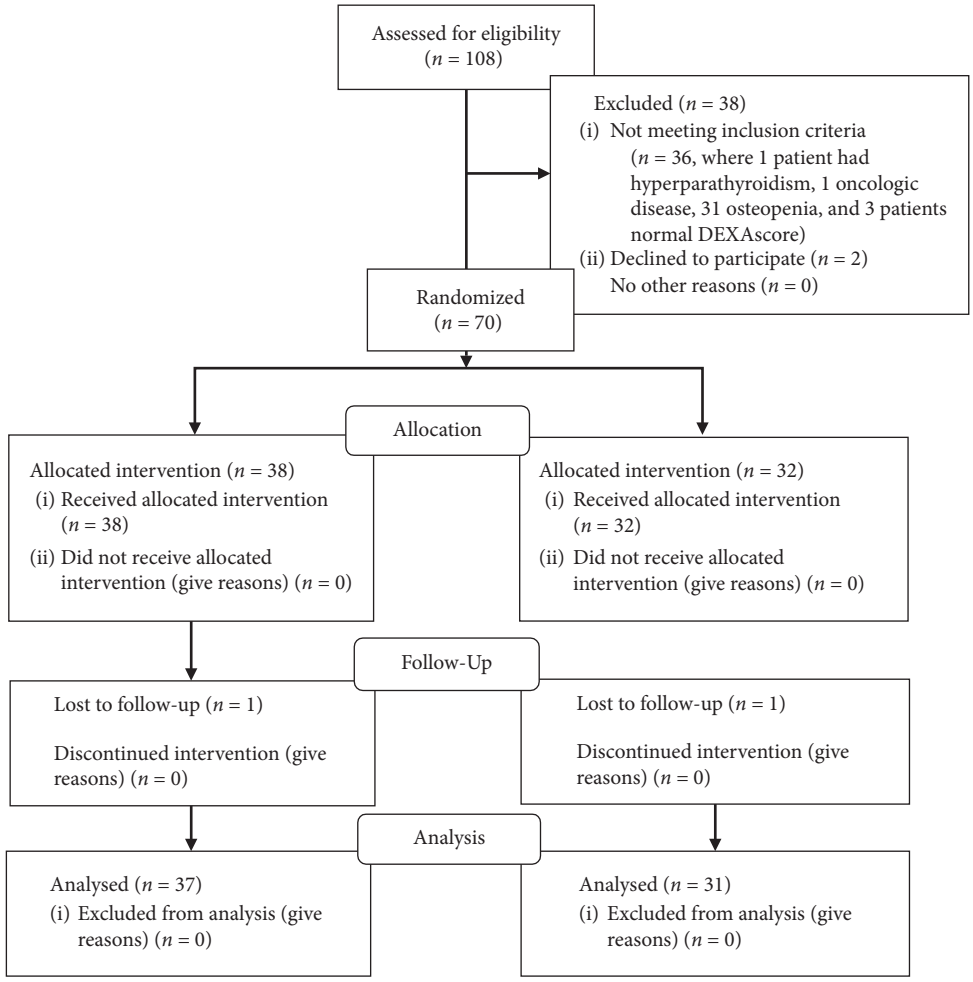

Figure 1: Participants flowchart.

rehabilitation, in Belgrade, (2) female patients of age between 65 and 70 years or even younger having any of the risk factors for osteoporosis (such as positive family history on a low-energy fracture, early menopause, prolonged amenorrhea) [1, 2], (3) being sedentary at the beginning of the study and during previous 6 months, which was conducted as not performing any exercise and fast walking for more than 15 minutes, more than twice/weekly for the above-mentioned period.

Exclusion criteria were as follows: previous history of osteoporotic fracture, perimenopausal status, metabolic bone disease, oncological diseases, hyperparathyroidism, corticosteroid therapy applied longer than 3 months, any hormonal therapy, liver and kidney dysfunction, resting blood pressure greater than 160/95 mmHg, and participation in any kind of physical activity for the last 6 months. The treatment consisted of a 12-week supervised exercise program proscribed to the patients in EG, while patients in CG did not take part in any physical activity for 12 weeks (during the study program).

All participants were informed about the study design. After getting written informed consent patients were physically examined and included in the study.

The study protocol was approved by the Ethics Committee of the Institute for rehabilitation, in Belgrade (Serbia), protocol number 02/2119-1, and reviewed and approved by ClinicalTrials.gov identifier (NCT number: NCT03816449). During the research, we took care to protect the privacy and anonymity of the respondent's data. The research was performed in compliance with the relevant laws and institutional guidelines.

2.2. Exercise Program. The exercise program designed by our research group has been previously described [21]. Shortly, the exercise group included 37 postmenopausal women who practiced the combined exercise program: aerobic exercise, resistance training, and balance exercise.

Rapid walking, 3–5 km/h, was prescribed as aerobic exercise. The intensity of the training was determined according to the maximal heart rate and was approximately 70% of its value [22]. Patients had this kind of activity five days per week, 50 minutes per day, for 12 weeks.

Resistance training and balance exercises were prescribed as a supervised group program. This program included balance exercises and exercises for strengthening muscles of the upper and lower extremities. The intensity of the "strength and resistance exercise program" was progressively increased on the weekly basis starting from 3 to 5

repetitions with no additional weight load per training going up to 8–12 repetitions with an extra weight load applied with the use of straps ("TheraBand," Akron, Ohio-USA). Progression and maintenance of the weight load was decided together with the patient depending on the individual capacity [23]. The frequency of training was 3 times per week, each of 70-minute duration. The total exercise program lasted 12 weeks [21].

Certain functional assay [21] was used for monitoring the outcomes of the exercise performance. For the first 4 weeks patients had supervised exercise program with a trained exercise specialist at the Institute for Rehabilitation. After adopting technique of performing the exercises, participants continued to perform the same at home. They were told to write a diary of their regular exercise activity, while these dairies had been controlled three times during the study. Moreover, during the intervention period functional outcomes, such as Time-up and go test (TUG), sit to stand test (STS), and One leg Stance tests (OLST) had been conducted to evaluate patients' responses to exercise and objective the results. These tests had been observed before treatment and after the first and second months of treatment.

Patients from the control group (31 postmenopausal women) did not participate in any kind of exercise program, during the research period (12 weeks). For ethical reasons, after this period of time, the same exercise program had been proposed to patients from the control group, in order to accomplish complete treatment.

2.3. Testing Procedures

2.3.1. Gelatin Zymography for the Assay of Enzyme Activity of Serum MMP-9. Pre- and poststudy blood samples were taken after 12 h overnight fast at 8.00-9.00 a.m. The blood was collected in vacutainers; the serum was separated by centrifugation (3000 rpm) and then stored at −20°C for future examination [18–20].

The activity of matrix metalloproteinase 9 (MMP-9) was determined by sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS–PAGE) under nonreducing conditions and in gels with copolymerized gelatin [18–20]. MMP-9 (SIGMA-Aldrich, SAE0077 MMP-9-human, recombinant, ≥1,300 pmol/min/μg, expressed in HEK 293 cells) was used as a standard for molecular weight calibration and was applied onto a gel without further preparation [19–25].

Briefly, appropriately diluted with 20% sucrose solutions, samples of sera from both groups, EG and CG, were mixed with buffer for treatment of samples contained: 0.125 M Tris-HCl; 4% SDS, 20% v/v glycerol; and 0.02% Bromophenol Blue, pH 6.8, in a volume ratio 1 : 1 and preincubated at 37°C for 45 minutes. Then, samples were applied onto wells (10 μl/lane) and electrophoretically separated on 7.5% sodium dodecyl sulfate-polyacrylamide slab gels (Sodium Dodecyl Sulphate Polyacrylamide Gel Electrophoresis SDS–PAGE) containing copolymerized gelatin (1.0 mg/ml) under the conditions: $U = 150$ V, $A = 50$ mA, at +4°C for 90 minutes [18–20, 24].

Following electrophoresis, gels were washed three times for 20 min in renaturation buffer (2.5% Triton X-100), twice in double distilled water at +4°C, and then incubated for 24 h at 37°C in a buffer for enzyme assay (50 mmol/l Tris–Cl, pH 7.5 and 5 mmol/l $CaCl_2$ in a volume 100 ml) in a thermostatically controlled water bath (Lab-ThermKühner Shaker, Kühner, Switzerland) at 50 rotations in a minute. After the incubation, gels were stained with 0.05% (w/v) Coomassie Brilliant Blue G-250 dye (CBB G-250) in a mixture of methanol: acetic acid: water (2.5 : 1 : 6.5) and destained with solution which contained 4% methanol (4%) and acetic acid (8%). The appearance of the clear zone to the dark blue background of the gel that was colored with CBB G-250 indicated the gelatinase activity [18–20, 24]. Finally, gelatinolytic activities were analyzed densitometrically using ImageJ 1.48v software (National Institutes of Health, Bethesda, MD, USA), calculating the densitometric value of the lyses against a dark blue background on zymography gels which quantified the surface and the intensity of the lysis bands after scanning of gels. MMP-9 electrophoretic migration was compared to known gelatinase molecular weight standard [20, 24]. Gels were photographed wet with background lighting and dried under vacuum between porous cellophane sheets and stored at room temperature. Gelatin substrate digestion levels were quantified as relative proteinase activity, comparing to relative activity of standard MMP-9, and recalculated according to activity of standard, which was applied in quantity of 10 ng/ml into corresponding concentrations of ng/ml.

2.3.2. Enzyme-Linked Immunosorbent Assay (ELISA) for TIMP-1. TIMP-1 was determined using the enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's recommendations.

