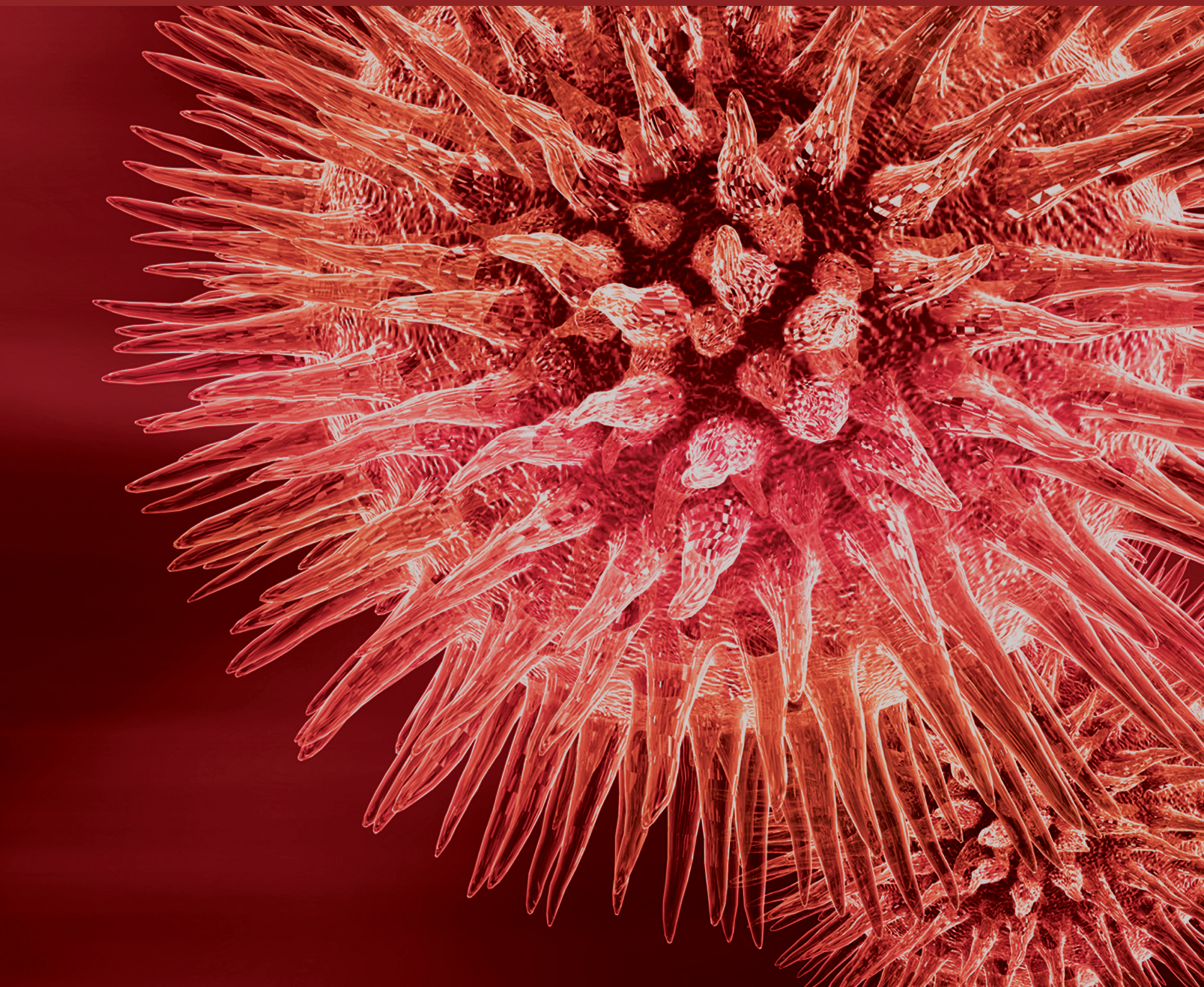
BioMed Research International

Approaches in Physical Activity: From Basic to Applied Research 2017

Lead Guest Editor: Danilo S. Bocalini
Guest Editors: Julien S. Baker, Leonardo dos Santos, Bruce Davies, and Emmanuel G. Ciolac



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Editorial

Approaches in Physical Activity: From Basic to Applied Research 2017

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1. Introduction

Changes in the modern lifestyle including diets high in salt, sugar, and fat and low physical activity have contributed to the increasing incidence and prevalence of chronic diseases. Several nonpharmacological strategies have been developed aiming at promoting a healthy lifestyle to reduce drug dose and polypharmacy and decrease morbidity and mortality. This reform in the lifestyle is an attitude that should be encouraged in all sectors of health care.

In this way, special attention had been addressed to oxidative stress and free radical (FR). A FR is a molecule with an unpaired electron in its outer orbital and is produced during normal cellular metabolism [1]. High levels of radicals can damage cells by reacting with cellular components (e.g., proteins and lipids). This form of damage is called oxidation and can result in a lethal injury to all cells [2]. The adverse effects of excess free-radical formation have been hypothesized to lead to cancer, atherosclerosis, aging, and even exercise-associated oxidative damage. Aerobic organisms would not survive without mechanisms that counteract the detrimental effects of free radicals. The system includes the fat-soluble antioxidants such as vitamin E and beta-carotene (a vitamin A precursor); the major water-soluble antioxidant, vitamin C; antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), and selenium-dependent glutathione peroxidase (GPX); and low-molecular-weight compounds such as glutathione [3]. These components preserve homeostasis during most normal cell function and mild oxidative stress. When free-radical production is excessive, however, or when the antioxidant system is overwhelmed, such as during nutritional deficiencies or exhaustive exercise, such imbalances may favour an “oxidative stress situation”

In the past two decades, accumulating evidence has shown that unaccustomed and strenuous exercise induces an imbalance between free-radical production and the body’s antioxidant defence systems [4]. However, it remains unknown whether increased free-radical production is an unwanted consequence of exercise that promotes further inflammation and tissue damage, or if the body regulates oxidant production to control inflammation and repair. Performance also decreases in rats fed a vitamin E-deficient diet, thus implicating vitamin E in protecting against exercise-induced free-radical generation and injury (Zerba E et al., 1990).

Animal studies have shown promising results [5]: vitamin E supplementation at supraphysiologic doses for a minimum of 5 weeks can decrease lipid peroxide levels with exhaustive exercise. To be effective at all, vitamin E must be given for at least 2 weeks before exercise, and five times the RDA for vitamin E may be necessary to prevent free-radical damage. These findings should be balanced against human studies that have not demonstrated convincing evidence for exercise-induced oxidative stress damage. Duthie et al. (1990) found no difference in levels of plasma alpha- or beta-tocopherol in runners following a half marathon. Lovlin et al. [6] actually noted a decrease in plasma malondialdehyde levels, a marker for lipid peroxidation, in cyclists exercising at 40% to 70% VO_2max. The selected articles produced here in this special addition present data looking at the mechanisms involved in oxidative stress.

The studies contained in this special issue include recent and topical research studies that investigate training adaptations for different populations, the effects of being physically active on lifestyle and different physiological systems, and the consequences of training. This exciting edition provides the reader with novel research investigating the role of physical activity on different outcomes and provides the researcher, scientist, and student with an interesting insight into the several adaptive process of on populations.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Julien S. Baker
Bruce Davies
Leonardo dos Santos
Emanuel Ciolac
Danilo Sales Bocalini

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Research Article

Multicomponent Exercise Improves Physical Functioning but Not Cognition and Hemodynamic Parameters in Elderly Osteoarthritis Patients Regardless of Hypertension

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The present study aimed to investigate the impact of a 6-month multicomponent exercise program (MCEP) on physical function, cognition, and hemodynamic parameters of elderly normotensive (NTS) and hypertensive (HTS) osteoarthritis patients. A total of 99 elderly osteoarthritis patients (44 NTS and 55 HTS) were recruited and submitted to functional, cognitive, and hemodynamic evaluations before and after six months of a MCEP. The program of exercise was performed twice a week at moderate intensity. The physical exercises aggregated functional and walking exercises. Results indicate that 6 months of MCEP were able to improve one-leg stand and mobility (walking speeds) of osteoarthritis patients regardless of hypertension. On the other hand, cognitive and hemodynamic parameters were not altered after the MCEP. The findings of the present study demonstrate that 6 months of MCEP were able to improve the physical functioning (i.e., usual and maximal walking speed and balance) of osteoarthritis patients regardless of hypertensive condition.

1. Introduction

Osteoarthritis (OA) is the most common joint disorder in the world [1]. The incidence of OA increases according to aging, affecting more than 35% of the older adult population [1, 2]. The great concern regarding OA is its poor prognosis, since the progression of this disease collaborates with a severe impairment in physical functionality, reducing the capacity to perform the activities of daily living (ADL) and, consequently, the quality of life of elderly people [3, 4].

There is a growing body of evidence indicating that OA is associated not only with an impaired physical functioning but also with cardiovascular risk factors, such as hypertension [5–9]. In fact, data have demonstrated that hypertension and arterial stiffness, which have a key role in the genesis and progression of hypertension, stand out among the myriad of cardiovascular risk factors associated with OA (e.g., hyperinsulinemia, hyperglycemia, and low-grade inflammation) [6–9]. Taken together, these evidences may indicate a worse prognosis to hypertensive osteoarthritis (HTS-OA) patients due to the close relationship of OA and hypertension with numerous adverse outcomes.

It is worth mentioning that several findings have proposed that HTS patients can present impaired functional capacity, cognition, and adaptability in response to physical exercise when compared to normotensive (NTS) patients [5, 10–12]. On the other hand, HTS patients present larger reductions in blood pressure values after physical exercise programs compared to NTS patients [13, 14]. Therefore, it is possible to infer that HTS-OA patients can present an impaired adaptability in the physical and cognitive domains, while a large reduction in blood pressure is expected after physical exercise programs when these patients are compared to NTS-OA. However, this hypothesis has never been tested.

Physical exercise has been mentioned as a profitable nonpharmacological tool able to counteract the deleterious effects of OA and hypertension [13–15]. Recently, the American College of Sports and Medicine (ACSM) advises that physical exercise programs for health promotion should include different exercise regimes (e.g., aerobic, resistance, balance, and flexibility) in an attempt to offer a large number of stimuli, probably causing superior beneficial effects [16, 17]. Multicomponent exercise program (MCEP) emerges as a kind of exercise able to contemplate ACSM recommendations because its design allows the performance of different modalities of exercise (e.g., aerobic, resistance, stretching, and balance) mixed in the same exercise session or routine [18].

Evidence has demonstrated beneficial effects of MCEP on the physical functioning and cognitive parameters of OA patients [19–21], and similar findings have been observed in HTS patients [20]. However, the experiments were designed based on low sample sizes, short periods of intervention (i.e., 3 months), and subjective methods for physical evaluation (e.g., questionnaires), limiting better inferences. Furthermore, to the best of our knowledge, the effects of a MCEP on physical functioning, cognition, and hemodynamic parameters of HTS-OA patients have not been elucidated. Lastly, there is no evidence exploring if hypertension may impair the adaptability of OA patients in response to physical exercise.

Therefore, the present study aimed to investigate the impact of a 6-month MCEP on physical functioning, cognition, and hemodynamic parameters of OA patients. Moreover, we investigated if hypertension could impair the adaptability of OA patients in response to physical exercise.

2. Methods

2.1. Design. The present investigation has a quasi-experimental design, which aimed to determine the effects of a 6-month MCEP on functional, cognitive, and hemodynamic parameters of normotensive (NTS) and hypertensive (HTS) elderly patients with lower limb osteoarthritis (OA) (Figure 1). Therefore, patients were submitted to functional, cognitive, and hemodynamic evaluations before and after 6 months of a MCEP. Experiments were developed in the city of Poá, state of São Paulo, Brazil, in 2016.

2.2. Subjects. Initially, 99 elderly volunteers, clinically diagnosed with lower limb OA, were recruited by convenience from two specialized healthcare centers for older adults in a town located in the metropolitan area of São Paulo, Brazil. Subsequently, two groups (NTS-OA [$n = 44$] and HTS-OA [$n = 55$]) were divided from the initial sample based on the diagnosis of hypertension.

Eligibility criteria for this study were based on the presence of a clinical diagnosis of lower limb OA, hypertension (to HTS-OA group), and age ≥60 years. Patients of both sexes were accepted in the study. Patients who presented changes

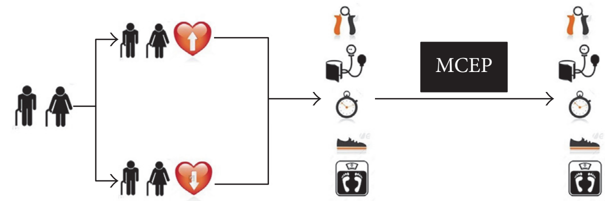

Figure 1: The experimental design used in the present study.

of antihypertensive medication during the study, missing values, physical (e.g., angina) and/or psychological (e.g., fear) discomfort during exercise sessions, cerebrovascular disease (e.g., stroke), pulmonary disease, neurological or psychiatric disease (e.g., Parkinson's or Alzheimer's disease), musculoskeletal disorders, chronic rheumatic condition other than OA, allocation for arthroplasty (i.e., end-stage hip and knee OA), comorbidities associated with greater risk of falls and any kind of dizziness, and blurred vision or lightheadedness when rising or remaining standing for long, which could indicate orthostatic hypotension and/or labyrinthitis, were absent from more than three sessions of physical exercise, and did not complete the entire battery of evaluations were excluded. We also excluded participants who were prescribed hormone replacement therapy and/or psychotropic drugs. It is worth mentioning that the volunteers were not under the use of medications to treat symptoms of OA, only hypertension (HTS-OA group). However, they reported making occasional (once every 15–30 days) use of analgesics, anti-inflammatories, and/or muscle relaxants. Therefore, we excluded volunteers that started a chronic pharmacological treatment for OA symptoms for the duration of the study. The use of medications and exclusion criteria data were collected from medical records (chart review) of each subject. In addition, since OA patients may present pain, muscle fatigue, or even low muscle strength during the performance of the tests, the time to perform the test was not an exclusion criterion, given that the volunteer could take as long as necessary to perform the test. Lastly, volunteers that scored 0 in the one-leg stand test were not excluded from the present study, if they performed the other tests. This occurred because a null result in this test indicates a low physical performance and not a missing value.