The ELISA kit (Elabscience Biotechnology Inc., 2019–2020) was used for in vitro quantitative determination of human serum TIMP-1 with 0.10 ng/ml sensitivity, 0.16–10 ng/mL detection range, and no significant cross-reactivity or interference between Human TIMP-1 and analogues. Briefly, the Sandwich-ELISA principle used consists in the microplate precoated with a primary human anti-TIMP-1 specific antibody; TIMP-1 standards (for the standard curve formation) or study samples were added to the plate and let to combine with the specific antibody; then a secondary, biotinylated detection antibody specific for Human Ig G and Avidin-Horseradish Peroxidase (HRP) conjugate were added successively to each microplate well and incubated. Free components were washed away and finally the substrate solution was added to each well and left for the enzymatic reaction to occur. Only those wells that contained Human TIMP-1 appeared blue in color, which turned into yellow after the addition of stop solution and its optical density (OD) was measured at 450 nm ± 2 nm using a microplate reader (Rayto RT-6100). The OD values were then plotted on the standard curve for evaluation of TIMP-1 concentrations in each sample (sera of EG and CG).

2.4. Statistical Analysis. This is the primary analysis of these data. All statistical analyses were performed using the SPSS package program version 20.0 (IBM corporation). Complete-case analysis was performed without missing values imputation. Results were presented as mean ± standard deviation. Student's *t*-test or Mann–Whitney *U* test was used to determine the difference between the two groups. Differences between pre- and poststudy values of the intervention period were determined by using Wilcoxon Signed Ranks test.

The mean difference between the exercise and the control groups after 12 weeks was assessed by linear regression analysis (the mean difference is reported as β). Changes in MMP-9, TIMP-1, and MMP-9/TIMP-1 ratio were analyzed with the randomization group and baseline values as explanatory measures. Skewed continuous dependent variables were natural log-transformed before regression analysis. All p values < 0.05 (two-tailed) were considered significant.

3. Results

3.1. General Clinical Characteristics of Postmenopausal Osteoporotic Female Patients. Prestudy values of BMI (Body Mass Index), lumbar and neck *T*-score, biochemical parameters, and age were not significantly different between groups (EG and CG groups). Serum level of 25 (OH) vitamin D, total calcium, 24 h urinary calcium, Phosphate, 24 h urinary Phosphate, Creatinine, Creatinine Clearance, Albumin, Total Protein, Osteocalcin, Diuresis, Alkaline Phosphatase (ALP), Thyroid-Stimulating Hormone (TSH), Free Thyroxine (FT4), and Parathyroid Hormone (PTH) were measured at baseline in all participants. These parameters in both groups were insignificantly different (Table 1), except for Creatinine Clearance ($p = 0.017$).

3.2. Changes during the Specific Exercise Program. Comparing the enzyme activity of serum MMP-9 ($p = 0.075$) and TIMP-1 ($p = 0.777$) at baseline, there was no statistically significant difference between groups. A significant difference was noted between pre- and postenzyme activity of serum MMP-9 ($p = 0.009$), TIMP-1 ($p < 0.001$), and MMP-9/TIMP-1 ratio ($p < 0.001$) in EG (Table 2). No high significant differences have been noted between pre- and postenzyme activity of serum MMP-9 ($p = 0.583$) and TIMP-1 ($p = 0.210$) in CG (Table 2), only for the MMP-9/TIMP-1 ratio, a statistically significant change ($p = 0.028$) was noted. The 12-week exercise program caused a significant decrease in the enzyme activity of serum MMP-9, as well as increased TIMP-1 in EG, while these differences have not been significant in CG (Figure 2).

Regression analysis demonstrated a significant mean difference in TIMP-1 after 12 weeks of follow-up between groups adjusted for age, baseline BMI, Vitamin D, and total PTH and Ca ($\beta = -322.08$ [95% CI-436.74–207.41]; $p \leq 0.001$) and in MMP-9/TIMP-1 ratio after 12 weeks of follow-up between groups adjusted for age, baseline BMI, and Vitamin D ($\beta = 24.02$ [95% CI-13.32–34.73]; $p \leq 0.001$). This result remained significant after adjustments for age, baseline BMI, Vitamin D, and total PTH and Ca: TIMP-1 ($\beta = -318.32$ [95% CI-433.44–203.21]; $p \leq 0.001$), MMP-9/TIMP-1 ratio ($\beta = 23.73$ [95% CI-13.00–34.46]; $p \leq 0.001$) (Table 3).

4. Discussion

It is well known that bone loss diseases, such as osteoporosis and rheumatoid arthritis, occur as a result of excessive bone resorption and bone remodeling imbalance correlated with increased catabolic processes and increased osteoclast activity [1, 2]. Enhanced osteoclast activity increases expression of MMP-9 which stimulates osteoclast reabsorption and degrades extracellular matrix proteins and collagen type I [5]. This role of MMP-9 is well documented in studies with wild-type mice which showed an excellent correlation between MMP-9 and invasion of osteoclasts into the core of diaphysis [13]. Moreover, studies on animal models also proved that MMP-9 can be a marker for osteoclast activity [5]. Widely used ovariectomized rat model recently showed a significant decrease in MMP9 activity, observed by means of gelatin zymography, after pharmacological treatment [14]. Finally, human studies confirmed the overexpression of MMP-9 in subjects suffering from osteoporosis [26].

Based on these facts, we hypothesized that well designed, controlled, 12-week exercise program could cause the inhibition of osteoclasts activity associated with the downregulation of MMP9 activity.

To test this hypothesis, we investigated changes in MMP-9 activity before and after the exercise program using gelatin zymography as a molecular technique.

In our study, we have tried to evaluate the response of enzyme activity of serum MMP-9 and TIMP-1 on appropriate treatment in postmenopausal osteoporosis, which must include pharmacological and nonpharmacological therapy. Taking into account the role of bisphosphonates in regulating activation pathways for MMPs in general and in osteoporosis [27, 28], as well as the necessity of proscribing adequate exercise program, we were interested in the role of supervised exercise program in this regulation, specifically. We proposed that pharmacological and nonpharmacological "agents," working together, would have the ability to modulate MMPs activity in a period of 3 months. Studies on serum or plasma levels of gelatinase and their inhibitors showed an early release of MMP-9 after acute exercise of sufficient intensity, while data on TIMP-1 and the other MMPs were more contrasting. Most of the studies dealing with the effects of training indicated a trend toward reduction in blood gelatinase levels, once again more clear for MMP-9 which is in line with our results. The results were related to an anti-inflammatory effect of regular exercise and were more evident when training consisted of aerobic activities [7]. A few data available about resistance exercise suggest opposite effects on gelatinase concentrations [7, 29, 30].

We reported decreased enzyme activity of MMP-9 (Figure 3), as well as increased TIMP-1 in the serum of female patients with postmenopausal osteoporosis, who had

Table 1: Initial clinical and biochemical characteristics for OP female patients in the exercise group and controls.

	Exercise $N = 37$	Controls $N = 31$	p value[1]
Age (years)	64.27 ± 5.61	64.39 ± 4.50	0.924
BMI	26.00 ± 4.48	25.42 ± 3.59	0.556
25 hydroxy vitamin D (nmol/L)	47.03 ± 17.51	45.61 ± 19.83	0.579[2]
Calcium, total (mmol/L)	2.44 ± 0.16	2.46 ± 0.21	0.659
24 hour urinary calcium (mmol/24H)	4.72 ± 4.07	4.61 ± 1.64	0.157[2]
Calcium ionized (mmol/L)	1.31 ± 0.26	1.34 ± 0.26	0.743
Phosphate (mmol/L)	1.120.21	1.34 ± 1.23	0.985[2]
24 hour urinary Phosphate (mmol/24H)	17.54 ± 7.79	14.32 ± 6.54	0.061[2]
Creatinine (μmol/L)	67.39 ± 9.92	72.93 ± 7.69	0.128
Creatinine urine (mmol/24H)	8.96 ± 2.94	9.11 ± 2.10	0.392[2]
Creatinine clearance (ml/min)	87.06 ± 13.46	79.72 ± 11.14	0.017
Albumin (g/L)	48.41 ± 5.46	48.11 ± 4.54	0.804
Total protein (g/L)	75.56 ± 7.62	73.34 ± 5.80	0.178
PTH (ng/L)	55.00 ± 30.31	54.17 ± 20.89	0.618[2]
FT4 (pmol/L)	14.49 ± 2.98	13.95 ± 3.99	0.319[2]
TSH (μIU/L)	2.62 ± 2.03	2.76 ± 1.16	0.162[2]
Osteocalcin (ng/ml)	24.14 ± 11.72	27.52 ± 9.43	0.048[2]
Diuresis (ml) ℙ	2050.27 ± 472.80	2170.97 ± 466.15	0.209[2]
ALP (U/L)	72.59 ± 30.15	74.71 ± 32.23	0.554[2]
T-score $L1$–$L4$	−2.65 ± 0.89	−2.84 ± 0.74	0.268[2]
T-score neck	−2.59 ± 0.80	−2.42 ± 0.85	0.336[2]

[1]Data are expressed as mean ± SD. Biochemical data are before treatment. $p < 0.005$ vs. controls. [1]Student's t-test. [2]Mann–Whitney test.

Table 2: Changes in enzyme activity of serum MMP-9, TIMP-1, and MMP-9/TIMP-1 ratio in EG and CG.

	Baseline	12 weeks	p value[1]
MMP-9 (ng/mL)			
Exercise group	785.19 ± 511.76	456.57 ± 284.90	0.009
Control group	731.19 ± 788.3	595.06 ± 481.19	0.583
p value[2]	0.075	0.538	
TIMP-1 (ng/mL)			
Exercise group	27.59 ± 30.06	350.32 ± 313.93	<0.001
Control group	26.74 ± 28.75	32.64 ± 25.21	0.210
p value[2]	0.777	<0.001	
Ratio MMP-9/TIMP-1			
Exercise	46.97 ± 38.86	1.59 ± 0.82	<0.001
Control group	34.59 ± 40.69	25.37 ± 32.56	0.028
p value[2]	0.018	<0.001	

[1]Wilcoxon Signed Ranks test. [2]Mann–Whitney test.

been involved in a 12-week exercise program, compared with those who have not got any physical activity treatment. These results point to the statistically significant reduction of the MMP-9/TIMP-1 ratio in EG (Figure 2).

On the contrary, in the CG, we reported no statistically significant slight increase of enzyme activity of serum MMP-9 and slight decrease of TIMP-1. These slight changes resulted in a statistically significant change in the MMP-9/TIMP-1 ratio in CG, which was probably induced by bisphosphonates therapy only. Comparing the results from both groups, we concluded that patients from the exercise group had better treatment.

In this study, we revealed a statistically significant decrease in the enzyme activity of serum MMP-9 in osteoporotic patients who had been training with resistance, walking, and balance exercise (Figure 3). The experimental evidence showed an early upregulation of MMP-9 and TIMP-1 expression by a specific 12-week exercise program. There is a growing body of evidence that MMP-9 and their tissue inhibitor do have important roles and show significant changes after exercise [29] which is in line with our results showing increased TIMP-1. Contrasting results have been published by Buyukyazi [31], who have reported no significant changes in the circulation of MMP-9 and TIMP-1 in postmenopausal healthy women after 8-week physical activity, which included walking only. Several studies demonstrated some acute changes in MMP-9 and TIMP-1 levels due to exercise [31]. These findings may suggest that there are some changes in the myofiber basement membrane via the MMP pathway in response to muscle damaging exercise [31]. The contradiction may result from the modes of the exercise programs since all the aforementioned studies measured the acute effects; however, we tried to demonstrate the chronic effects of endurance training in osteoporosis. Although a few papers reported decreased or unaltered circulating MMP-9 levels in osteoporotic patients on bisphosphonates therapy, none of them specially considered the influence of combined therapy (bisphosphonates and exercise) on the MMP-9 and TIMP-1 serum level. To our knowledge, this is the first study which underlined the tremendously important role of exercise in combination with bisphosphonate therapy and their influence in regulating the activity of serum MMP-9 and TIMP-1 in a follow-up period of 3 months in postmenopausal Serbian osteoporotic women. As we have shown in this paper, the possibility to assay the enzyme activity of serum MMP-9 and TIMP-1 may reflect a matrix turnover in osteoporotic patients according to the adequate treatment. Moreover, this can provide a valuable tool for

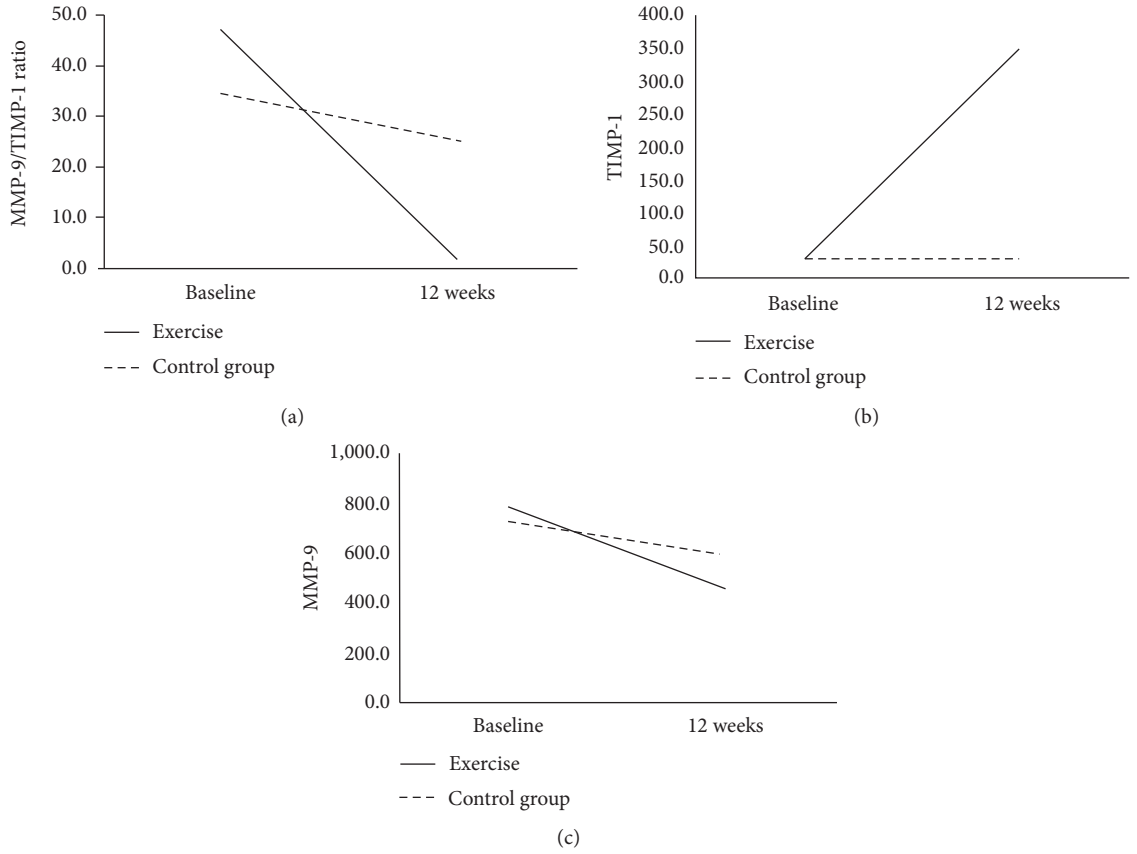

Figure 2: MMP-9, TIMP-1, and MMP-9/TIMP-1ratio followed over time in EG and CG.

Table 3: The difference between enzyme activity of serum MMP-9, TIMP-1, and MMP-9/TIMP-1 ratio in the exercise and control groups after 12 weeks adjusted for baseline values of age, BMI, vitamin D, and total PTH and Ca.

	Adjusted[1] β	95% CI	p value	Adjusted[2] β	95% CI	p value
MMP-9 (ng/mL)	143.54	−45.13–332.21	0.133	147.08	−43.95–338.12	0.129
TIMP-1 (ng/mL)	−322.08	−436.74–207.41	<0.001	−318.32	−433.44–203.21	<0.001
Ratio MMP-9/TIMP-1	24.02	13.32–34.73	<0.001	23.73	13.00–34.46	<0.001

Adjusted[1] β: adjusted for age, baseline BMI, and baseline Vitamin D. Adjusted[2] β: adjusted for age, BMI, Vitamin D, total PTH, and Ca. 95% CI: 95% confidence interval.

Figure 3: Serum activity of MMP-9 in the EG obtained by gelatin zymography. Representative protein bands of the MMP-9 protein are shown (a) before and (b) after the 12-week exercise program.

evaluating osteoporotic patient response on well designed exercise training. Since MMP-9 was demonstrated to regulate the occurrence and development of osteoporosis [8] it may serve as a potential marker for the prediction and diagnostic method for postmenopausal osteoporosis. Also, if this marker was to be used clinically as a surrogate marker for techniques designed primarily or secondarily affecting ECM structure, consideration should be given to different reference ranges in younger and older osteoporotic patients, as well as their medical therapy. The facts described above suggest that the reduction of bone turnover is perhaps the most important factor during the course of osteoporosis, which can be achieved by using appropriate physical activity, as well as some pharmacotherapy. Thus the demonstration of MMP-9 and TIMP-1 in serum of female patients with postmenopausal osteoporosis provides information about bone turnover and its changing depending on exercise therapy.

5. Conclusion

The present findings indicate that exercise has significant effects on the enzyme activity of serum MMP-9 and TIMP-1 in humans, in vivo. Secondary, postmenopausal osteoporotic women can quickly reduce the risk of fall and improve their BMD, if they are willing to undergo intensive lifestyle modification. The real challenge is to maintain these lifestyle changes beyond 3 month exercise program. A moderate intensity, long duration program accompanied by pharmacotherapy and diet is proposed.

With its supervised prospective nature, this is the first study that examined changes in enzyme activity of serum MMP-9, TIMP-1, and MMP-9/TIMP-1 ratio in postmenopausal osteoporotic women following 12-week exercise program which included resistance training, balance exercise, and walking, besides medical therapy.

The main limitation of the study is its relatively small sample size and relatively small follow-up period, which may represent a source of bias. We had to form small groups due to the strict inclusion and exclusion criteria and the need for strict supervision.

Before our conclusions will be clinically applied, larger-randomized controlled multicenter studies will be required to validate our findings including the links (if any) to gene polymorphisms that may influence MMP/TIMP levels.

Data Availability

The data used to support the findings of this study are included within the article.

Disclosure

None of the funding bodies had any role in the design of the study, collection, analysis, and interpretation of data and in writing the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

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References

[1] J. A. Kanis, C. Cooper, R. Rizzoli, and J.-Y. Reginster, "European guidance for the diagnosis and management of osteoporosis in postmenopausal women," *Osteoporosis International*, vol. 30, no. 1, pp. 3–44, 2019.