All volunteers signed the informed consent form and completed all measurements. This study was approved by the Research Ethics Committee of the University of Campinas (UNICAMP) under protocol number 835.733. This study was developed in accordance with the Declaration of Helsinki and according to Resolution 196/96 of the National Health Council.

Since both healthcare complexes serve a large number of patients and the medical team (i.e., nurse, physician, and physical educator) is of limited size, the pathological conditions were simply recorded by the head physician and head nurse of each center. A specialist (i.e., rheumatologist and cardiologist) who was not affiliated to and was outside the center then made the diagnosis of OA and/or hypertension, according to the specific guidelines of each disease (i.e., American College of Rheumatology [ACR] [22, 23] and Brazilian Society of Cardiology [BSC] [24], resp.).

2.3. Evaluations. All volunteers were instructed to refrain from any exhausting physical activity for a period of 96 h earlier and drinking alcoholic and caffeinated beverages 24 h before testing. Although alimentary ingestion was not controlled, subjects were instructed to maintain their food intake during the study period. Baseline evaluations (i.e., pre) were performed 5 days (i.e., 120 hours) before the beginning of the MCEP. Likewise, the final evaluations were performed on the fifth day after the last exercise session. The protocol used for morphological, functional, cognitive, and hemodynamic evaluations was mentioned by our group elsewhere [10, 11].

2.4. Morphological Measurements. A body weight scale with stadiometer Filizola® (Brazil) was used for weight (kg) and height (cm) measurements. An anthropometric tape (flexible and inextensible) Sanny® (Brazil) was used to measure waist (WC), hip (HC), and neck (NC) circumferences. For evaluations, subjects wore light clothing, in the standing position, with head held erect and eyes forward, with the arms relaxed at the side and feet in parallel (i.e., together). The WC was evaluated at the midpoint between the last floating rib and the highest point of the iliac crest. HC was evaluated at the highest point of the buttocks. NC was measured at the height of the gland cricoid cartilage prominence. All the subjects were evaluated twice, and the highest value was used for analysis.

2.5. Functional Evaluations. Two experienced researchers applied each test. While one was responsible for detailing the operational procedures, demonstrating the test before the evaluation, quantifying the evaluation time, and evaluating the motor gesture, the other ensured the safety of the participant. After the end of the explanation and before the start of the tests, volunteers performed a familiarization trial to ensure the understanding of the test. Then, the volunteers performed all tests twice, and the best result obtained in each test was used in the analysis. The tests were distributed in a room as stations and were performed in a circuited fashion one after the other. A one-minute interval between trials was provided. During all tests, verbal encouragement was provided to ensure that volunteers achieved the best possible performance without compromising safety. During TUG, walking speed test at maximal pace, and sit-to-stand tests, researchers provided stimulus such as *come on, faster!*; *a little more!*; and *let's go!* During OLS, verbal encouragement was provided to keep the participant focused on the test. Therefore, the volunteers were stimulated with the following sentences: *focus!*; *keep your posture!*; and *very good!* During handgrip test, the researchers repeatedly used the following sentences: *as much force as possible!; let's go!;* and *more strength!* For the countermovement jump test, verbal encouragement was only provided before the test, with the following sentence: *jump as high as you can using all your strength!* Regarding six-minute walk test, researchers told the volunteers that they were close to finalizing the test (i.e., *come on!; force!; there is little left!*).

2.5.1. Sit-to-Stand Test. Volunteers were requested to rise from a chair five times as quickly as possible with arms folded across the chest. The stopwatch was activated when the volunteer raised their buttocks off the chair and was stopped when the volunteer seated back at the end of the fifth stand.

2.5.2. One-Leg Stand Test. The one-leg stand test was performed with the volunteers standing in a unipodal stance with the dominant lower limb, the contralateral knee remaining flexed at 90°, the arms folded across the chest, and the head straight. A stopwatch was activated when the volunteer raised their foot off the floor and was stopped when the foot touched the floor again. The maximum performance time was up to 30 seconds, considered the best test result.

2.5.3. Walking Speed Test (Usual and Maximal). Walking speed was measured over three meters. This distance was chosen due to space limitations. It is worth mentioning that a high concordance has been observed between the results recorded after 3-meter and 6-meter courses [25]. In the test, volunteers were required to walk five meters at their usual and fastest possible cadences (without running). Before the evaluation, both feet of each volunteer were to remain on the starting line. The measurement was started when a foot reached the one-meter line and was stopped when a foot reached the four-meter line. The one-meter intervals at the beginning and at the end of the course were used to avoid early acceleration and/or deceleration.

2.5.4. Timed "Up and Go" (TUG) Test. The TUG test involves getting up from a chair (total height: 87 cm; seat height: 45 cm; width: 33 cm;), walking three meters around a marker placed on the floor, coming back to the same position, and sitting back on the chair. The subjects who started the test wore their regular footwear, with their back against the chair, arms resting on the chair's arms, and the feet in contact with the ground. A researcher instructed the volunteers, on the word "go," to get up and walk as fast as possible without compromising safety in the demarcation of three meters on the ground, turn, return to the chair, and sit down again. Timing was started when the volunteer got up from the chair and was stopped when the participant's back touches the backrest of the chair. A stopwatch (1/100 second accuracy) was used for time evaluation, and a longer time taken to perform the test indicates a lower performance.

2.6. Cognitive Evaluation: Executive Function (EF)

2.6.1. TUG Cognitive Test. TUG cognitive test was accomplished to evaluate EF. This test is performed as the conventional TUG; however, a cognitive task (verbal fluency, animal category) should be accomplished during the motor task. Therefore, after the signal of the evaluator, volunteer performed the route—stand up from the chair, walk three meters, turn around, walk three meters back, and sit down again—naming as many animals as they could remember. This task should be performed aloud, allowing the evaluators to confirm if the volunteers were, in fact, accomplishing the task. The time expanded to perform the task was recorded for evaluation [26].

2.7. Hemodynamic Measurements. The procedures for measurement of blood pressure were adapted from the VII Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) [27]. In summary, patients remained in a sitting position on a comfortable chair for 15 minutes in a quiet room. After this period, an appropriate cuff was placed at approximately the midpoint of the upper left arm (heart level). An automatic, noninvasive, and validated [28] arterial blood pressure monitor (Microlife-BP 3BT0A, Microlife, Widnau, Switzerland) was used to measure systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). During blood pressure recording, volunteers remained relaxed in the sitting position, with parallel feet at one shoulder width, both forearm and hands on the table, supinated hands, backs against the chair, without move or talk. The volunteer did not have access to blood pressure values during measurement. The evaluation lasted approximately 80 seconds and was performed three times with one minute of rest among the measurements. The mean of measurements of each volunteer was used in the final analysis. Mean arterial pressure (MAP), double product (DP), and pulse pressure (PP) were evaluated according to the following equations: $\mathrm{MAP} = [\mathrm{SBP} + (2 * \mathrm{DBP})]/3$, $\mathrm{DP} = \mathrm{SBP} * \mathrm{HR}$, and $\mathrm{PP} = \mathrm{SBP} - \mathrm{DBP}$. The size of the arm cuff was selected after measuring the arm circumference of each participant (Sanny, São Paulo, Brazil). All volunteers were evaluated within the first two months after the update of the medical records.

2.8. Multicomponent Exercise Program (MCEP). The MCEP was performed twice a week, on nonconsecutive days, during 26 weeks at the fitness center of an institutional center for elderly care and living (Centro de Convivência do Idoso [CCI]), Poá, Brazil. The program was designed to offer exercises that would mimic activities of daily life (ADL) gestures, thereby inducing neuromuscular adaptations to keep the subjects capable of performing the ADL. Each exercise session was composed of 12 different exercise stations. Each exercise session structure was defined by the sequence of one functional exercise followed immediately by a brief walk. Exercise session was composed of approximately 12 minutes of functional exercises, 24 minutes of walk, and 12 minutes of rest. Each session of exercise was composed of approximately 50 patients. A professional physical trainer with long experience in exercise training with elderly people supervised all sessions. Volunteers were instructed to avoid the Valsalva maneuver during the performance of exercises.

The functional exercises were changed during the whole program. However, they always represented ADL with a high necessity of the activity of the lower limbs, for example, stand up and sit on a chair, pick up a weight off the floor and put it on top of a structure, and transfer a weight from one place to another. Balance and proprioception exercises also comprised functional exercises, as one-leg stand. At most, three balance and/or proprioception exercises were used in each session. To complete the list of physical exercises, upper limbs resistance exercises were added.

All functional exercises were performed for one minute. The brief walk was performed for two minutes. Thus, after the end of each functional exercise, volunteers should walk from one point to another (30 m), around a cone, come back to the initial line (30 m), and start the path again until completing the two minutes. A rest interval of 60 seconds was adopted between the stations [11].

2.9. Exercise Intensity Control. The control of exercise intensity was accomplished by the rating of perceived exertion (RPE) method using the adapted Borg scale (2001) (i.e., CR-10) [29], which was used to ensure that volunteers performed the exercises in the desired intensity. This scale is composed of eleven numbers (i.e., 0, 1, 2, 3, 4,. . .) and eight descriptors (i.e., rest; very, very easy; easy; moderate; somewhat hard; hard; very hard; and maximal), which represents the perception of effort of the subject in front of an exercise load. The higher the reported number, the greater the sensation of effort [29]. During the performance of functional—except for balance exercises—and resistance exercises, volunteers were instructed to maintain the physical activity intensity in 3–5, which represents moderate (i.e., 3), somewhat hard (i.e., 4), and hard (i.e., 5) descriptors. For that, a large picture of RPE scale (i.e., 4 meters high and 1.30 meters wide) was positioned on the wall in the gym's room. The increase in the exercise intensity was based on alterations in the cadence of the performance (i.e., faster) for functional exercises and walk. Moreover, for resistance exercises, volunteers could use elastic bands (EXTEX Sports, São Paulo, Brazil) and dumbbells to reach the intensity prescribed.

2.10. Statistical Analyses. Normality of data was tested using the D'Agostino-Pearson omnibus normality test. Student's t-test for independent samples and Mann–Whitney test were used for comparisons between the groups (unpaired) for parametric and nonparametric samples, respectively. Student's t-test for dependent samples and Wilcoxon's signed-rank test were used for intragroup comparisons (paired) for parametric and nonparametric samples, respectively. Cohen's effect size d was calculated to assess the magnitude of the results. The effect size was classified according to Rhea (2004) [30]. The level of significance was 5% ($P < 0.05$) and all procedures were performed using the Statistical Package for the Social Sciences software (New York, USA).

3. Results

No adverse events occurred during the sessions of exercise or during any of the evaluations. The subjects were not absent for more than three sessions of physical exercise. Adherence to the physical exercise program was 100% (0 dropouts). Volunteers did not report any changes in food intake and in the number/class of medications during the study.

Table 1: Comparison between the groups regarding the morphological and hemodynamic parameters.

Variables	NTS-OA (n = 44)	HTS-OA (n = 55)
Subjects' characteristics		
Age (years)	63.9 ± 3.7 (60–71)	68.4 ± 6.4 (60–85)
Weight (kg)	66.6 ± 11.8 (48.1–89.8)	73.7 ± 14.1 (44–109)*
Height (cm)	154.5 ± 2.5 (1.5–1.9)	160.1 ± 6.0 (1.4–1.7)
BMI (kg/m^2)	26.6 ± 4.3 (16.6–39.7)	28.8 ± 5.7 (20.3–43.4)*
WC (cm)	92.5 ± 12.4 (63–124)	100.5 ± 13.3 (72–133)*
HC (cm)	102.5 ± 8.1 (88–120)	107.6 ± 12.1 (89–141)*
NC (cm)	35.4 ± 2.9 (30–45)	36.8 ± 3.2 (30–44)*
Knee OA (%)	5.3	18.2
Hip OA (%)	68.2	69.1
Knee and hip OA (%)	40.0	20.0
Female (%)	92.3	90.9
Mean of medication	—	1.4 ± 1.4
Drug class (%)		
Diuretic	—	69.1
Beta-blocker	—	34.5
ANG-II receptor antagonist	—	16.4
ACE inhibitor	—	9.1
Calcium channel blockers	—	3.6
Hemodynamic parameters		
SBP (mmHg)	127.6 ± 14.6 (96–162)	135.6 ± 18.2 (99–181)*
DBP (mmHg)	76.3 ± 9.7 (58–97)	76.8 ± 11.9 (58–109)
MAP (mmHg)	89.2 ± 21.9 (73–114)	94.7 ± 17.7 (78–123)
HR (bpm)	79.3 ± 10.0 (53–108)	74.2 ± 11.3 (35–113)*
DP (mmHg·bpm)	9693 ± 2906 (6625–17496)	9930 ± 2587 (4270–14238)
PP (mmHg)	48.9 ± 16.7 (18–79)	57.6 ± 17.8 (30–97)

Data are presented as mean ± SD (min–max). NTS: normotensive; HTS: hypertensive; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; DP: double product; PP: pulse pressure; $^*P < 0.05$ versus NG; ANG: angiotensin; ACE: angiotensin-converting enzyme.