[2] F. Cosman, S. J. de Beur, M. S. LeBoff et al., "Clinician's guide to prevention and treatment of osteoporosis," *Osteoporosis International*, vol. 25, no. 10, pp. 2359–2381, 2014.

[3] K. B. S. Paiva and J. M. Granjeiro, "Matrix metalloproteinases in bone resorption, remodeling, and repair," *Progress in Molecular Biology and Translational Science*, vol. 148, pp. 203–303, 2017.

[4] H. P. H. Liang, J. Xu, M. Xue, and C. Jackson, "Matrix metalloproteinases in bone development and pathology: current knowledge and potential clinical utility," *Metalloproteinases In Medicine*, vol. 3, pp. 93–102, 2016.

[5] A. Grigoryan, "Serum concentrations of matrix metalloproteinase-9, -13 and TIMP-1 in an ovariectomized wistar rat model of osteoporosis," *Archives of the Balkan Medical Union*, vol. 52, no. 4, pp. 391–396, 2017.

[6] Y. Kim, J. Kim, H. Lee et al., "Tetracycline analogs inhibit osteoclast differentiation by suppressing MMP-9-mediated histone H3 cleavage," *International Journal of Molecular Sciences*, vol. 20, no. 16, p. 4038, 2019.

[7] R. Lo Presti, E. Hopps, and G. Caimi, "Gelatinases and physical exercise: a systematic review of evidence from human studies," *Medicine (Baltimore)*, vol. 96, no. 37, p. e8072, 2017.

[8] X. Zheng, Y. Zhang, S. Guo, W. Zhang, J. Wang, and Y. Lin, "Dynamic expression of matrix metalloproteinases 2, 9 and 13 in ovariectomy-induced osteoporosis rats," *Experimental and Therapeutic Medicine*, vol. 16, no. 3, pp. 1807–1813, 2018.

[9] B. Sun, J. Sun, X. Han et al., "Immunolocalization of MMP 2, 9 and 13 in prednisolone induced osteoporosis in mice," *Histology and Histopathology*, vol. 31, no. 31, pp. 647–656, 2016.

[10] M. Kocic, Z. Stojanovic, and M. Lazovic, "Relationship between fear of falling and functional status in nursing home residents aged older than 65 years," *Geriatrics & Gerontology International*, vol. 17, no. 10, pp. 1470–1476, 2017.

[11] L. M. Giangregorio, S. McGill, J. D. Wark et al., "Too fit to fracture: outcomes of a delphi consensus process on physical activity and exercise recommendations for adults with osteoporosis with or without vertebral fractures," *Osteoporosis International*, vol. 26, no. 3, pp. 891–910, 2015.

[12] A. Keshishian, N. Boytsov, R. Burge et al., "Examining the treatment gap and risk of subsequent fractures among females with a fragility fracture in the US Medicare population," *Osteoporosis International*, vol. 28, no. 8, pp. 2485–2494, 2017.

[13] A. Andrea, K. Kenneth, and H. Kurt, "Extracellular matrix networks in bone remodeling," *The International Journal of Biochemistry & Cell Biology*, vol. 65, pp. 20–31, 2015.

[14] L. J. Chai, "The antiosteoporosis effects of zhuanggu guanjie pill in vitro and in vivo," *BioMed Research International*, vol. 2018, Article ID 9075318, 11 pages, 2018.

[15] D. Maugeri, C. Mamazza, F. L. Giudice et al., "Interleukin-18 (IL-18) and matrix metalloproteinase-9 (MMP-9) in postmenopausal osteoporosis," *Archives of Gerontology and Geriatrics*, vol. 40, no. 3, pp. 299–305, 2005.

[16] D. Nascimento, R. Durigan, R. Tibana, J. Durigan, J. Navalta, and J. Prestes, "The response of matrix metalloproteinase-9 and -2 to exercise," *Sports Medicine*, vol. 45, no. 2, pp. 269–278, 2015.

[17] E. Howe, B. Shea, J. Dawson et al., "Exercise for preventing and treating osteoporosis in postmenopausal women," *Cochrane Database System Reviews*, vol. 7, Article ID CD000333, 2011.

[18] G. Makowski and M. Ramsby, "Autoactivation profiles of calcium-dependent matrix metalloproteinase-2 and -9 in inflammatory synovial fluid: effect of pyrophosphate and

bisphosphonates," *Clinica Chimica Acta*, vol. 358, no. 1-2, pp. 182–191, 2005.

[19] G. La Rocca, I. Pucci-Minafra, A. Marrazzo, P. Taormina, and S. Minafra, "Zymographic detection and clinical correlations of MMP-2 and MMP-9 in breast cancer sera," *British Journal of Cancer*, vol. 90, pp. 1414–1421, 2004.

[20] K. Gopcevic, B. Rovcanin, D. Kekic, Z. Krivokapic, and V. Dragutinovic, "Matrix metalloproteinase-2 and -9, lactate and malate dehydrogenase and lipid peroxides in sera of patients with colorectal carcinoma," *Folia Biologica*, vol. 63, pp. 190–196, 2017.

[21] Influence of exercise program on serum matrix metalloproteinases and functional status in women with postmenopausal osteoporosis, https://clinicaltrials.gov/ct2/show/NCT03816449.

[22] N. Sydo, S. S. Abdelmoneim, S. L. Mulvagh, B. Merkely, M. Gulati, and T. G. Allison, "Relationship between exercise heart rate and age in men vs women," *Mayo Clinic Proceedings*, vol. 89, no. 12, pp. 1664–1672, 2014.

[23] G. A. Borg, "Psychophysical bases of perceived exertion," *Medicine & Science in Sports & Exercise*, vol. 14, no. 5, pp. 377–381, 1982.

[24] G. S. Makowski and M. L. Ramsby, "Calibrating gelatin zymograms with human gelatinase standards," *Analytical Biochemistry*, vol. 236, no. 2, pp. 353–356, 1996.

[25] T. Vartio and M. Baumann, "Human gelatinase/type IV procollagenase is a regular plasma component," *FEBS Letters*, vol. 255, no. 2, pp. 285–289, 1989.

[26] C. Bolton, M. Stone, P. Edwards, J. Duckers, W. Evans, and D. Shale, "Circulating matrix metalloproteinase-9 and osteoporosis in patients with chronic obstructive pulmonary disease," *Chronic Respiratory Disease*, vol. 6, no. 2, pp. 81–87, 2009.

[27] X. Tong, X. Chen, and S. Zhang, "The effect of exercise on the prevention of osteoporosis and bone angiogenesis," *BioMed Research International*, vol. 2019, Article ID 8171897, 8 pages, 2019.

[28] F. R. Deliberador, A. M. Sebastiani, J. Gerber et al., "Effect of local application of alendronate and parathyroid hormone on craniofacial bone repair-a preliminary study," *Brazilian Dental Journal*, vol. 29, no. 5, pp. 435–445, 2018.

[29] D. C. Jinga, A. Blidaru, I. Condrea et al., "MMP-9 and MMP-2 gelatinases and TIMP-1 and TIMP-2 inhibitors in breast cancer: correlations with prognostic factors," *Journal of Cellular and Molecular Medicine*, vol. 10, no. 2, pp. 499–510, 2006.

[30] M. L. Urso, J. R. Pierce, J. A. Alemany, E. A. Harman, and B. C. Nindl, "Effects of exercise training on the matrix metalloprotease response to acute exercise," *European Journal of Applied Physiology*, vol. 106, no. 5, pp. 655–663, 2009.

[31] G. Buyukyazi, C. Ulman, F. Taneli, D. Aksoy, H. Tıkız, and Z. Arı, "The effects of an 8-week walking program on serum lipids, circulation matrix metalloproteinase-9 and tissue inhibitor of metalloproteinase-1 in post- menopausal women," *Turkish Journal of Biochemistry*, vol. 33, no. 4, pp. 154–162, 2008.

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Research Article

Dynamics of Changes in Isometric Strength and Muscle Imbalance in the Treatment of Women with Low back Pain

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The aim of the study was to evaluate the dynamics of isometric changes in strength and muscular lumbar-pelvic imbalances in the treatment of women with low back pain. Forty-one women, nineteen in the study group (A) and twenty-two in the control group (B), participated in the study. Magnetic resonance imaging (MRI) was performed to assess the degree of degenerative changes in the lumbar spine. The diagnosis of isometric muscle strength and their imbalances was performed with the Tergumed 700 device. After six weeks of therapy in the study group (A), there was a significant improvement in the strength of all the examined muscle groups. However, in the control group (B), significant improvement occurred only in the strength of the lumbar flexor muscles and the flexor muscles on the left side. Furthermore, there was a significant intensification of the imbalance of left flexor muscle strength compared to right flexor strength in group B. Significant differences in favour of the study group (A) concerned the strength of the rotator muscles to the left, the strength of the extensor muscles of the lumbar spine, the strength of the flexors of the lumbar spine to the right, and the balance of the strength of the lumbar spine flexors to the left compared to the strength of the flexor muscles to the right. Therapy with the Tergumed 700 system leads to an increase in the muscle strength of the lumbar and pelvic complex, compensating for its imbalance, bringing beneficial effects in the treatment of low back pain.

1. Introduction

Low back pain is one of the most commonly diagnosed diseases of the osteoarticular system [1]. It is also the most frequently reported ailment [2] and the second main cause of sickness absence [3]. It is the most common cause of the inability to perform work [4] and is one of the main causes of physical disability of people below the age of 45 [5]. Pain syndromes can be divided into specific and nonspecific [6, 7]. Myofascial overloads, ligament injuries, and psychogenic factors are considered to be the causes of those nonspecific [8, 9]. Specific pains are most often caused by a herniated nucleus, spondylolisthesis, spinal canal stenosis, degenerative changes of the interappendix joints, vertebral fractures, spinal tumours, or inflammatory diseases [10, 11]. Pain sensations may be dull and diffuse but may also be shooting, stabbing, causing a burning or stinging sensation [12, 13]. In the population, nonspecific back pain is the most common, that is, the basis for which the specific pathology that causes the pain cannot be found [14, 15]. In acute pain, appearing for the first time in life, only 2% of patients can determine its cause [16, 17]. The incidence of this disease entity causes a significant burden on the state budget. The largest direct costs are generated by diagnostics, treatment, and rehabilitation, while indirect costs are disability pensions, benefits, and sick leaves at work [18, 19].

There are many suggestions in the available literature for conservative treatment of low back pain [20, 21]. Properly targeted kinesiotherapy plays a dominant role [22, 23]. In recent years, various devices have been developed to create optimal conditions for conducting isolated exercises regarding the lumbar region of the spine [24]. Tergumed is one such system used in the diagnosis and therapy of low back pain.

Research conducted using this system, however, generally took the short duration of therapy into account, which

hindered its objective assessment. There is also a lack of research on the dynamics of changes in strength and muscle imbalance at individual periods of therapy, or comparison of results with the control group. Therefore, there was a need to conduct a comprehensive, objective, and controlled clinical study as well as a thorough analysis of the dynamics of changes in muscle activity and their imbalances [25].

For stabilization, the spine needs both muscle strength and stiffness, to which the muscles contribute. Due to the recognition of the close relationship between muscle function and low back pain, a new paradigm has been developed regarding the function and dysfunction of the deep muscle system. Moreover, the characteristics of exercises necessary for the rehabilitation of patients with low back pain have also been determined. This model has contributed to the modification of programmes for the rehabilitation of patients with this type of ailment by introducing rotation and extension exercises [26–28]. Basically, there are two main modes of action aimed at improving the protective function of muscles in relation to the spine joints. The first of them utilises the principle of minimising the forces affecting the lumbar spine during basic motor activity, and the second the optimal control of the lumbar-pelvic complex. Patients suffering from low back pain may demonstrate a lack of muscle tone normalization even after the pain subsides [29, 30]. Therefore, in this study, the authors focused on the assessment of isometric muscle strength and muscle balance [31].

The aim of the study was to assess the dynamics of changes in isometric strength and muscular imbalances of the lumbar and pelvic complex in the treatment of women with low back pain. The authors assumed that this therapy, by developing muscle strength and improving balance, improves the stabilization of the lumbar-pelvic complex and demonstrates beneficial effects in the treatment of people with low back pain.

2. Materials and Methods

Forty-one women aged 60–75 took part in the study ($X = 65.3$; SD = 6.5). They were patients of the Rehabilitation Clinic who were diagnosed with low back pain. The inclusion criteria were low back pain, degenerative changes of the lumbar spine visible in magnetic resonance imaging, age 60–75 years, patient's consent to participate in the study, and not undergoing lumbar spine rehabilitation with a different kinesiotherapy method than the one applied in the study at the time of research.

The exclusion criteria were less than 3 months from the onset of the acute discopathy phase, fresh fractures, short remission intervals in the course of rheumatic diseases, inflammatory diseases at the stage of exacerbation, for example, ankylosing spondylitis, hernia (abdominal, inguinal), osteoporosis with mineral density of bones up to 80% of the average for a given age, cancer, and spinal deformities.

Magnetic resonance imaging (MRI) was performed to assess the degree of degenerative changes in the lumbar spine. Randomly tested using a computer number generator, the subjects were assigned to two groups. The study group (A) comprised nineteen participants, while the control group (B) totalled twenty-two subjects.

In the study group (A), central stabilization exercises and therapy using the Tergumed 700 system were performed. In the control group (B), only central stabilization exercises were performed. The therapy lasted 6 weeks. All research procedures were carried out in accordance with the 1964 Declaration of Helsinki and with the consent of the Bioethics Committee at the Regional Medical Chamber in Kraków (Poland) No. 73/KBL/OIL/2016 from May 4, 2016.

2.1. Assessment of the Dynamics of Isometric Changes in Muscular Strength and Muscular Imbalances of the Lumbar-Pelvic Hip Complex. The muscle strength test of the lumbar-pelvic hip complex was performed using the Tergumed 700 system. This system was TÜV Süd 0123 certified and met the requirements of Directive 93/42 EEC [32]. The test was performed in flexion, extension, lateral flexion (left/right), and rotation (left/right). The test took place in a seated position. Each device was adapted to the patient. The authors made sure that the axis of motion was correct and that the subject was well stabilized. Isometric strength of the muscles was tested. The measurement was carried out using a built-in dynamometer (Nm). On each of the four Tergumed devices, a strength and muscle imbalance test was performed. One test repetition and two research repetitions were carried out, from which the average value was calculated. The examination was performed four times: before and after two, four, and six weeks of therapy.

2.1.1. Central Stabilization Training. Central stabilization training was conducted on the basis of a scheme developed by Richardson et al. [33]. It consisted of three stages: training of local segmental control, of segmental control in a closed chain, and of segmental control in an open chain. A warm-up using cycloergometers and deep muscle activation in low positions was also performed. The ability to properly activate muscles was palpated, enabling the transition during training to exercises in higher positions. Coordination and balance exercises were carried out with the use of Swiss balls, aerodynamic discs, sphere segments, and elastic bands. In addition, exercises for stretching and relaxing contracted muscles were used. Central stabilization training in both groups (A and B) was conducted equally by the same physiotherapist and was applied for 30 minutes, 5 days a week, and for 6 weeks from May 2016 to March 2017.

2.1.2. Therapy Using the Tergumed 700 System. Tergumed 700 is a line of 4 devices for diagnosis and therapy of the lumbar spine. Each device was responsible for 4 main directions of spinal movement (extension, flexion, lateral bend, and rotation). Before therapy, a maximum muscle strength test was performed on each device. Based on the test, an individual therapy plan using feedback was generated. The therapy was aimed at improving strength and compensating for muscular imbalances. The test also allowed for painless treatment. Thanks to programming the

therapy based on the patient's current-condition test, it was a therapy that met the criteria of evidence-based medicine. The therapy followed the instructions given by Stevens [25, 34]. In the case of extension and flexion, 30–40% of maximum muscle work was used to activate the appropriate muscle groups. However, in terms of flexion and lateral flexion, this increased up to 60% of maximum muscle work. The loads gradually increased by 5% every 3 days. Patients initially performed 3 sets of exercises of 10 repetitions on each device. The number of repetitions was also gradually increased to 18 in the series. Therapy with the Tergumed 700 system was only carried out in the study group (A), for 1 hour a day, 5 days a week, and for 6 weeks, from May 2016 to March 2017.

2.2. Applied Statistical Methods. Analysis of variance (ANOVA) was used to assess the dynamics of isometric changes in strength and muscular imbalances. The above calculations were performed using the Statistica StatSoft computer program and the Microsoft Office Excel spreadsheet. Statistically significant differences were assumed for $p < 0.05$.

3. Results

In the study group (A), the average body height (cm) was ($X = 162.65$; SD = 5.86; $V = 3.6$), body mass totalled (kg) ($X = 75.05$; SD = 10.44; $V = 13.90$) and BMI equalled (kg/m^2) ($X = 28.43$; SD = 4.14; $V = 14.55$). In the control group (B), the average body height (cm) was ($X = 161.47$; SD = 5.41; $V = 3.35$), body mass equalled (kg) ($X = 73.05$; SD = 15.11; $V = 20.68$) and BMI totalled (kg/m^2) ($X = 28.04$ (kg/m^2), SD = 5.88; $V = 20.976$). In both groups, the majority of subjects were overweight.

3.1. Dynamics of Changes in Muscular Strength and Muscular Imbalances of the Lumbar-Pelvic Hip Complex in the Study Group (A). In the study group (A), the greatest absolute differentiation occurred for the strength of the extensor muscles of the lumbar spine, examined after 2 weeks of therapy (SD = 51.25), while the relative differentiation for rotator muscle strength to the left in the preliminary study was ($V = 50.02$ Nm) (Table 1). The largest absolute and relative differences in muscle balance concerned the ratio of flexor muscle strength to the left to flexor muscle strength to the right after 2 weeks of therapy (SD = 0.47, $V = 42.21$) (Table 1).

In the study group (A), there was a significant ($p < 0.005$) improvement in all examined muscle groups. After 6 weeks of therapy, the strength of the lumbar flexor muscles improved significantly ($p = 0.018$) from an initial value of 61.54 Nm to 86.61 Nm (Table 2). The strength of the lumbar spine extensor muscles improved significantly ($p = 0.001$) from an initial value of 105.85 Nm to 159.59 Nm (Table 2). Also, the rotation force to the left improved significantly ($p = 0.001$), from the initial value of 26.65 Nm to the value of 46.005 Nm (Table 2). The strength of the muscles rotating the lumbar spine to the right improved significantly ($p = 0.001$) from the initial value of 28.10 Nm to 46.5 Nm (Table 2). There was also a significant improvement in the strength of the lumbar flexor muscles to the left ($p = 0.039$), from an initial value of 36.72 Nm to 53.71 Nm (Table 2). The right flexor muscles of the lumbar spine also improved significantly ($p = 0.049$) from an initial value of 37.7 Nm to 52.07 Nm after 6 weeks of therapy (Table 2).

The balance of all tested lumbar-pelvic complex muscles was correct at individual measurement periods (Table 2). The strength of the antagonistic muscle groups was balanced.