Table 1 shows the main characteristics of NTS-OA and HTS-OA. It is possible to observe that NTS and HTS volunteers presented an overweight phenotype (BMI ≥ 25 kg/m^2). The analysis of circumferences is in congruence with BMI results and indicates that the volunteers were at a moderate-to-high cardiovascular risk. In relation to sex, our sample presented high prevalence of older women when compared to older men. This pattern is in concordance with previous findings of global burden of diseases studies in which higher prevalence of lower-limb OA was observed in women than in men regardless of the site affected by the disease (i.e., knee or hip) [31, 32]. Although authors have not proposed the main mechanisms responsible for this phenomenon, the marked decrease in sex hormones observed during menopause, primarily oestrogen, has been considered a possible factor to explain the higher predisposition presented by older women to OA when compared to older men [33, 34]. The mean of medications was 1.4 per volunteer, considering that 3.6% utilized ≥3 medications, 29.1% used 2 medications, and 67.3 used only one medication. Diuretic (69.1%) was the most prevalent class of antihypertensive medication, followed by beta-blocker (34.5%), angiotensin-II receptor antagonist (16.4%), angiotensin-converting enzyme inhibitor (9.1%), and calcium channel blockers (3.6%).

Hypothesis test showed that HTS-OA presented higher body mass, BMI, WC, HC, NC, SBP, and HR when compared to NTS-OA.

Table 2 shows the anthropometric parameters. MCEP was not effective to cause significant changes in anthropometric parameters of NTS-OA or HTS-OA. In addition, the magnitude of alterations (Δ [%]) was not different between the groups.

Cognitive and functional parameters are shown in Table 3. A significant increase in one-leg stand (NTS-OA = +101.9%; HTS-OA = +107.5%) and maximal walking speed (NTS-OA = +253.7%; HTS-OA = +270.0%) was observed in NTS-OA and HTS-OA patients. However, only HTS-OA presented a significant increase in usual walking speed performance (+18.8%). Exercise training did not cause significant improvements in sit-to-stand, TUG, or TUG exercise

Table 2: Effect of MEP on anthropometric parameters.

Variable	NTS-OA	HTS-OA
Body mass (kg)		
Pre	66.6 ± 11.8 (48.1–89.8)	73.7 ± 14.1 (44–109)
Post	65.3 ± 11.9 (49–106.6)	74.9 ± 13.9 (44–105)
Δ (%)	−0.79	6.51
ES	0.10 (trivial)	−0.08 (trivial)
Height (cm)		
Pre	154.5 ± 2.5 (1.5–1.9)	160.1 ± 6.0 (1.4–1.7)
Post	153.5 ± 5.8 (1.4–1.9)	157.0 ± 6.8 (1.4–1.8)
Δ (%)	−2.6	−1.7
ES	0.22 (trivial)	0.48 (trivial)
BMI (kg/m^2)		
Pre	26.6 ± 4.3 (16.6–39.7)	28.8 ± 5.7 (20.3–43.4)
Post	27.8 ± 4.3 (20.5–42.7)	30.4 ± 5.8 (19–44.5)
Δ (%)	7.0	10.4
ES	−0.27 (trivial)	−0.27 (trivial)
Waist circumference (cm)		
Pre	92.5 ± 12.4 (63–124)	100.5 ± 13.3 (72–133)
Post	94.2 ± 10.7 (74–114)	100.3 ± 19.4 (71–144)
Δ (%)	3.6	1.6
ES	−0.14 (trivial)	0.01 (trivial)
Hip circumference (cm)		
Pre	102.5 ± 8.1 (88–120)	107.6 ± 12.1 (89–141)
Post	101.6 ± 10.3 (64–129)	104.1 ± 18.1 (87–143)
Δ (%)	−0.1	−1.8
ES	0.09 (trivial)	0.22 (trivial)
Neck circumference (cm)		
Pre	35.4 ± 2.9 (30–45)	36.8 ± 3.2 (30–44)
Post	35.2 ± 5.5 (30–41)	37.7 ± 8.4 (32–43)
Δ (%)	−0.2	3.2
ES	0.04 (trivial)	−0.14 (trivial)

Data are presented as mean ± SD (min–max); NTS: normotensive; HTS: hypertensive; BMI: body mass index; ES: effect size (min–max).

Table 3: Effect of MEP on functional parameters.

Variable	NTS-OA	HTS-OA
Sit-to-stand (s)		
Pre	11.1 ± 3.4 (8–20.7)	10.6 ± 2.6 (5–16.7)
Post	10.8 ± 3.1 (6.3–20.5)	10.4 ± 2.6 (5–16.9)
Δ (%)	−1.1	6.1
ES	0.09 (trivial)	0.07 (trivial)
One-leg stand (s)		
Pre	18.3 ± 13.4 (0–30)	15.6 ± 11.4 (0–30)
Post	24.0 ± 8.3 (0–30)$^\alpha$	21.8 ± 9.1 (0–30)$^\alpha$
Δ (%)	101.9	107.5
ES	−0.51 (small)	−0.60 (small)
Usual walking speed (m/s)		
Pre	0.82 ± 0.20 (0.5–1.7)	0.90 ± 0.22 (0.5–1.7)
Post	2.19 ± 0.50 (1.3–3.6)	2.29 ± 0.60 (0.4–1.3)$^\alpha$
Δ (%)	−7.8	−10.6
ES	0.34 (trivial)	0.69 (small)
Maximal walking speed (m/s)		
Pre	0.91 ± 0.30 (0.5–2)	0.94 ± 0.30 (0.6–1.8)
Post	1.73 ± 0.30 (1.2–2.5)$^\alpha$	1.74 ± 0.40 (1.2–1.8)$^\alpha$
Δ (%)	−70.7	71.4
ES	2.75 (large)	3.81 (large)
TUG (s)		
Pre	6.53 ± 1.52 (5.1–10.9)	7.34 ± 1.26 (5.4–10.3)
Post	6.86 ± 1.23 (5–10.9)	7.05 ± 2.04 (5–13.6)
Δ (%)	4.3	−2.2
ES	−0.23 (trivial)	0.17 (trivial)
TUG with a cognitive task (s)		
Pre	7.41 ± 1.50 (4.7–12.6)	8.30 ± 1.96 (5.7–16.9)
Post	7.91 ± 1.69 (5–11.9)	8.43 ± 2.57 (5–17.9)
Δ (%)	11.0	4.8
ES	−0.31 (trivial)	−0.05 (trivial)

Data are presented as mean ± SD (min–max); NTS: normotensive; HTS: hypertensive; TUG: timed up and go; ES: effect size; $^\alpha P < 0.05$ versus pre.

with a cognitive task. The magnitudes of changes (Δ [%]) in the functional and cognitive parameters were similar in the groups after the MCEP.

Table 4 shows the hemodynamic parameters. NTS-OA did not present significant alteration in any of the hemodynamic parameters. On the other hand, HTS-OA presented a significant increase in HR.

4. Discussion

The main findings of the current study indicate that a 6-month MCEP is able to improve physical functioning of OA patients. However, contrary to our hypothesis, the cognitive and hemodynamic parameters were not altered after the MCEP, thereby indicating that HTS condition did not impair the adaptability of OA patients to physical exercise.

Just a few studies have explored the effects of MCEPs on physical function of samples composed exclusively of elderly OA patients. In addition, most of these investigations have used subjective methods (i.e., self-rated questionnaires) to measure physical function, which may not reflect the real state of the evaluated parameter [15]. As for studies that directly assessed physical function, Levy et al. [20] observed an increased transfer capacity (i.e., 8-foot up and go) in older adults with OA after 3 months of MCEP. Similarly, middle-aged and older adults with OA from the study of Ağlamış et al. [19] presented an improved lower-body muscle strength (i.e., chair stand) in response to a 3-month MCEP.

Table 4: Effect of MEP on hemodynamic parameters.

Variable	NTS-OA	HTS-OA
SBP (mmHg)		
Pre	127.6 ± 14.6 (96–162)	135.6 ± 18.2 (99–181)
Post	128.3 ± 17.8 (94–178)	138.9 ± 20.9 (87–196)
Δ (%)	2.2	2.0
ES	−0.04 (trivial)	−0.16 (trivial)
DBP (mmHg)		
Pre	76.3 ± 9.7 (58–97)	76.8 ± 11.9 (58–109)
Post	73.8 ± 11.4 (49–113)	78.0 ± 15.0 (59–149)
Δ (%)	−1.9	1.6
ES	0.23 (trivial)	−0.08 (trivial)
MAP (mmHg)		
Pre	89.2 ± 21.9 (73–114)	94.7 ± 17.7 (78–123)
Post	91.9 ± 12.5 (65–125)	96.2 ± 20.4 (69–196)
Δ (%)	−0.3	1.2
ES	−0.15 (trivial)	−0.07 (trivial)
HR (bpm)		
Pre	79.3 ± 10.0 (53–108)	74.2 ± 11.3 (35–113)
Post	79.6 ± 10.2 (51–102)	78.6 ± 11.3 (58–130)$^{\alpha}$
Δ (%)	2.2	2.3
ES	−0.02 (trivial)	−0.38 (trivial)
DP (mmHg·bpm)		
Pre	9693 ± 2906 (6625–17496)	9930 ± 2587 (4270–14238)
Post	10206 ± 1869 (4794–14596)	10530 ± 3194 (6438–17640)
Δ (%)	4.5	6.6
ES	−0.20 (trivial)	−0.20 (trivial)
PP		
Pre	48.9 ± 16.7 (18–79)	57.6 ± 17.8 (30–97)
Post	54.3 ± 13.5 (18–81)	59.6 ± 16.8 (27–99)
Δ (%)	16.8	10.5
ES	−0.35 (trivial)	−0.11 (trivial)

Data are presented as mean ± SD (min–max); NTS: normotensive; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; DP: double product; PP: pulse pressure; $^{\alpha}P < 0.05$ versus pre.

These results differ from the present study, where transfer capacity—evaluated by TUG test—and lower-body muscle strength—evaluated by chair stand test—did not change after 6 months of MCEP. It is worth mentioning that MCEPs are characterized by a session of exercise that comprises a mix of different exercise regimes, allowing different designs of MCEP, which can explain most of the different results observed between the studies. In fact, it is possible to observe that Levy et al. [20] proposed a MCEP composed of aerobic, resistance, balance, core strength, calisthenics, flexibility, dance, and muscle power exercises.

Interestingly, the evaluation of transfer capacity is strongly associated with muscle power [35, 36], and improvements in this physical capacity are stimulus-dependent (i.e., higher velocity concentric muscle contractions) [37]. However, different from Levy et al. [20], the current MCEP was not composed of muscle power exercises, and this feature may be indicated as the main factor responsible for the different results observed between the trials. However, Levy et al. [20] offer a poor description about their MCEP, because the variables associated with exercise prescription (e.g., intensity, volume, density) were absent in the materials and methods section, limiting its external validity and better comparisons between the studies.

In relation to Ağlamış et al. [19], the authors proposed a MCEP composed of a progressive strength training component, characterized by lower-limb and respiratory exercises performed in a circuit fashion, where each exercise was repeated 3 times (i.e., 3 sets). In the current study, each functional and resistance exercise was performed just once, and findings from original studies and meta-analytic regression have demonstrated that multiple-set resistance training programs are superior to single-set resistance training programs to elicit increase in muscle strength [38, 39]. Therefore, it is possible to infer that the differences between the studies regarding the improvements in lower-limb muscle strength are the product of an insufficient resistance training program offered by us in our MCEP.

However, it should be stressed that our MCEP was designed to be offered in public health programs that have to deal with a large number of patients, making it difficult to prescribe such exercise. Therefore, although the performance of a progressive resistance training with optimal volume (~3 sets per exercise) seems to be the ideal approach to improve the neuromuscular function of older adults [16, 40], it does not fit into MCEP targeting public health programs.

In addition to the aforementioned findings, we observed significant increases in balance (i.e., one-leg stand test) and mobility (i.e., usual and maximal walking speed tests) after the MCEP. These results have large external validity because these physical capabilities are predictors of adverse health-related events in elderly adults. Indeed, balance is a well-known predictor of falls, since balance disorders account for 17% of the causes of fall in elderly adults [41]. In relation to mobility, walking speed reflects the functioning of several body systems, including but not limited to the cardiovascular, musculoskeletal, respiratory, and neural systems [42]. In addition, several observational studies have demonstrated that a limited walking speed is associated with adverse outcomes, such as lower extremity limitations, difficulty or inability to perform the ADL, cognitive impairment, falls, and mortality [42–44]. Lastly, walking speed test is a diagnostic tool in the context of sarcopenia [45].

Regarding the cognitive parameters, EF was selected as our cognitive assessment, since it aggregates several cognitive abilities, such as planning, problem-solving, identification, observation, conclusions about the outcomes, and inhibition of influencing factors [46].