3.2. Dynamics of Changes in Muscle Strength and Muscular Imbalances of the Lumbar-Pelvic Hip Complex in the Control Group (B). In the control group (B), the greatest absolute differentiation was demonstrated by the strength of the lumbar extensor muscles examined after 2 weeks of therapy (SD = 53.69), while relative differentiation, rotator muscle strength to the right of the lumbar region, and preliminary examination totalled ($V = 62.23$) (Table 3).

The greatest absolute differentiation of muscle balance concerned the ratio of rotator muscle strength to the left compared with rotator muscle strength to the right, examined after 6 weeks (SD = 1.84). Relative differentiation, however, concerned the ratio of rotator muscle strength to the left compared to the strength of rotator muscle to the right, examined after 4 weeks of therapy ($V = 395.18$) (Table 3).

Flexor muscle strength improved significantly ($p = 0.002$) from an initial value of 50.37 Nm to 74.06 Nm after 4 weeks, only to slightly deteriorate after 6 weeks of therapy to 73.83 Nm (Table 2). The strength of the flexor muscles to the left improved significantly ($p = 0.030$) from 29.27 Nm to 46.8 Nm after 6 weeks of therapy (Table 2).

There was a significant ($p = 0.010$) worsening of the left flexor muscle balance compared to right flexor strength after 6 weeks of therapy. The strength of both of these muscle groups did not balance (Table 2).

3.3. Comparison of the Dynamics of Changes in Muscle Strength and Muscular Imbalances of the Lumbar-Pelvic Hip Complex in Groups A and B. Before therapy, muscle strength and their imbalance did not show significant differences between groups A and B.

After 2 weeks of therapy, there were significant ($p = 0.03$) differences in the strength of the rotator muscles to the left of the lumbar region (Nm). In group A, there was greater improvement in muscle strength responsible for spinal rotation to the left (40.2 Nm) compared to the control group (28.28 Nm) (Table 4).

After 4 weeks of therapy, a significantly ($p = 0.03$) better result was observed in the study group (A) compared to the control group (B) in the strength of the left rotator muscles. The test group (A) achieved an average result of 42.353 Nm and the control group (B) 31.42 Nm (Table 4). In addition, a significantly ($p = 0.01$) better result was observed in the strength of the muscles rotating the lumbar spine to the right in group A. In the study group (A), this force was 45.43 Nm and in the control group (B), 31.82 Nm (Table 4).

Table 1: Variables of muscle strength and their imbalance in the study group (A).

Variable	Prelim-test X; SD	Prelim-test CV	Test after 2 weeks X; SD	Test after 2 weeks CV	Test after 4 weeks X; SD	Test after 4 weeks CV	Test after 6 weeks X; SD	Test after 6 weeks CV
Strength of flexor muscles in lumbar spine section	61.54 ± 19.05	30.95	76.85 ± 29.94	38.96	81.23 ± 24.43	30.08	86.61 ± 24.79	28.63
Strength of extensor muscles in lumbar spine section	105.82 ± 28.45	26.88	142.71 ± 51.25	35.91	154.97 ± 37.87	24.44	159.6 ± 45.02	28.21
Strength of rotator muscles in left direction of lumbar spine section	26.65 ± 13.33	50.02	40.2 ± 16.64	41.4	42.35 ± 12.93	30.52	46.01 ± 16.04	34.88
Strength of rotator muscles in right direction of lumbar spine section	28.1 ± 10.45	37.18	37.3 ± 14.25	38.2	45.43 ± 14.38	31.65	46.5 ± 18.5	39.79
Strength of flexor muscles in left direction of lumbar spine section	36.72 ± 17.8	48.47	45.16 ± 19.68	43.58	50.63 ± 20.2	39.89	53.71 ± 17.88	33.3
Strength of flexor muscles in right direction of lumbar spine section	37.7 ± 14.5	38.48	42.72 ± 16.55	38.73	50.44 ± 20.36	40.37	52.07 ± 18.81	36.12
Ratio of flexor to extensor muscle strength	0.59 ± 0.14	23.09	0.56 ± 0.16	29.29	0.55 ± 0.18	32.36	0.56 ± 0.15	26.01
Ratio of rotator muscle strength in left direction to rotator muscle strength in right direction	0.94 ± 0.23	24.82	1.12 ± 0.36	32.37	0.91 ± 0.25	27.59	1.04 ± 0.27	25.72
Ratio of flexor muscle strength in left direction to flexor muscle strength in right direction	0.97 ± 0.23	23.99	1.1 ± 0.47	42.21	1.04 ± 0.22	21.54	1.05 ± 0.24	22.56

Table 2: Differences in muscle strength and imbalance before and after 6 weeks of therapy in the study group (A) and the control group (B) demonstrated by analysis of variance (ANOVA).

Variable	F	p
Study group (A)		
Strength of flexor muscles in lumbar section	3.57	**0.018**
Strength of extensor muscles in lumbar section	6.54	**0.001**
Strength of rotator muscles in left direction of lumbar section	6.16	**0.001**
Strength of rotator muscles in right direction of lumbar section	6.44	**0.001**
Strength of flexor muscles in left direction of lumbar section	2.94	**0.039**
Strength of flexor muscles in right direction of lumbar section	2.75	**0.049**
Control group (B)		
Strength of flexor muscles in lumbar section	5.34	**0.002**
Strength of flexor muscles in left direction of lumbar section	3.13	**0.030**
Ratio of flexor muscle strength in left direction to flexor muscle strength in right direction	4.05	**0.010**

After 6 weeks of therapy, the difference between groups in left rotator muscle strength remained ($p = 0.02$) in favour of the study group (A). On average, in the study group (A), the result was 46.01 Nm and in the control group (B), 33.1 Nm (Table 4). This also applies to extensor muscle strength ($p = 0.02$), which in the study group (A) increased to 159.6 Nm compared to the result in the control group (B) of 121.68 Nm (Table 4). There was also a significant ($p = 0.02$) difference in lumbar spine flexor muscle strength to the right in favour of the study group. In the study group (A), the average value of this force was 52.07 Nm and in the control group (B), 38.92 Nm (Table 4).

A significant ($p = 0.03$) difference was also observed in the balance of lumbar flexor muscle strength to the left compared with the right flexor muscle strength. Imbalance in the study group (A) remained within normal limits (1.05

Table 3: Variables of muscular strength and their imbalance in the control group (B).

Variable	Prelim-test X; SD	Prelim-test CV	Test after 2 weeks X; SD	Test after 2 weeks CV	Test after 4 weeks X; SD	Test after 4 weeks CV	Test after 6 weeks X; SD	Test after 6 weeks CV
Strength of flexor muscles in lumbar spine section	50.38 ± 23.24	46.13	67.81 ± 22.95	33.84	74.06 ± 20.38	27.51	73.83 ± 23.74	32.16
Strength of extensor muscles in lumbar spine section	93.59 ± 43.66	46.66	120.06 ± 53.69	44.72	129.42 ± 46.43	35.88	121.68 ± 51.57	42.38
Strength of rotator muscles in left direction of lumbar spine section	20.88 ± 12.99	62.23	28.28 ± 16.2	57.29	31.42 ± 17.28	54.99	33.1 ± 17.99	54.36
Strength of rotator muscles in right direction of lumbar spine section	24.03 ± 14.86	61.84	32.62 ± 18.89	57.92	31.82 ± 16.28	51.17	37.53 ± 20.53	54.71
Strength of flexor muscles in left direction of lumbar spine section	29.26 ± 17.79	60.79	37.52 ± 19.43	51.77	41.78 ± 20.46	48.98	46.8 ± 20.89	44.65
Strength of flexor muscles in right direction of lumbar spine section	30.01 ± 15.17	50.56	36.11 ± 15.49	42.91	39.3 ± 16.12	41.02	38.92 ± 16.44	42.23
Ratio of flexor to extensor muscle strength	0.57 ± 0.23	40.63	0.62 ± 0.18	28.58	0.6 ± 0.15	24.51	0.7 ± 0.32	45.39
Ratio of rotator muscle strength in left direction to rotator muscle strength in right direction	0.88 ± 0.34	38.51	1.01 ± 0.59	58.06	6.8 ± 0.85	395.18	1.28 ± 1.84	143.5
Ratio of flexor muscle strength in left direction to flexor muscle strength in right direction	0.97 ± 0.23	23.24	1.01 ± 0.25	24.79	1.08 ± 0.28	25.94	1.21 ± 0.21	17.02

Table 4: Differences in the dynamics of changes in muscle strength and their imbalance between the study group (A) and the control group (B) demonstrated by analysis of variance (ANOVA).

	Variable	Group A (Nm) X; SD	Group B (Nm) X; SD	F	p
Differences between study (A) and control (B) groups after 2 weeks of therapy	Rotator muscle strength in left direction of lumbar section	40.2 ± 16.64	28.28 ± 16.2	5.38	**0.03**
Differences between study group (A) and control group (B) after 4 weeks of therapy	Rotator muscle strength in left direction of lumbar section	42.35 ± 12.93	31.41 ± 17.28	5.13	**0.03**
	Rotator muscle strength in right direction of lumbar section	45.43 ± 14.38	31.82 ± 16.28	7.93	**0.01**
Differences between study group (A) and control group (B) after 6 weeks of therapy	Strength of extensor muscles in lumbar spine section	159.59 ± 45.02	121.68 ± 51.59	6.19	**0.02**
	Rotator muscle strength in left direction of lumbar section	46.01 ± 18.04	33.10 ± 18	5.79	**0.02**
	Extensor muscle strength in right direction of lumbar section	52.07 ± 18.81	38.90 ± 16.44	5.71	**0.02**
	Ratio of flexor muscle strength in left direction to flexor muscle strength in right direction	1.05 ± 0.24	1.21 ± 0.21	4.99	**0.03**

on average), while in the control group (B), an abnormal increase in the strength of the flexor muscles to the left was observed compared to the flexors to the right (average 1.21) (Table 4).