Although in the literature there is a lack of specific studies investigating the behavior of EF in elderly OA patients, several findings describe that the aging process is strongly associated with executive dysfunction [26]. Furthermore, just a few investigations have evaluated the effect of MCEPs on cognitive domains of older adults [47, 48] and, to the best of our knowledge, just one study investigated OA patients [19].

In this study, Ağlamış et al. [19] observed a significant increase in the mental health of OA patients after the MCEP. However, the cognitive evaluation was based on the SF-36 health survey questionnaire, limiting the discussion. Nevertheless, it is important to mention that the effects of exercise training on the cognitive domains are still unclear, making inferences impossible. Therefore, more investigations about the effects of different MCEP on cognitive domains of OA are still necessary.

As aforementioned, there is a growing number of evidences indicating that OA patients present high prevalence of cardiovascular risk factors, including high blood pressure [5–8]. Nevertheless, for the first time in literature, we tested the hypothesis *(H1)* that multicomponent exercise could elicit a significant decrease in blood pressure values of OA patients. However, confirming the null hypothesis *(HO)*, the hemodynamic parameters of OA patients were not different in the periods before and after exercise regardless of hypertension.

Although the molecular pathways responsible for this link are mostly unknown, several mechanisms have been proposed to be responsible for this phenomenon, such as chronic low-grade inflammation, aging, obesity, and medications [7]. Regarding low-grade inflammation, authors have described that this state occurs in response to repeated knee trauma and biomechanical overloading in OA patients [7]. This seems to be plausible because OA grade is associated with arterial stiffness and matrix metalloproteinase-3 (MMP3) [8], which are activated by an inflammatory state [7].

Furthermore, the proinflammatory cytokines elicit the production of reactive oxygen species (ROS) that act in the development of endothelial dysfunction, decreasing the bioavailability of vasodilatory substances (e.g., nitric oxide [NO]) [49].

It is noteworthy that investigations [50, 51] that approached a resistance component performed at higher intensities than was used in the current study observed a significant decrease in blood pressure values, which was associated with significant alterations in inflammatory markers (i.e., C-reactive protein and TNF-α), NO bioavailability, and fat mass. Regarding the aerobic component, studies using a larger frequency, volume, and intensity when compared to our MCEP have demonstrated regulation of ROS production and an increase in NO levels [52, 53]. Therefore, it is possible that the exercise regimes (e.g., resistance and aerobic) mixed in our MCEP were not able to reverse the aforementioned environment probably present in HTS-OA patients (e.g., endothelial dysfunction and decreased NO bioavailability), consequently failing to activate the physiological mechanisms necessary to cause reductions in blood pressure.

In addition, findings have been discussing that HTS patients may present an impaired adaptability to physical stimulus when compared to NTS patients. In fact, evidences have discussed a possible association between hypertension and low physical capacity and cognition [5, 10–12]. However, the findings have demonstrated conflicting results. The current study adds evidence to previous studies [5, 10–12] and indicates that hypertension did not impair the adaptability to physical exercise.

Furthermore, the magnitude of changes in blood pressure values after aerobic and/or resistance exercise seems to be dependent on preexercise values, since HTS patients show a larger decrease in blood pressure after exercise when compared to NTS patients [13, 14]. However, in the present study, data did not confirm previous investigations and indicate that hypertension did not alter the magnitude of changes in blood pressure values of OA patients after MCEP.

Some limitations of the present study should be mentioned and addressed in future studies for a better understanding about the effects of MCEP in OA patients, such as the lack of information regarding the educational level of the volunteers, blood analyses of the participants, evaluation of other cognitive domains, other designs of multicomponent exercise, a sedentary CG, and information regarding OA severity. Regarding the latter, it should be stressed that our volunteers were only clinically classified, and the severity of OA was not considered in the analysis. Therefore, future studies should investigate the relation of the results of the present study to the extent of OA. In addition, it is possible to observe high prevalence of elderly women in our sample. In an attempt to observe the effects of sex bias on the present study, data were reanalyzed based only on female volunteers (Supplementary Material [SM]; Figures SM1 and SM2). It is worth mentioning that similar results were observed in elderly women when compared to the total sample. Therefore, future studies should verify if these data are replicated in samples composed only of men.

5. Conclusion

In conclusion, data from the present study demonstrate that 6 months of MCEP were able to improve physical functioning (i.e., balance and mobility) of OA patients regardless of hypertensive condition.

Disclosure

The authors alone are responsible for the content and writing of the paper.

Conflicts of Interest

The authors report no conflicts of interest.

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Supplementary Materials

Supplementary Materials may be observed in Figures SM1 and SM2. Figure SM1: functional and cognitive parameters. Data are presented as mean ± SD; NTS: normotensive; HTS: hypertensive; TUG: timed up and go; $\alpha P < 0.05$ versus pre. Figure SM2: hemodynamic parameters. Data are presented as mean ± SD; NTS: normotensive; HTS: hypertensive; SBP: systolic blood pressure; DBP: diastolic blood pressure; MAP: mean arterial pressure; HR: heart rate; DP: double product; PP: pulse pressure; $\alpha P < 0.05$ versus pre. *(Supplementary Materials)*

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Research Article

Relationship between Joint Position Sense, Force Sense, and Muscle Strength and the Impact of Gymnastic Training on Proprioception

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The aims of this study were (1) to assess the relationship between joint position (JPS) and force sense (FS) and muscle strength (MS) and (2) to evaluate the impact of long-term gymnastic training on particular proprioception aspects and their correlations. 17 elite adult gymnasts and 24 untrained, matched controls performed an active reproduction (AR) and passive reproduction (PR) task and a force reproduction (FR) task at the elbow joint. Intergroup differences and the relationship between JPS, FS, and MS were evaluated. While there was no difference in AR or PR between groups, absolute error in the control group was higher during the PR task ($7.15 \pm 2.72^{\circ}$) than during the AR task ($3.1 \pm 1.93^{\circ}$). Mean relative error in the control group was 61% higher in the elbow extensors than in the elbow flexors during 50% FR, while the gymnast group had similar results in both reciprocal muscles. There was no linear correlation between JPS and FS in either group; however, FR was negatively correlated with antagonist MS. In conclusion, this study found no evidence for a relationship between the accuracy of FS and JPS at the elbow joint. Long-term gymnastic training improves the JPS and FS of the elbow extensors.

1. Introduction

Muscle strength (MS) is one of the most important factors affecting human performance. It allows athletes to overcome external load applied to the body and thus allows movement. While many studies have investigated ontogenetic [1, 2] and training-induced [3, 4] development of MS, little attention has been paid to the proprioceptive system which controls force production. According to Proske and Gandevia [5], proprioception is the sense of relative localization and movement of the body in space and the sense of tension, effort, and balance. The nervous system receives information from proprioceptors located in muscles (muscle spindles), tendons (Golgi tendon organs), joints, and the skin, which transmit afferent information regarding mechanical stimuli generated within the musculoskeletal system [6]. The afferent information reaches the central nervous system, where it is processed along with the corollary induced information of the effort to control the body position and movement and the sense of force [5].

Studies investigating proprioception have focused mainly on joint position sense (JPS) or kinesthesia, while interest in force sense (FS) is limited. FS is possible due to the nervous system integrating tensile information from muscular proprioceptors (muscle spindles and Golgi tendon organs) with the sense of effort induced centrally [7, 8]. At present, researchers do not agree as to which of the above mechanisms plays the dominant role in FS [9].

There is some limited evidence for an association between MS and proprioception. Several studies have shown that greater MS is associated with improved balance control [10–12] and strength training has been found to improve JPS at the shoulder [13]. Authors also point out that accurate proprioception at the shoulder joint is possible due to balanced strength between reciprocal muscles [14]. As muscle spindles are the primary proprioceptors involved in JPS [15] and are also involved in FS [16–18], there may be a relationship between these two aspects of proprioception and MS.

Research regarding the relationship between FS and JPS is also limited. Kim et al. [19] found no correlation between JPS and FS at the ankle joint in subjects with functional ankle instability and in an uninjured control group; however, authors acknowledge that participants varied in physical activity, gender, and level of injury. Moreover, as FS is more accurate in the upper limb [20], research at the elbow joint may yield different results. A good proprioception in the elbow joint is necessary to achieve high performance in sports like gymnastics, baseball, and basketball and many others [21, 22]. On the other hand, sport activities often lead to injuries which impair proprioception in the elbow joint. Therefore, the first aim of this study was to establish the relationship between FS, JPS, and MS at the elbow joint. While strength training interferes with JPS [13, 23], the authors hypothesized that FS would be positively correlated with MS.

Previous research has found that sport and strength training can affect JPS [13, 24, 25], while research regarding FS is limited. Therefore, the second aim of this study was to compare the accuracy of FS and JPS in athletes and nonathletes using gymnasts as the athlete group as gymnastics requires both excellent upper body strength and excellent precision in muscle tension. It was hypothesized that the gymnast group would demonstrate greater accuracy in JPS and FS in comparison to untrained adults. Despite the overall impact of gymnastics on upper body strength, training is directed at developing extensor strength in particular [26]. The impact of training on FS in flexors and extensors may therefore be different.

2. Materials and Methods

2.1. Participants. Seventeen elite adult gymnasts and 24 age-matched untrained controls were recruited. Their basic anthropometrical characteristics are shown in Table 1. All athletes were in the competitive training phase and trained for about 24 hours in six training sessions per week. The control group was comprised of physically active Tourism and Recreation students, none of whom participated in structured sports training. The criterion for participants' inclusion was no medical history of injuries or neuromuscular disorders that may have affected the elbow joint. Additionally, athletes had to practice artistic gymnastics since they were six or seven years old and compete at least at a national level. The study was approved by the Bioethical Commission and all participants signed informed consent forms.

2.2. Procedures. This study consisted of two parts. In part one, body composition analysis and muscle strength evaluation were conducted. In part two, JPS and FS at the elbow joint were evaluated. Both parts took place in the morning about 2-3 hours after the first meal and in a state of good hydration. Participants were prohibited from exercising 24 hours prior to the study. In the case of the gymnasts, measurements were performed on Mondays before the first training due to the fact that Sunday was the only day of rest for gymnasts.

Body composition analysis was conducted using the InBody 770 bioelectrical impedance analyzer (BioSpace, Korea) in the morning prior to breakfast. Body fat and lean arm mass were recorded and archived for torque normalization purposes. Prior to strength testing, participants completed a warm-up on the Monark 891E hand cycle ergometer (Monark Exercise AB, Sweden) involving five minutes of arm cranking using a power output of 1 W/kg and a crank rate of 60 rev/min. Maximal MS at the elbow was then tested using the Biodex System 4 isokinetic dynamometer (Biodex Medical Systems, Inc., Shirley, NY, USA). Each participant sat with his/her dominant elbow resting on a leather support. The position of each participant was adjusted to obtain 45° and 90° angles at the glenohumeral and elbow joints, respectively. Participants' position was the same for all procedures. Limb dominance was determined by participants' preferred writing hand. Participants performed three isometric 4 s maximal voluntary contractions (MVC) for elbow flexion and extension in random order. Between each repetition, participants had at least 30 s rest to reduce fatigue. During testing, participants had visual feedback and were given verbal encouragement. The highest peak torque from three trials was taken for analysis.

JPS was then evaluated using the Biodex System 4 isokinetic dynamometer. The reliability of this device in JPS assessment of the elbow and other joints was previously shown [27, 28]. Prior to testing, participants were familiarized with the test using different random target angles. During testing, participants made three attempts to reproduce (remember) a 90° angle at the elbow joint without visual cues both actively (AR) and passively (PR) using their dominant limb. Before each attempt to reproduce the target angle, participants' elbow joints were set to the target angle from a random starting point, and they were asked to feel and remember the position. Participants began in a neutral position at the elbow (full extension, 0°) where an MVC of the elbow flexors was performed to condition the muscle and induce thixotropic effect during PR [29]. Participants were then asked to reproduce (always in the direction of flexion) the target angle beginning from a random start position and indicate that they reached it by pressing a button held in the contralateral hand. During PR testing, the participant's elbow was moved passively by the device at a constant motion of $0.5^{\circ}\cdot s^{-1}$. During AR testing, participants' actively flexed their elbow, stopping at the point where they felt they

Table 1: Anthropometric and muscle strength characteristics of participants.

	Gymnasts (n = 17) Mean ± SD	Nontrained (n = 24) Mean ± SD
Age (years)	20.54 ± 3.51	19.84 ± 0.93
Body mass (kg)	68.26 ± 7.02	73.23 ± 8.49
Height (cm)	170.32 ± 4.16	177.96 ± 4.90
Body mass index ($kg{\cdot}m^{-2}$)	23.48 ± 1.59	23.14 ± 2.49
Body fat (%)	$7.37 \pm 4.27^{**}$	11.65 ± 3.16
Arm lean mass (kg)	4.02 ± 0.57	3.77 ± 0.61
Elbow flexion peak torque		
Absolute (N)	$66.21 \pm 13.30^{***}$	49.97 ± 12.11
Arm lean mass, normalized ($N{\cdot}kg^{-1}$)	$16.52 \pm 2.43^{***}$	13.36 ± 2.87
Elbow extension peak torque		
Absolute (N)	70.15 ± 15.26	64.70 ± 14.31
Arm lean mass, normalized ($N{\cdot}kg^{-1}$)	17.42 ± 2.54	17.16 ± 2.97

Significant difference between groups at $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

had reached 90° flexion. Different reproduction modes were used to evaluate whether muscle thixotropy would affect the analyzed relationships. To assess the accuracy and direction of bias of the JPS performance, the absolute and constant errors were calculated, respectively. The constant error was calculated as the mean of difference between the target angle and the recorded reproduction angle in three trials. The absolute error was calculated as the previous one, but the absolute difference between the target and the reproduced angle was taken to analysis.

FS was then evaluated using the Biodex System 4 isokinetic dynamometer using the unilateral remembered force reproduction (FR) test. The high reliability of FR measurements using the device was shown previously [30]. It should be noted that this test assesses torque reproduction rather than force, but for convenience, it will be described as FR. The target force was displayed via visual feedback to participants given the opportunity to familiarize themselves with the task. The participants were blindfolded and asked to reproduce the target force and sustain it for 4 s. Participants were tested at 20% and 50% of MVC at elbow flexors and extensors in random order. A one-minute rest was given between trials to avoid fatigue. The mean relative error (mean absolute difference between target and reproduction torque during FR) for accuracy and the range of relative error for force steadiness expressed in % MVC were recorded. To evaluate the direction of bias, the constant error was also calculated as the mean difference between the target and the reproduction torque during FR (% MVC). Three trials were conducted at each force level with the mean taken for analysis.

2.3. Statistical Analysis. Intergroup comparison of anthropometric and strength characteristics was assessed using unpaired t-tests. Pearson's correlation coefficient was calculated to study the relationship between FS, JPS, and MS. It was performed separately for each group to assess the impact of long-term gymnastic training on these relations. The magnitude of the effect size of the correlation was evaluated according to Cohen [31] with its further modification by Hopkins [32].

Two sets of ANOVA tests were then performed. First, two-way (2 *groups* × 2 *muscles*) ANOVAs of repeated measures were performed to compare FS performance between gymnasts and the controls in two reciprocal muscle groups (elbow flexors and extensors). Second, two-way (2 *groups* × 2 *modes*) ANOVAs of repeated measures were performed to compare JPS performance between two groups in AR and PR. Shapiro-Wilk and Levene's tests were performed to check the normal distribution and the homogeneity of variance, respectively. The level of significance was set at $\alpha = 0.05$ for all the tests. All analyses were performed with Statistica 12 (StatSoft Inc., Tulsa, OK, USA). To assess the required sample size, the power analysis for interactions between effects in two-way ANOVA of repeated measures was conducted using G∗Power ver. 3.1.9.2 software [33]. It was shown that the minimal total sample size for the medium effect size f with power of 0.8 and 0.05 level of significance was equal to 24 subjects.

3. Results

3.1. Muscle Strength. Results for isometric peak torque produced by elbow flexors and extensors are shown in Table 1. Elbow flexion peak torque was greater in the gymnast group, while no difference was found for elbow extension between groups.

3.2. Joint Position Sense. ANOVA test results, effect sizes, and post hoc test results for JPS are shown in Table 2. There was a significant main group effect on JPS performance. The gymnasts group had a 31% lower absolute error than the control group. The main mode effect was also significant with 96% greater absolute error in PR than in AR. The post hoc test of interaction of both effects showed that the above differences were due to higher absolute error in PR in the control group in comparison to the rest modes in

Table 2: Results of the two-way ANOVA with repeated measures in elbow JPS and FR performance.

Task	Indicator	Effect	F	p	Effect size (η^2)	Post hoc
JPS	Absolute error	Group × mode	8.47	<0.01**	0.18	PR: C > AR: C, G
		Group	13.26	<0.01**	0.25	G < C
		Mode	30.37	<0.01***	0.43	PR > AR
	Constant error	Group × mode	17.52	<0.01**	0.31	C: PR < G: PR, AR; PR: C, G < AR: C
		Group	0.40	0.53	0.01	
		Mode	66.59	<0.01***	0.63	PR < AR
FR 20% MVC	Mean relative error	Group × muscle	0.57	0.45	0.02	
		Group	0.21	0.65	<0.01	
		Muscle	0.57	0.45	0.02	
	Mean constant error	Group × muscle	0.24	0.63	<0.01	
		Group	2.96	0.09	0.07	
		Muscle	0.01	0.91	<0.01	
	Range of relative error	Group × muscle	0.06	0.81	<0.01	
		Group	3.84	0.06	0.09	
		Muscle	7.38	<0.01**	0.15	Extension > flexion
FR 50% MVC	Mean relative error	Group × muscle	4.86	0.03*	0.11	C: Extension > flexion
		Group	1.91	0.17	0.05	
		Muscle	4.53	0.04*	0.10	Extension > flexion
	Mean constant error	Group × muscle	2.24	0.14	0.05	
		Group	2.72	0.11	0.07	
		Muscle	1.21	0.27	0.03	
	Range of relative error	Group × muscle	1.20	0.28	0.03	
		Group	0.33	0.57	<0.01	
		Muscle	0.18	0.68	<0.01	

JPS: joint position sense; FR: force reproduction; MVC: maximal voluntary contraction; PR: passive reproduction; AR: active reproduction; C: control group; G: gymnasts. Significant effect or interaction at $^{*}p < 0.05$, $^{**}p < 0.01$, and $^{***}p < 0.001$.

either gymnasts or controls (Figure 1(a)). The analysis of the constant error showed similar results to the absolute error; however, the main group effect was insignificant. The main mode effect was significant, showing that participants during PR undershot the target angle by about $5.4 \pm 3.5^{\circ}$, while during AR they slightly overshot it ($0.1 \pm 3.1^{\circ}$). The interaction of both effects showed that this undershot was mainly due to PR performance of the control group, which had significantly lower values of the constant error in comparison to AR and both reproduction modes in gymnasts (Figure 1(b)).

3.3. Force Sense. ANOVA test results, effect sizes, and post hoc test results for FS are shown in Table 2. For 20% MVC, there was no significant main effect or interaction in the mean relative error (Figure 2(a)). The elbow extensors had a 10% higher range of relative error than the elbow flexors. For 50% MVC, there was a significant muscle effect as well as its interaction with the group effect in the mean relative error. The extensors had a 36% higher mean relative error in comparison to flexors. The post hoc test of interaction showed that these differences were due to 61% higher mean relative error values of elbow extensors in controls in comparison to their elbow flexors (Figure 2(b)). No effects were seen in the mean constant error. The only visible effect in the range of relative error was the muscle effect. In the extensor muscles, there was a 14% higher range of the relative error in comparison to flexor muscles. Gymnasts showed 10% higher results than controls, although the difference was insignificant.

3.4. Correlation Analysis. Pearson's correlation test results are shown in Table 3. Firstly, the relationship between JPS and FS performance was analyzed. A significant correlation was found between AR absolute error and the range of relative error for the 20% MVC flexion task ($r = 0.48$, $p < 0.05$) in the control group. For the same task, there was also a significant correlation between the AR absolute error and the FR mean constant error ($r = 0.50$, $p < 0.05$). No linear correlation was found with PR. In the gymnast group, there was also no correlation found for either AR or PR regarding the absolute error. On the other hand, gymnasts' AR constant error was significantly correlated with the mean constant and relative errors for 20% ($r = -0.68$, $p < 0.05$) and 50% ($r = 0.49$, $p < 0.05$) MVC extension tasks, respectively. Gymnasts' AR constant error was also correlated with the range of the relative error for 20% and 50% MVC extension tasks ($r = -0.57$, $p < 0.05$ and $r = -0.62$, $p < 0.05$, resp.). The outcome for gymnasts' PR constant error was similar, although instead of extension tasks it was correlated with the mean constant error in 20% ($r = -0.49$, $p < 0.05$) and the mean relative

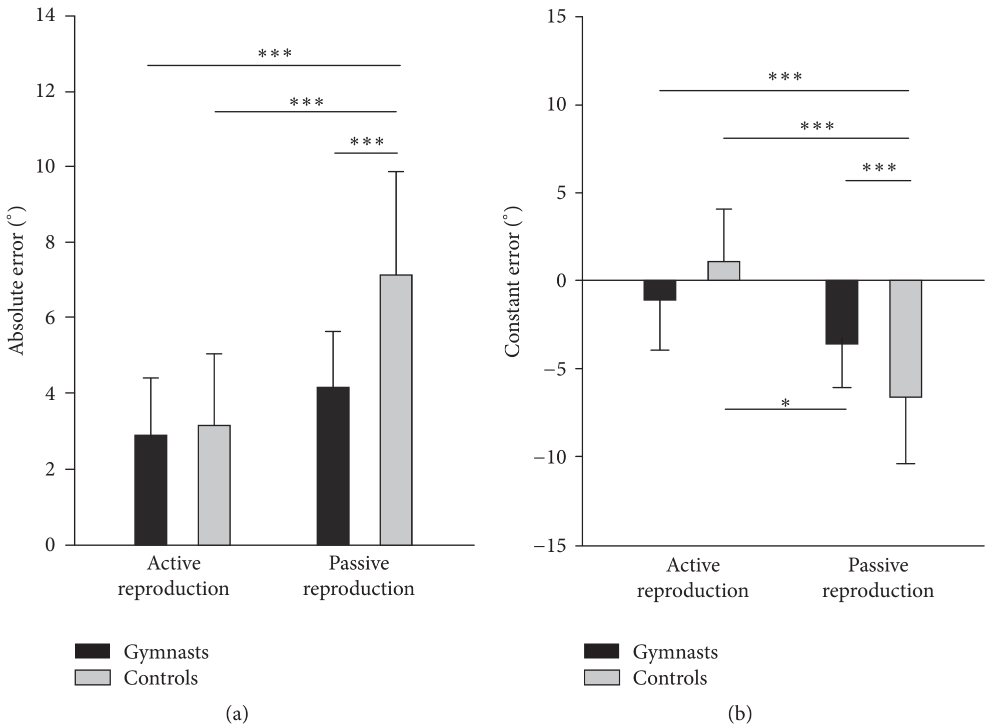

Figure 1: Joint position sense performance in the elbow joint. Absolute error (a) and constant error (b) are shown as mean ± SD. Significant difference at $^{*}p < 0.05$ and $^{***}p < 0.001$.

error in 50% ($r = 0.56$, $p < 0.05$) MVC flexion tasks. The PR constant error was also correlated with the range of the relative error for 20% MVC flexion task ($r = -0.54$, $p < 0.05$).

Secondly, the relationship between proprioception performance (FS, JPS) and MS was analyzed. For the 20% MVC flexion task, a significant correlation was found between mean relative error and absolute peak torque of elbow extension ($r = -0.47$, $p < 0.05$) in the control group. In the gymnast group, a significant correlation was found between ALM-normalized peak torque at the elbow extensors and both the mean relative and constant errors ($r = -0.55$–0.58, $p < 0.05$). For the 50% MVC flexion task, no significant correlations were found in either group. For the 20% MVC extension task, a linear significant correlation was found between controls' mean relative error and absolute peak torque in elbow flexion ($r = -0.42$, $p < 0.05$). No significant correlations were found in the gymnast group. Considering JPS, only in gymnasts was the AR constant error significantly correlated with ALM-normalized peak torque at the elbow flexors ($p = 0.52$, $p < 0.05$). No significant correlations were found between PR and MS variables.

4. Discussion

This study had two purposes. The first one was to evaluate the relationship between of MS, JPS, and FS, whereas the other one was to evaluate the impact of long-term gymnastic training on JPS and FS performance and the relationship between them. In the control group, a relationship between JPS and FS performance was seen only during the AR task. While the linear relationship between the accuracy of JPS and FR performance was insignificant, the AR higher absolute error was associated with overestimating the target force during 20% MVC flexion task. The absolute error of JPS during the AR task was also positively correlated with the range of the relative error during the same task, suggesting a possible common regulation mechanism with the steadiness of FR rather than with the accuracy of FS. One possible mechanism may be the sense of effort [34] which plays a role in the FS [9] but not in the PR task when the limb is supported [15]. However, in both modes, the reference position was set passively and therefore no additional effort cues (due to gravity force) should be transferred into the reproduction. Furthermore, the control group had lower absolute errors in AR in comparison to PR, which may suggest that muscle thixotropy was affecting results rather than additional effort cues [35]. This is consistent with the view that the muscle spindles are the main proprioceptors involved in JPS, as well as the view that effort has no effect on elbow JPS [36, 37]. Contrary to JPS, Scotland et al. [9] found that proprioceptors played little to no role during unilateral remembered FR tasks. Previous research has also found a relationship between force steadiness and postural control during quiet standing [38, 39], suggesting that the proprioceptive system has a common mechanism with force steadiness when muscles are being actively contracted. Interestingly, while gymnasts showed higher performance in PR than controls, there was no correlation between force steadiness and JPS accuracy