4. Discussion

In the treatment of low back pain, it is of key importance to know the cause of the ailment and focus therapy on the problem occurring in a given patient. In developed societies, we are increasingly dealing with people who work long hours every day in a seated position [35]. In the case of weakening of the lumbar-pelvic hip complex muscles or their large imbalance, the rapid onset or asymmetrical lifting of a small weight can result in unilateral overload, muscle spasm, and trauma to the spine. This is because a sedentary lifestyle results in a loss of muscle mass and a gradual, systematic decrease in strength and flexibility.

Most studies available in the literature regarding physiotherapy in low back pain assessing individual methods or therapies are based on the evaluation of the training programme. Patients are examined before and after therapy, and in some cases, additionally in the middle of the therapy [36]. In this study, the authors evaluated the dynamics of changes in the strength of the lumbar-pelvic hip complex muscles and the equalization of their imbalances 4 times: before therapy, and after 2, 4, and 6 weeks of its duration.

Many authors have evaluated the effects of treating low back pain similarly as in the authors' research. Pranata et al. [37] investigated the coordination of lumbar extensor muscle work in patients with low back pain. Biofeedback was used in the form of a sinusoid, on which the indicator of the isometric force with which the patient exercised moved. Maximum values during the exercise oscillated between 20% and 50% of the patient's maximum isometric strength. A much smaller degree of sinusoid mapping (both voltage increase and relaxation) was observed in comparison to the control group without low back pain. There were also correlations between the increase in sinusoidal mapping during the return to the starting position and the increase in disability measured by the Oswestry questionnaire. In these studies, it has been shown that the control of extensor muscles in the lumbar region is impaired among patients with low back pain. Training using the Tergumed 700 system applied by the authors of this study was also based on biofeedback in the form of a sinusoid, which, as it has been shown in studies, has a positive effect on impaired muscle coordination.

França et al. [29] compared central stabilization training with strength training in fighting back pain, reducing disability and activating the transverse abdominal muscle. Both types of training gave satisfactory results, but central stabilization training proved to be more effective, mainly in the area of transverse abdominal muscle activation. However, as stated by Stevens et al. [38], strength-coordination training with the use of the Tergumed 700 system also activates the multifunctional muscle, especially when loaded with 30% of the maximum extension force. In these studies, it has been shown that strength training also affects deep muscle activity. In the research conducted by Parkkola et al. [39], it was also indicated that patients with low back pain had weakened muscles compared to the control group, as demonstrated by the isometric force test. Ruas and Viera [40] conducted a study on muscle strength and imbalance in low back pain, the results of which demonstrated that imbalance, mainly of flexor muscle strength relative to extensor muscle strength, may be associated with chronic lumbar spine pain.

Although pain syndromes are a complex and multifactorial problem, many authors associate them with muscle weakness [41]. As reported by Rossi et al. [42], therapy of back pain syndromes should include training of the efficiency and strength of muscles, mainly of the extensors. As reported by Steele et al. [43], such training should be conducted with the pelvis stabilized so as to exclude the involvement of other muscles, for example, the hip extensors. From the research by Catala et al. [44], it may be assumed that dorsal muscle training is beneficial in reducing lumbar pain among patients with low back pain. Patients who experience lumbar pain due to lumbar pain syndrome have reduced strength in their trunk muscles, mainly the extensors [44]. The legitimacy of the authors' research is also confirmed by other authors. Wang et al. [45] conducted a study regarding the impact of a 12-week standardized training programme on patients with low back pain. The results of the study showed significant improvement in muscular strength as well as compensation of flexion and extensor muscles of the lumbar region. In this study, the positive effect of training using the Tergumed system on muscle strength has been exhibited. However, a disadvantage of this study was the lack of precise specification of the group of subjects. Haag et al. [46] used the Tergumed system in their research to assess the strength of the dorsal muscles in athletes complaining of and not reporting pain in the lumbar spine. In the second group without pain, significantly higher isometric strength of the trunk muscles was observed. Nitera-Kowalik et al. [47] conducted studies on the impact of comprehensive therapy using the Tergumed system on improving coordination, compensating for muscular imbalances, the degree of disability caused by low back pain, and reducing pain sensations in patients treated at sanatoriums. Improvement in muscle imbalances was observed here for all of the examined muscle groups. However, this study did not include a control group.

In this study, in group A, in which the Tergumed 700 system was additionally used, there was a significant improvement in the strength of all the examined muscle groups after 6 weeks of therapy. Increased muscle strength responsible for extension of the lumbar spine and rotation to the left occurred after 2 weeks. This maintained after 4 and 6 weeks of therapy. The strength of the muscles rotating clockwise improved after 4 weeks and was maintained after 6 weeks of therapy. On the other hand, the strength of the trunk flexor muscles and those responsible for lateral flexion improved in the final measurement period. This suggests that the 6-week training programme is optimal for achieving strength improvement in all of the examined muscle groups.

The definitely worse results obtained in muscle strength in the control group (B) suggest that traditional central stabilization training has less of an effect on muscle strength. The differences between groups A and B became apparent after 2 weeks of therapy in terms of the force of rotation to the left. Then, after 4 and 6 weeks of therapy, the difference concerned the strength of both-sided rotation, extension, and flexion to the right. Muscle imbalance of the lumbar-pelvis-hip complex in the study group (A) remained within normal limits (1.05 on average), while in the control group (B), an abnormal increase in the strength of the flexor muscles to the left compared with the flexors to the right (average 1.21) was observed.

Therapy using the Tergumed system, through its programming based on objective patient examination, is effective in treating low back pain. Its use is also supported by economic considerations because one therapist can simultaneously rehabilitate 4 patients according to individual programmes. It is also important that objective examination

before and after therapy allows verification of the applied therapeutic programme.

5. Conclusions

After 6 weeks of therapy in the study group (A), there was a significant improvement in the strength of all examined muscle groups. However, in the control group (B), significant improvement only occurred in the strength of the lumbar flexor and flexor muscles on the left side. In addition, in group B, there was significant deterioration of imbalance regarding the left flexor muscle strength compared to the right flexor strength. Significant differences in favour of the study group (A) concerned the strength of the rotator muscles to the left, the strength of the extensor muscles of the lumbar spine, the strength of the flexors of the lumbar spine to the right, and the balance of strength of the flexors of the lumbar spine to the left compared with the strength of the flexor muscles to the right. Therapy with the Tergumed 700 system leads to an increase in the muscle strength of the lumbar-pelvic complex and compensation for its imbalance, which provides beneficial effects in the treatment of low back pain.

Data Availability

The data and materials supporting the conclusions of this article are included within the article.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

Authors' Contributions

J. W. was responsible for conceptualisation, data collection, analysis, formal analysis, methodology, and writing the original draft; A. K. was responsible for data collection, formal analysis, writing, reviewing, and editing.

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References

[1] T. Vos, A. D. Flaxman, M. Naghavi et al., "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990–2010: a systematic analysis for the global burden of disease study 2010," *The Lancet*, vol. 380, no. 9859, pp. 2163–2196, 2012.

[2] N. J. Manek and A. J. MacGregor, "Epidemiology of back disorders: prevalence, risk factors, and prognosis," *Current Opinion in Rheumatology*, vol. 17, no. 17, pp. 134–140, 2005.

[3] L. Lidgren, "The bone and joint decade 2000–2010," *Bull World Health Organ*, vol. 81, no. 9, p. 629, 2003.

[4] D. I. Rubin, "Epidemiology and risk factors for spine pain," *Neurologic Clinics*, vol. 25, no. 2, pp. 353–371, 2007.

[5] P. M. Kent and J. L. Keating, "The epidemiology of low back pain in primary care," *Chiropractic & Osteopathy*, vol. 13, no. 1, pp. 13–20, 2005.

[6] M. H. Halliday, A. N. Garcia, A. B. Amorim et al., "Treatment effect sizes of mechanical diagnosis and therapy for pain and disability in patients with low back pain: a systematic review," *Journal of Orthopaedic & Sports Physical Therapy*, vol. 49, no. 4, pp. 219–229, 2019.

[7] T. Kienbacher, E. Fehrmann, R. Habenicht et al., "Diagnostic value of trunk flexion-extension testing in old chronic low back pain patients," *European Spine Journal*, vol. 26, no. 2, pp. 510–517, 2017.

[8] P. Watson, C. Booker, C. Main, and A. Chen, "Surface electromyography in the identification of chronic low back pain patients: the development of the flexion relaxation ratio," *Clinical Biomechanics*, vol. 12, no. 3, pp. 165–171, 1997.

[9] A. Bergmark, "Stability of lumbar spine: a study in mechanical engineering," *Acta Orthopaedica Scandinavica*, vol. 60, no. 230, pp. 1–54, 1989.

[10] K. Rose-Dulcina, S. Genevay, D. E. Dominguez, S. Armand, and N. Vuillerme, "O 086–relation between the flexion-relaxation phenomenon and back extensor endurance in non-specific chronic low back pain patients," *Gait & Posture*, vol. 65, no. 1, pp. 176-177, 2018.

[11] Y. Javadian, M. Akbari, G. Talebi et al., "Influence of core stability exercise on lumbar vertebral instability in patients presented with chronic low back pain: a randomized clinical trial," *Caspian Journal of Internal Medicine*, vol. 6, no. 2, pp. 98–102, 2015.