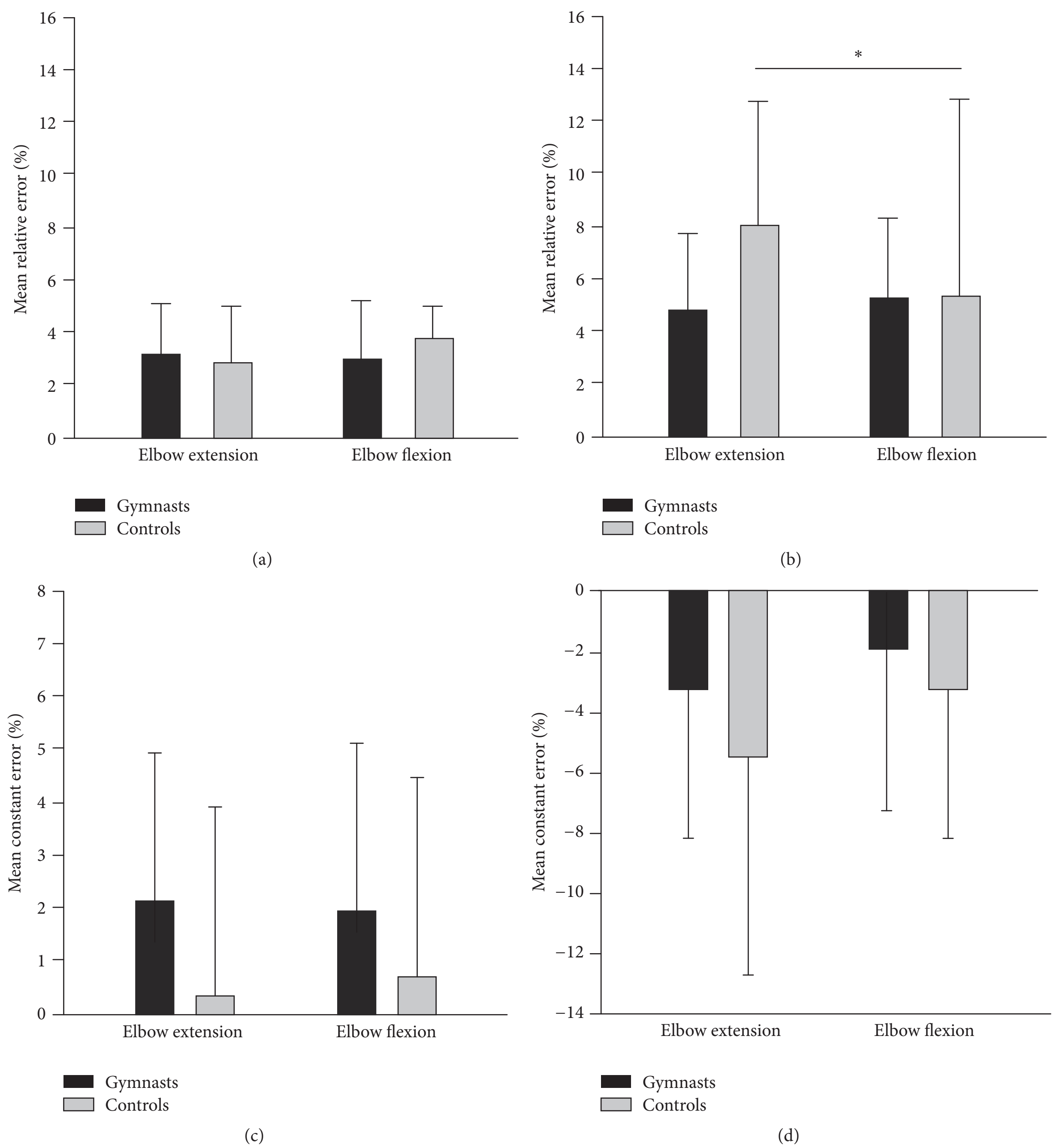

Figure 2: Force reproduction performance in the elbow joint. Mean relative and constant errors of 20% MVC (a, c) and 50% MVC (b, d) task are shown as mean ± SD. Significant difference at $^{*}p < 0.05$.

in terms of the absolute error. This suggests that long-term gymnastic training has no impact on this relationship. However, the increased force steadiness was associated with overshooting the target angle in AR of JPS. On the other hand, gymnasts did not differ from controls during the AR task but did show a tendency towards a higher range of relative error during 20% MVC tasks. Therefore, changes in controlling the steadiness of FR could be responsible for group differences in the relationship between JPS and the steadiness of FR. It was expected that gymnasts would exhibit a substantially lower range of relative error (higher force steadiness), not the opposite, as it was shown that strength training is able to increase the force steadiness [40]. Nevertheless, it should be pointed out that, despite slightly worse steadiness, gymnasts had better accuracy in 50% MVC extension task. To summarize, despite intergroup differences in JPS and FS, these results support previous research demonstrating no linear correlation between accuracy of JPS and FS [19, 41].

The FR task in the study used MVC to set the target level of torque. It was therefore expected that FR performance

Table 3: Pearson's correlation analysis of the muscle strength and proprioception performance.

	Joint position sense				Muscle strength			
	AR		PR		PT flexion		PT extension	
	AE	CE	AE	CE	AV	ALM	AV	ALM
Joint position sense AR								
AE	/	/	/	/	ns	ns	ns	ns
CE	/	/	/	/	ns	0.52 (G)	ns	ns
Joint position sense PR								
AE	/	/	/	/	ns	ns	ns	ns
CE	/	/	/	/	ns	ns	ns	ns
FR 20% MVC flexion								
Mean RE	ns	ns	ns	ns	ns	ns	−0.47 (C)	−0.55 (G)
Mean CE	0.50 (C)*	ns	ns	−0.49 (G)	ns	ns	ns	−0.58 (G)
RE range	0.48 (C)	ns	ns	−0.54 (G)	ns	ns	ns	ns
FR 20% MVC extension								
Mean RE	ns	ns	ns	ns	−0.42 (C)	ns	ns	ns
Mean CE	ns	−0.68 (G)	ns	ns	ns	ns	ns	ns
RE range	ns	−0.57 (G)	ns	ns	ns	ns	ns	ns
FR 50% MVC flexion								
Mean RE	ns	0.49 (G)	ns	0.56 (G)	ns	ns	ns	ns
Mean CE	ns	ns	ns	ns	ns	ns	ns	ns
RE range	ns	ns	ns	ns	ns	ns	ns	ns
FR 50% MVC extension								
Mean RE	ns	ns	ns	ns	ns	ns	ns	ns
Mean CE	ns	ns	ns	ns	ns	ns	ns	ns
RE range	ns	−0.62 (G)	ns	ns	ns	ns	ns	ns

/ indicates the correlation between the same proprioceptive performances, which was not analyzed. AE: absolute error; ALM: arm lean mass normalized values; AR: active reproduction; AV: absolute values; CE: constant error; FR: force reproduction; MVC: maximal voluntary contraction; PR: passive reproduction; PT: peak torque; RE: relative error. * (G) and (C) indicate significant correlation in gymnasts and controls, respectively ($p < 0.05$), and "ns" indicates nonsignificant correlation.

would be correlated with agonist MS. However, a negative correlation was found between FR performance and peak torque of the antagonist muscle group. That is, the stronger the elbow extensors were, the lower the relative error during flexion task was, and vice versa. It is possible that the cocontraction of the antagonist muscle group contributes to joint stabilization allowing for greater FR accuracy [42, 43]. A lack of correlation between FR and agonist MS is consistent with previous research which found no significant correlation between agonist MS and FS in the knee joint of untrained adults [44]. In case of gymnasts, the relationship between antagonist MS and FS accuracy was seen only during 20% MVC flexion and involved ALM-normalized peak torque of extensors instead of absolute values. Normalization of peak torque as well as the muscle coactivation gives insight into neuromuscular coordination in muscle groups acting at particular joints [45–47]. It was expected that, due to long-term training, gymnasts would exhibit better neuromuscular coordination than untrained controls [26, 48]. In the study, gymnasts had higher normalized elbow flexion strength than controls. In addition, it was previously shown that gymnasts have lower coactivation of the antagonist muscles during the elbow flexion task [26]. These results suggest that gymnastic training decreases the torque reducing effect of extensor cocontraction during flexion tasks. This may explain the observed positive correlation of overshooting the target angle in AR of JPS with elbow flexors MS and also the previously discussed higher range of absolute error as the cocontraction of reciprocal muscle increased the steadiness [49].

Previous studies have found that physical activity and strength training can improve proprioceptive performance following injury [50]. However, Ashton-Miller et al. [25] noted that most of these studies did not evaluate the single elements of proprioception like JPS or kinesthetic threshold and focused instead on more complex postural control during balance tests. In the current study, it was shown that gymnasts had similar performance in both AR and PR, while the control group was twice as accurate during AR than during PR. The lower accuracy of the control group during PR was due to the fact that most of them underestimate the target angle. This suggests that long-term training allowed the gymnasts to overcome the thixotropic effect present during the PR task. One of the mechanisms responsible for that could be increased muscle spindle sensitivity and γ-afferent activation in the gymnast group [23]. This is supported by previous research which found that dancers demonstrate greater JPS performance at lower (1.5–2.5 times) [51] and upper (up to 3 times) limbs [52, 53] compared with untrained people. Also, athletes of other sports not associated with aesthetics and the control of body segments in space were shown to have 2.7 times better active JPS performance [54]. Furthermore, Pánics et al. [24] showed that proprioceptive training resulted in up to 2.5 times greater JPS performance among handball players. This suggests that JPS is trainable even in healthy subjects.

This study also investigated the difference in FR between the elbow flexors and extensors. Although no difference in FS accuracy was found during the 20% MVC task, a lower range of relative error in force steadiness was found in the flexor muscles. The opposite was found during the 50% MVC task with greater accuracy found in the flexor group. Both results of FS accuracy and force steadiness could be explained by the role and dominant muscle fibre type of each muscle group [55, 56]. The elbow flexors are meant for quick and precise movements while the extensors have a tonic and antigravity role. The lower accuracy of the extensors during the 50% MVC task was seen in the control group while in gymnasts there was no difference in FS accuracy between muscles. This outcome supports the theory that that long-term gymnastic training improves FS at the extensors during higher-load tasks but not during low-load tasks. Similarly, Smith et al. [57] showed that six weeks of strength training has no impact on the accuracy of FS at the ankle joint during 20% and 30% MVC tasks. This is probably the first time the muscle dependent effect of long-term training on the FS was shown. An interesting relationship was found between JPS and FR of antagonistic muscles in gymnasts. The overshoot performance in FR 20% MVC extension task was associated with underestimating the target angle in AR, while the same direction of bias during FR in flexion task gave the same result but in PR. This could also suggest that gymnastic training had a differentiating impact on the proprioception system in antagonistic muscles, but the mechanisms of this outcome, central, peripheral, or both, need future research.

Limitations. One of the study limitations was that the JPS measurements included only one target angle (90°) not based on the participants' total range of movement. While usage of additional target angles could increase the reliability of outcome, it was decided to preserve a similar elbow joint angle condition for the MS, JPS, and FR assessment. Moreover, such a target angle avoids additional cues from the soft tissue stretch, and apposition at the ends of range influences the accuracy of JPS [58]. The second limitation is that the study's design was unable to account for the role of Golgi tendon organs in the measured proprioception performance. While the receptors' afferent information contributes to FS, many authors show that their role might be less present due to the central mechanism of proprioception.

5. Conclusions

While there is no evidence for a linear relationship between the accuracy of FS and JPS, force steadiness and JPS may use common mechanisms. Long-term gymnastic training appears to result in greater JPS accuracy performance and to reduce the difference in FS between reciprocal muscle groups at the elbow joint by increasing accuracy at the extensor muscles.

Conflicts of Interest

The authors have no conflicts of interest regarding the publication of this paper.

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Research Article

Multicomponent Exercise Improves Hemodynamic Parameters and Mobility, but Not Maximal Walking Speed, Transfer Capacity, and Executive Function of Older Type II Diabetic Patients

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The present study aimed to investigate the effects of a 6-month multicomponent exercise program (MCEP) on functional, cognitive, and hemodynamic parameters of older Type 2 diabetes mellitus (T2DM) patients. Moreover, additional analyses were performed to evaluate if T2DM patients present impaired adaptability in response to physical exercise when compared to nondiabetic volunteers. A total of 72 T2DM patients and 72 age-matched healthy volunteers (CG) were recruited and submitted to functional, cognitive, and hemodynamic evaluations before and after six months of a MCEP. The program of exercise was performed twice a week at moderate intensity. Results indicate T2DM and nondiabetic patients present an increase in mobility (i.e., usual walking speed) after the MCEP. However, improvements in maximal walking speed, transfer capacity, and executive function were only observed in the CG. On the other hand, only T2DM group reveals a marked decline in blood pressure. In conclusion, data of the current study indicate that a 6-month MCEP improves mobility and reduce blood pressure in T2DM patients. However, maximal walking speed, transfer capacity, and executive function were only improved in CG, indicating that T2DM may present impaired adaptability in response to physical stimulus.

1. Introduction

The aging process leads to several alterations in the functioning of some, if not all, physiological systems, collaborating with the development of chronic diseases, such as Type 2 diabetes mellitus (T2DM). Indeed, over 11 million older people presented a clinical diagnosis of T2DM in the United States of America in 2014, representing around 25% of this population [1].

The progression of T2DM leads to the development of poor outcomes, such as diabetic peripheral neuropathy, which is known by its deleterious effects on muscle architecture and functioning, reducing muscular functionality (e.g., mobility, transfer capacity) [2–4].

Several studies have indicated that T2DM patients have a poor cognitive status when compared to age-matched healthy volunteers [5–9]. Although cognition is formed by several capacities (e.g., memory, attention, and inhibition), most authors have highlighted the key role of executive function in the management of T2DM since T2DM patients with executive dysfunction present a high risk to medical assistance [8]. These data deserve concern, mainly in older adults, because the Pan American Health Organization (PAHO) stated independence (i.e., physical function) and autonomy (i.e., cognitive capacity) as two factors corresponding to the concept of health in this population [10].