[12] P. Li, Y. Nie, J. Chen, and N. Ning, "Application progress of surface electromyography and surface electromyographic biofeedback in low back pain," *Chinese Journal of Reparative and Reconstructive Surgery*, vol. 31, no. 4, pp. 504–507, 2017.

[13] H. S. Desai and R. S. Bisen, "Lumbar flexion relaxation phenomenon in the patients with acute and subacute mechanical low back pain and normal subjects," *International Journal of Research in Medical Sciences*, vol. 5, no. 3, pp. 1011–1014, 2017.

[14] C. Amroz, A. Scott, A. Ambroz, and E. O. Talbott, "Chronic low back pain assessment using surface electromyography," *Journal of Occupational and Environmental Medicine*, vol. 42, no. 6, pp. 660–669, 2000.

[15] F. Zhou, H. Li, G. Song et al., "Analysis of surface electromyography of patients with low back pain based on different movement patterns," in *Proceedings of the 2016 IEEE International Conference on Information and Automation*, pp. 1154–1158, Ningbo, China, 2016.

[16] J. Abboud, F. Nougarou, I. Pagé, V. Cantin, D. Massicotte, and M. Descarreaux, "Trunk motor variability in patients with non-specific chronic low back pain," *European Journal of Applied Physiology*, vol. 114, no. 12, pp. 2645–2654, 2014.

[17] J. P. Correia, R. Oliveira, J. R. Vaz, L. Silva, and P. Pezarat-Correia, "Trunk muscle activation, fatigue and low back pain in tennis players," *Journal of Science and Medicine in Sport*, vol. 19, no. 4, pp. 311–316, 2016.

[18] A. Heydari, A. V. F. Nargol, A. P. C. Jones, A. R. Humphrey, and C. G. Greenough, "EMG analysis of lumbar paraspinal muscles as a predictor of the risk of low-back pain," *European Spine Journal*, vol. 19, no. 7, pp. 1145–1152, 2010.

[19] M. M. Panjabi, "The stabilizing system of the spine: part I—function, dysfunction, adaptation, and enhancement," *Journal of Spinal Disorders*, vol. 5, no. 4, pp. 383–389, 1992.

[20] J. Key, *Back Pain: A Movement Problem*, Elsiever, Edenburg, South Africa, 2010.

[21] A. Plaskiewicz, K. Kałużny, and B. Kochański, "The use of physical therapy in the treatment of pain lumbar spine," *Journal of Education, Health and Sport*, vol. 5, no. 5, pp. 11–20, 2015.

[22] C. J. Snijders, M. T. L. M. Ribbers, H. V. de Bakker, R. Stoeckart, and H. J. Stam, "EMG recordings of abdominal and back muscles in various standing postures: validation of a biomechanical model on sacroiliac joint stability," *Journal of Electromyography and Kinesiology*, vol. 8, no. 4, pp. 205–214, 1998.

[23] C. L. N. Rodacki, A. L. F. Rodacki, C. Ugrinowitsch, D. Zielinski, and R. B. Costa, "Spinal unloading after abdominal exercises," *Clinical Biomechanics*, vol. 23, no. 1, pp. 8–14, 2008.

[24] P. W. Hodges and C. A. Richardson, "Inefficient muscular stabilization of the lumbar spine associated with low back pain: a motor control evaluation of transversus abdominis," *Spine*, vol. 21, no. 22, pp. 2640–2650, 1996.

[25] V. K. Steveens, T. G. Parlevliet, P. L. Coorevits, N. N. Mahieu, K. G. Bouche et al., "The effect of increasing resistance on trunk muscle activity during extension and flexion exercises on training devices," *Journal of Electromyography and Kinesiology*, vol. 18, no. 3, pp. 434–445, 2008.

[26] S. M. McGill, *Low Back Disorders: Evidence Base Prevention and Rehabilitation*, Human Kinetics Leeds, Pudsey, UK, 2016.

[27] J. Simińska, K. Pietkun, I. Głowacka et al., "Przegląd zaleceń postępowania fizjoterapeutycznego stosowanego w bólu kręgosłupa w odcinku lędźwiowym," *Journal of Education, Health and Sport*, vol. 6, no. 8, pp. 454–466, 2016.

[28] W. Stryła and A. Pogorzała, *Rehabilitacja Medyczna*, UM, Poznań, Poland, 2011.

[29] F. R. França, T. N. Burke, E. S. Hanada, and A. P. Marques, "Segmental stabilization and muscular strengthening in chronic low back pain: a comparative study," *Clinics*, vol. 65, no. 10, pp. 1013–1017, 2010.

[30] Y. Young-Dae and L. Yeon-Seop, "The effect of core stabilization exercises using a sling on pain and muscle strength of patients with chronic low back pain," *The Journal of Physical Therapy Science*, vol. 24, no. 8, pp. 671–674, 2012.

[31] J. A. Hides, R. Donelson, D. Lee, H. Prather, S. A. Sahrmann, and P. W. Hodges, "Convergence and divergence of exercise-based approaches that incorporate motor control for the management of low back pain," *Journal of Orthopaedic & Sports Physical Therapy*, vol. 49, no. 6, pp. 437–452, 2019.

[32] E. Ridder, L. Danneels, A. Vleeming, G. Vanderstraeten, M. Van Ranst, and J. Van Oosterwijck, "Trunk extension exercises: how is trunk extensor muscle recruitment related to the exercise dosage?," *Journal of Electromyography and Kinesiology*, vol. 25, no. 4, pp. 681–688, 2015.

[33] C. Richardson, P. Hodges, and J. Hides, *Therapeutic Exercise for Lumbopelvic Stabilization: A Motor Control Approach for the Treatment and Prevention of Low Back Pain*, Churchill Livingstone, London, UK, 2nd edition, 2004.

[34] V. Steveens, E. Witvrouw, G. Vanderstraeten et al., "The relevance of increasing resistance on trunk muscle activity during seated axial rotation," *Physical Therapy in Sport*, vol. 8, no. 1, pp. 7–13, 2007.

[35] M. Szpala, A. Skorupińska, and K. Kostrz, "Występowanie zespołów bólowych kręgosłupa—przyczyny i leczenie," *Pomeranian Journal of Life Sciences*, vol. 63, no. 3, pp. 41–47, 2017.

[36] K. Mianowski, W. Kaczmarek, G. Kamiński, R. Rosołek, and M. Stańczuk, "The stand for rehabilitation of the human spine," *Pomiary Automatyka Robotyka*, vol. 19, no. 4, pp. 55–62, 2015.

[37] A. Pranata, L. Perraton, D. El-Ansary et al., "Lumbar extensor muscle force control is associated with disability in people with chronic low back pain," *Clinical Biomechanics*, vol. 46, no. 46, pp. 46–51, 2017.

[38] V. K. Stevens, T. G. Parlevliet, P. L. Coorevits et al., "The effect of increasing resistance on trunk muscle activity during extension and flexion exercises on training devices," *Journal of Electromyography and Kinesiology*, vol. 18, no. 3, pp. 434–445, 2008.

[39] R. Parkkola, U. Rytökoski, and M. Kormano, "Magnetic resonance imaging of the discs and trunk muscles in patients with chronic low back pain and healthy control subjects," *Spine*, vol. 18, no. 7, pp. 830–836, 1993.

[40] C. Ruas and A. Viera, "Do muscle strength imbalances and low flexibility levels lead to low back pain? A brief review," *Journal of Functional Morphology and Kinesiology*, vol. 2, no. 3, 2017.

[41] A. W. Pienaar and J. G. Barnard, "Development, validity and reliability of a new pressure air biofeedback device (PAB) for measuring isometric extension strength of the lumbar spine," *Journal of Medical Engineering & Technology*, vol. 41, no. 3, pp. 216–222, 2017.

[42] D. M. Rossi, M. H. Morcelli, A. C. Cardozo, B. S. Denadai, M. Gonçalves, and M. T. Navega, "Discriminant analysis of neuromuscular variables in chronic low back pain," *Journal of Back and Musculoskeletal Rehabilitation*, vol. 28, no. 2, pp. 239–246, 2015.

[43] J. Steele, S. Bruce-Low, S. Low, and D. Smith, "A review of the specificity of exercises designed for conditioning the lumbar extensors," *British Journal of Sports Medicine*, vol. 49, no. 5, pp. 291–297, 2015.

[44] M. Catala, A. Schroll, G. Laube, and A. Arampatzis, "Muscle strength and neuromuscular control in low back pain: elite athletes versus general population," *Frontiers in Neuroscience*, vol. 7, no. 3, 2018.

[45] L. Wang, L. Zhang, and S. Xu, "12 weeks tergumed standardized exercise impact on chronic nonspecific back pain," *Chinese Journal of Rehabilitation Medicine*, vol. 28, no. 10, pp. 939–941, 2013.

[46] T.-B. Haag, A. S. Schneider, C. Beckmann, M. Handel, C. Schneider, and H. M. Mayer, "A test battery to investigate back pain in female soccer players," *Sport Sciences for Health*, vol. 12, no. 3, pp. 361–367, 2016.

[47] A. Nitera-Kowalik, W. Bujalski, A. Durda et al., "Zastosowanie systemu tergumed w kompleksowej rehabilitacji pacjentów z zespołami bólowymi kręgosłupa leczonych w 21 wojskowym szpitalu uzdrowiskowo—rehabilitacyjnym w Busku—Zdroju," *Kwart Ortop*, vol. 3, pp. 268–280, 2009.