In addition, the physiopathology of T2DM is strongly associated with a number of alterations in the mechanisms of blood pressure control (e.g., elevated activity of the renin-angiotensin system, autonomic dysfunction), which may trigger the development of high blood pressure in these patients [11, 12]. Indeed, it is worth mentioning that populational data have suggested that more than 50% of the T2DM patients present a clinical diagnosis of hypertension, consequently increasing the poor prognosis in this population [13].

Lastly, T2DM is accompanied by a number of other alterations in the cerebral (i.e., low cerebral blood flow) and muscular (i.e., altered muscular protein metabolism, increased oxidative stress) apparatus [14–19]. In addition to impairing the homeostasis of the organic system, these aforementioned features may reduce the adaptability of T2DM patients in response to physical stimulus (e.g., exercise training [ET]).

Interestingly, an inability to adapt in response to physical exercise may be one more negative factor in the context of T2DM since ET has been shown to improve morphofunctional, cognitive, and hemodynamic parameters of patients with different conditions and could be used to reverse or even stabilize the clinical symptoms of T2DM patients.

In fact, aerobic exercise, for example, is widely known for its key role in the control of blood pressure of healthy and hypertensive patients [20]. Resistance training is suggested as an excellent approach to cause muscular hypertrophy and improve neuromuscular parameters, such as muscle strength and power [21–24]. Moreover, a systematic review of randomized controlled trials indicated that improvements in balance—which is essential for the performance of functional tests, such as *Timed "Up and Go" [TUG]*—are dependent on postural instability, suggesting that balance training should be added in programs aimed at improving this physical capability [25].

Despite the beneficial effects of these interventions in the various above-mentioned domains, some organizational and operational difficulties appear when a long-term ET program is supposed to adequately provide these regimes of physical exercise alone within a periodization period for older T2DM patients. In this sense, multicomponent exercise program (MCEP) emerges as an alternative kind of ET able to combine different exercise regimes in the same exercise routine, thereby not requiring sessions of physical exercise with long duration while developing several physical capacities and skills [26].

Indeed, recently, we demonstrated that a 6-month MCEP was able to increase balance and mobility in normotensive and hypertensive patients [27]. However, the hemodynamic changes in response to the exercise program were not investigated, and our sample was composed of hypertensive and normotensive patients without T2DM. Therefore, the effects of MCEPs on T2DM patients still remain to be elucidated. To the best of our knowledge, just one investigation studied the effects of a MCEP on T2DM patients [28], but the findings were based on subjective methods (i.e., questionnaires).

Therefore, the present study aimed to investigate the effects of a 6-month MCEP on functional, cognitive, and hemodynamic parameters of older T2DM patients. In addition, we investigated if T2DM patients presented impaired adaptability in response to physical exercise when compared to age-matched healthy volunteers.

2. Materials and Methods

The findings present in the current study are part of a larger study which aimed to investigate the effects of MCEPs on functional, cognitive, and hemodynamic parameters of community-dwelling older adults with different chronic conditions (e.g., hypertension). The findings regarding hypertensive patients have been previously published by our group [27]. In the present trial, we used a single-group quasi-experimental design to determine the effects of a 6-month MCEP in the functional (i.e., mobility, maximal walking speed, lower limb muscle strength, balance, and transfer capacity), cognitive (i.e., executive function), and hemodynamic parameters of older Type 2 diabetes mellitus (T2DM) patients. Secondarily, to investigate if T2DM patients present impaired adaptability to ET, results were compared with a control group (CG) composed of age-matched healthy volunteers, who were submitted to the same protocol of MCEP. Therefore, volunteers were submitted to functional, cognitive and hemodynamic evaluations before and after a 6-month MCEP (Figure 1). We followed the methods of Coelho Junior et al. (2017) [29].

All volunteers signed the informed consent form and completed all measurements. This study was approved by the Research Ethics Committee of the University of Campinas (UNICAMP). This study was developed in accordance with the Declaration of Helsinki and according to Resolution 196/96 of the National Health Council.

3. Subjects

The sample consisted of community-dwelling older untrained volunteers from Poá, São Paulo, Brazil. Participants were recruited by convenience from a specialized healthcare center for older adults. Volunteers were asked verbally by the medical team and researchers about their participation in the study. Eligibility criteria for this study were based on the presence of a clinical diagnosis of T2DM and being aged ≥ 60 years. Subjects in the control group (CG) did not present a clinical diagnosis of T2DM. Patients of both sexes were accepted in the study. Patients who were absent in ≥3 subsequent sessions of exercise and unable to perform the TUG cognitive test [30] and presented a clinical diagnosis of hypertension, cardiovascular disease, cerebrovascular disease, neurological or psychiatric disease, pulmonary disease, musculoskeletal disorders, comorbidities associated with greater risk of falls, and any sign of orthostatic hypertension and/or labyrinthitis were excluded. One hundred forty-four participants (72 T2DM and 72 age-matched healthy [CG])

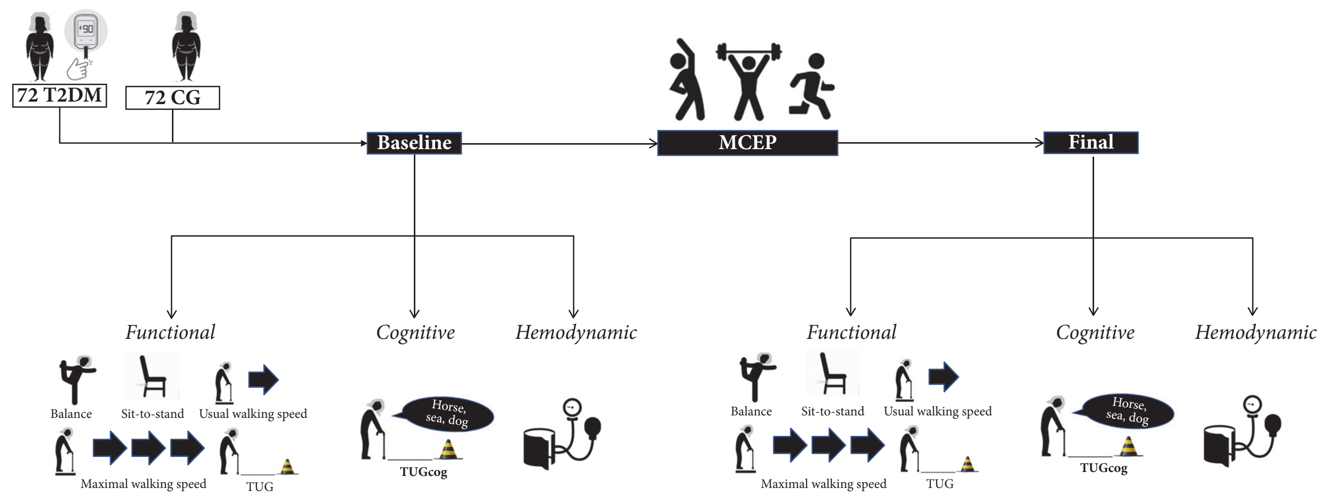

Figure 1: Experimental design of the current study.

completed all evaluations and were eligible to participate in the present study.

Subsequently, CG and T2DM groups were created according to the previous clinical diagnosis of T2DM. It should be stressed that the diagnosis of T2DM was made according to the guidelines of the *Brazilian Society of Diabetes*.

4. Evaluations

The participants were instructed to refrain from any exhausting activity for a period of 96-h before testing and drinking alcoholic and caffeinated beverages 24 h before testing. Subjects were requested to maintain their food intake during the entire protocol (i.e., ~6 months). Baseline evaluations (i.e., before) were performed 5 days (i.e., 120 hours) before the beginning of the MCEP. Likewise, the final evaluations were performed on the fifth day after the last exercise session.

4.1. Functional Parameters. Two experienced researchers applied each test. While one was responsible for detailing the operational procedures, demonstrating the test before the evaluation, quantifying the evaluation time, and evaluating the motor gesture, the other ensured the safety of the participant. After the end of the explanation and before the start of the tests, volunteers performed a familiarization trial to ensure the understanding of the test. The tests were performed twice, and the best result obtained was used in the final analysis. The tests were distributed in a room as stations and were performed in a circuited fashion one after the other. A one-minute interval between trials was provided. Verbal encouragement was provided throughout the tests to ensure that volunteers achieved the best possible performance without compromising safety. During TUG, walking speed test at maximal pace, and sit-to-stand tests researchers provided stimulus such as the following: "*Come on, faster!*"; *"A little more!"*; and; *"Let's go!"* During one-leg stand, verbal encouragement was provided to keep the participant focused on the test. Therefore, the volunteers were stimulated with the sentences: "*Focus! Keep your posture!*" and "*Very good!*" The present protocol has been published by our group elsewhere [29].

4.1.1. Sit-to-Stand Test. Volunteers were requested to rise from a chair five times as quick as possible with arms folded across the chest. The stopwatch was activated when the volunteer raised their buttocks off the chair and was stopped when the volunteer was seated back at the end of the fifth stand.

4.1.2. One-Leg Stand Test. The one-leg stand test was performed with the volunteers standing in a unipodal stance with the dominant lower limb, the contralateral knee remaining flexed at 90°, the arms folded across the chest, and the head straight. A stopwatch was activated when the volunteer raised their foot off the floor and was stopped when the foot touched the floor again. The maximum performance time was up to 30 seconds, considered the best test result.

4.1.3. Three-Meter Usual and Maximal Walking Speed Test. To measure 3-meter walking speed, a 3-meter walking speed test was performed. Volunteers were required to walk a distance of five meters at their usual and fastest possible cadences (without running). Before the evaluation, both feet of each volunteer were to remain on the starting line. The measurement was initiated when a foot reached the one-meter line and was stopped when a foot reached the four-meter line. The one-meter intervals at the beginning and end were used to avoid early acceleration and/or deceleration.

4.1.4. Timed "Up and Go" (TUG) Test. Transfer capacity was evaluated by the Timed "Up and Go" (TUG) test. The TUG test involves getting up from a chair (total height: 87 cm; seat height: 45 cm; width: 33 cm), walking three meters around a marker placed on the floor, coming back to the same position, and sitting back on the chair. The subjects started the test and wore their regular footwear, with their back against the chair, with arms resting on the chair's arms, and with the feet in contact with the ground. A researcher instructed the volunteers to, on the word "go," get up and walk as fast as possible without compromising safety in the demarcation of three meters on the ground, turn, return to the chair, and sit down again. Timing was started when the volunteer got up from the chair and was stopped when the participant's back touches the backrest of the chair. A stopwatch (1/100 second accuracy) was used for time evaluation, and a longer time taken to perform the test indicates a lower performance.

4.2. Executive Function (EF)

4.2.1. TUG Cognitive Test. TUG cognitive test was accomplished to evaluate EF. The motor task of this test is similar to the conventional TUG. However, a cognitive task (verbal fluency, animal category) must be accomplished during the motor task. Therefore, after the signal of the evaluator, the volunteer performed the route—stand up from the chair, walk three meters, turn around, walk three meters back, and sit down again—naming as many animals as he/she could remember. This task was performed aloud, allowing the evaluators to confirm if the volunteers were, in fact, accomplishing the task. The time expansion to perform the task was recorded to evaluation [30]. Briefly, the number of animals mentioned during the test was not recorded. However, one researcher was responsible for ensuring that the volunteers kept naming the animals throughout the whole test.

4.3. Hemodynamic Measurements. The procedures for measurement of blood pressure were adapted from the VII Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) [31]. In summary, volunteers remained in a sitting position on a comfortable chair for 15 minutes in a quiet room. After this period, an appropriate cuff was placed at approximately the midpoint of the upper left arm (heart level). An automatic, noninvasive, and validated [32] arterial blood pressure monitor (Microlife-BP 3BT0A, Microlife, Widnau, Switzerland) was used to measure systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR). During blood pressure recording, volunteers remained relaxed in the sitting position, with parallel feet at one shoulder width, both forearm and hands on the table, supinated hands, and back against the chair, without move or talk. The volunteer did not have access to blood pressure values during measurement. The evaluation lasted approximately 80 seconds and was performed three times with one minute of rest among the measurements. The mean of measurements of each volunteer was used in the final analysis. Mean arterial pressure (MAP), double product (DP), and pulse pressure (PP) were evaluated according to the following equations: $MAP = [SBP + (2 * DBP)]/3$, $DP = SBP * HR$, and $PP = SBP - DBP$. The size of the arm cuff was selected after measuring the arm circumference of each participant (Sanny, São Paulo, Brazil). All volunteers were evaluated within the first month after the update of the medical records.

5. Multicomponent Exercise Program (MCEP)

The MCEP was performed twice a week, on nonconsecutive days, during 26 weeks at the fitness center of an institutional center for elderly care and living (Centro de Convivência do Idoso [CCI]), Poá, Brazil [33]. The program was designed to offer exercises that would mimic activities of daily live (ADL) gestures, thereby inducing neuromuscular adaptations to maintain the subjects capable of performing the ADL. Twelve different exercises stations composed each exercise session. The structure of each exercise session was defined by the sequence of one functional exercise followed, immediately, by a brief walk. Therefore, exercise session was composed of approximately 12 minutes of functional exercises, 24 minutes of walk, and 12 minutes of rest. Approximately 50 patients composed each session of exercise. A physical trainer professional with larger expertise on exercise training to older people supervised all sessions (Gonçalvez IO). Volunteers were instructed to avoid the Valsalva maneuver during the performance of exercises.

The functional exercises were changed during the whole program. However, they always represented ADL with a large necessity of the activity of the lower limbs, for example, stand and seat from the chair, pick up a weight off the floor and put on top of a structure, and transfer a weight from one place to another. Balance and proprioception exercises also composed functional exercises, as one-leg stand. At most three balance and/or proprioception exercises were used in each session. To complete the list of physical exercises, upper limbs resistance exercises were added.

All functional exercises were performed for one minute. The brief walk was performed for two minutes. Thus, after the end of each functional exercise, volunteers must walk from one point to another (30 m), around a cone, come back to the initial line (30 m), and start the path again until completing the two minutes. A rest interval of 60 seconds was adopted between the stations.

6. Exercise Intensity Control

The control of exercise intensity was accomplished by an 11-point scale (CR-10) to measure the perceived exertion (RPE) [34], which was used to ensure that volunteers performed the exercises in the aimed intensity. This scale is composed of eleven numbers (i.e., 0, 1, 2, 3, 4, etc.) and eight descriptors (i.e., rest; very, very easy; easy; moderate; somewhat hard; hard; very hard; maximal), which represents the perception of effort of the subject in front of an exercise load. The higher the reported number, the greater the sensation of effort [34]. During the performance of functional—except for balance exercises—and resistance exercises, volunteers were instructed to maintain the physical activity intensity in 3–5—which represents moderate (i.e., 3), somewhat hard (i.e., 4), and hard (i.e., 5) descriptors. To that, a large picture of RPE scale (i.e., 4 meters high and 1.30 meters wide) was positioned on the wall in the gym's room. The increase in the exercise intensity was based on alterations in the cadence of the performance (i.e., faster), for functional exercises and walk. Moreover, for resistance exercises, volunteers could use elastic bands (EXTEX Sports, São Paulo, Brazil) and dumbbells to reach the intensity prescribed.

7. Statistical Analyses

Normality of data was tested using the *Kolmogorov-Smirnov* test. Baseline comparisons between the groups for age, morphology, and circumferences were performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test. A two-way ANOVA followed by a Dunnett post hoc test was performed to identify differences among the different times of evaluations and treatments. Cohen's effect size d was calculated to assess the magnitude of the results. The effect size was classified according to Rhea, 2004 [35], for untrained volunteers. The level of significance was 5% ($P < 0.05$) and all procedures were performed using the GraphPad Prism 6.0. (San Diego, California, USA).

8. Results

No adverse events occurred during the sessions of exercise or during any of the evaluations. The subjects were not absent for more than three sessions of physical exercise. Adherence to the physical exercise program was 100% (0 dropouts). This interesting result probably occurred because the present study was offered for older adults in need of public attention and the volunteers wait a long time to participate, so that we believe that most of them understood the importance of the exercise program in their lives. Indeed, before the beginning of the MCEP, some speeches were made in an attempt to make them understand the importance of the project. Moreover, it is possible to infer that the current MCEP was attractive to them, since it was composed of a mix of different exercise protocols, avoiding monotony. Other possible explanations for this rate of dropout are the kind of measurements that were performed—because we did not perform several evaluations or discouraging assessments (i.e., biopsy)—and the design of the program—because volunteers did not have to remain in a rigorously controlled state—and the exclusion criteria that were adopted since subjects were just excluded if they were absent from ≥3 subsequent sessions of exercise. Volunteers did not report any changes in food intake and or in the number/class of medications during the study.

Overall characteristics are shown in Table 1. BMI evaluation indicated that T2DM and CG presented an overweight and obese phenotype, respectively. However, statistical significant differences were not observed between the groups. Circumference values (i.e., WC, HC, WC/HC, and NC) are in line with BMI evaluation, since CG and T2DM presented a high cardiovascular risk. The hypothesis test indicated that T2DM presented a higher WC, HC, WC/HC, and NC when compared to CG.

Functional and cognitive parameters are shown in Table 2 and Figure 2. At baseline, T2DM presented higher TUG and TUGcog values when compared to CG, indicating an impaired performance in both tests compared to non-T2DM volunteers. There were no significant differences regarding the other parameters. A significant increase on usual walking speed was observed after the 6-month MCEP, regardless of T2DM. However, just CG displayed an improved performance in maximal walking speed and TUGcog (Figure 2). ES evaluation corroborates with the hypothesis test, since ES classification was always higher in the CG (i.e., *small* and *moderate*) when compared to T2DM (i.e., *trivial* and *small*) group (Table 2). Nevertheless, intergroup comparisons (i.e., Post and delta [Δ]) did not demonstrate significant differences between the groups after the MCEP. Lastly, sit-to-stand, one-leg stand, and TUG tests were not significantly altered in any of the groups after the exercise program.

Table 1: Characteristics of the older adults according to T2DM.

Variable	CG (n = 72)	T2DM (n = 72)	P
Age (years)	64.4 ± 5.7	66.0 ± 3.2	0.15
Weight (kg)	71.2 ± 13.8	75.8 ± 12.3	0.04
Height (m)	1.58 ± 0.0	1.58 ± 0.0	0.84
BMI (kg/m^2)	28.4 ± 2.2	30.3 ± 2.8	0.27
WC (cm)	97.5 ± 11.7	102.6 ± 10.7	<0.001
HC (cm)	104.4 ± 9.6	105.8 ± 13.7	0.07
WC/HC	0.93 ± 0.06	1.07 ± 0.99	0.09
NC (cm)	36.7 ± 3.6	38.0 ± 3.1	0.03

CG = control group; T2DM = Type 2 diabetes mellitus; BMI = body mass index; WC = waist circumference; HC = hip circumference; NC = neck circumference.

Hemodynamic parameters are shown in Table 3. At baseline, T2DM presented higher SBP values when compared to CG, while the other hemodynamic parameters were similar between the groups. T2DM presented a significant decrease in SBP, DBP, and MAP after the MCEP; whereas CG did not show significant alterations. ES evaluation are in line with the hypothesis test, since ES classification was always higher in the T2DM (i.e., *trivial and small*) when compared to CG (i.e., *trivial*). The intergroup comparisons (i.e., Post and delta [Δ]) after the MCEP did not demonstrate significant differences between the groups.

9. Discussion

The main findings of the present study indicate that T2DM patients show reduced executive function and transfer capacity when compared to nondiabetic volunteers (i.e., CG). On the other hand, T2DM presented higher blood pressure values than CG. Our data indicate that a 6-month MCEP is able to improve mobility in T2DM and nondiabetic patients, while a significant increase in maximal walking speed, transfer capacity, and executive function was only observed in CG. Lastly, T2DM patients presented a marked decline in the hemodynamic parameters, which was not observed in CG.

Our results are in line with prior cross-sectional and prospective populational studies that reported a decreased executive function in T2DM patients [5–9]. In the study of Qiao et al. (2006) [6], authors observed that T2DM patients presented a poor executive function (overall and in the subdomains [visuospatial, working memory]) and global function scores when compared to patients without

Table 2: Functional and cognitive parameters.

Variable	CG (n = 72)	T2DM (n = 72)
Sit-to-stand (repetitions)		
Pre	10.1 ± 1.5	10.6 ± 2.1
Post	10.3 ± 2.6	11.4 ± 5.8
ES	0.09 *(trivial)*	0.18 *(trivial)*
Δ	2.0	7.5
One-leg stand (s)		
Pre	16.9 ± 21.0	15.9 ± 11.9
Post	11.8 ± 9.7	20.7 ± 11.1
ES	0.31 *(trivial)*	0.41 *(trivial)*
Δ	−30.1	30.2
Usual walking speed (m/s)		
Pre	1.2 ± 0.2	1.2 ± 0.2
Post	1.8 ± 0.4^{b}	1.3 ± 0.2^{b}
ES	1.89 *(moderate)*	0.50 *(small)*
Δ	50	8.2
Maximal walking speed (m/s)		
Pre	1.7 ± 0.2	1.8 ± 0.4
Post	2.8 ± 0.2^{b}	1.7 ± 0.2
ES	2.5 *(moderate)*	0.31 *(trivial)*
Δ	38,4	−5.5
TUG (s)		
Pre	6.7 ± 1.1	7.3 ± 1.8^{a}
Post	7.1 ± 1.4	7.4 ± 2.1
ES	0.31 *(trivial)*	0.05 *(trivial)*
Δ	6.0	1.3
TUG with a cognitive task (s)		
Pre	7.4 ± 1.3	8.0 ± 2.1^{a}
Post	8.5 ± 2.0^{b}	8.5 ± 2.7
ES	0.65 *(small)*	0.20 *(trivial)*
Δ	14.9	6.2

CG = control group; T2DM = Type II diabetes mellitus; TUG = Timed "Up and Go"; ES = effect size; $^{a}P < 0.05$ versus CG; $^{b}P < 0.05$ versus baseline.

T2DM. These data deserve concern, since sufficient cognitive skills, mainly preserved executive function, are required for adherence and effectiveness of diabetes treatment because an elevated risk for hypoglycemia requiring medical assistance is observed in T2DM with cognitive dysfunction [8].

In addition, executive function seems to be associated with mobility capacity because an ability to process, integrate, and respond to multiple stimuli received during ambulation is necessary for a successful locomotion [36]. Indeed, executive dysfunction is associated with impaired gait and balance, which plays a key role in the TUG performance of healthy and cognitively impaired older adults [37]. Therefore, the reduced executive function presented by our T2DM patients may be associated with their impaired transfer capacity.

However, executive dysfunction is probably not the only factor responsible for the reduced TUG scores observed in the current study since T2DM progression synergistically with prolonged hyperglycemia exposure is known to result in diabetic peripheral neuropathy, which is associated with several deficiencies in the morphology and functioning of the skeletal muscle—such as denervation-reinnervation process and loss of motor axons and nerve excitability and conduction (i.e., demyelination)—resulting in accelerated muscle atrophy and fatigue and loss of muscle strength and power (i.e., muscle weakness), consequently reducing motor function (e.g., walking, climbing stairs) [2–4].

It is noteworthy that the current 6-month MCEP was not able to improve transfer capacity and executive function in T2DM, while a significant increase in mobility (i.e., usual walking speed) was observed. On the other hand, CG presented significant improvements in maximal walking speed, transfer capacity, and executive function. These data suggest that T2DM present a limited adaptability in response to physical exercise—at least on executive function and neuromuscular capabilities—when compared to age-matched healthy controls.

Findings of the present study are in line with other experiments, which demonstrated an increased mobility in T2DM patients after ET [for review see Cadore and Izquierdo, 2015 [38]]. However, only a few studies have been designed to

Table 3: Hemodynamic parameters.

	CG (n = 72)	T2DM (n = 72)
SBP (mmHg)		
Pre	129.1 ± 18.0	135.5 ± 17.0[a]
Post	129.3 ± 20.4	129.3 ± 21.7[b]
ES	0.01 *(trivial)*	0.31 *(trivial)*
Δ (%)	0.1	4.5
DBP (mmHg)		
Pre	77.0 ± 11.0	78.2 ± 9.5
Post	73.8 ± 9.9	70.5 ± 11.6[b]
ES	0.30 *(trivial)*	0.72 *(small)*
Δ (%)	−4.1	−10.2
MAP (mmHg)		
Pre	92.8 ± 16.9	97.3 ± 9.9
Post	89.3 ± 20.4	90.0 ± 14.0[b]
ES	0.18 *(trivial)*	0.60 *(small)*
Δ (%)	−3.7	−7.5
HR (bpm)		
Pre	77.1 ± 11.9	77.4 ± 12.8
Post	80.1 ± 14.1	77.6 ± 16.9
ES	0.22 *(trivial)*	0.01 *(trivial)*
Δ (%)	3.9	0.2
DP (mmHg ∗ bpm)		
Pre	9848 ± 2693	10527 ± 2412
Post	10040 ± 3177	10009 ± 2742
ES	0.06 *(trivial)*	0.20 *(trivial)*
Δ (%)	−2.0	−5.0
PP (mmHg)		
Pre	51.1 ± 15.8	57.2 ± 16.4
Post	53.5 ± 18.8	58.7 ± 15.1
ES	0.13 *(trivial)*	0.09 *(trivial)*
Δ (%)	4.7	2.6

Data are presented as mean ± SD; SBP = systolic blood pressure; DBP = diastolic blood pressure; MAP = mean arterial pressure; HR = heart rate; DP = double product; PP = pulse pressure; [a]$P < 0.05$ versus CG; [b]$P < 0.05$ versus baseline; ES = effect size.

investigate the effects of a MCEP in these variables, limiting our discussion.

In the trial of Baptista et al. (2017) [28], T2DM patients were submitted to a 24-month MCEP performed 3 days per week and composed of 30 minutes of aerobic exercise, 20 minutes of resistance exercise, and 20 minutes of balance and flexibility exercises. The program of exercise elicited significant improvements in physical functioning, but not in mental health. Nevertheless, it is worth mentioning that the findings of Baptista et al. (2017) [28] were based on a self-reported questionnaire (i.e., SF36), because the main objective of their study was to evaluate health related quality of life, strongly limiting further comparisons between our studies.

Therefore, in addition to the findings of Baptista et al. (2017) [28], our findings suggest that a MCEP composed of resistance, aerobic, and balance exercises performed at moderate intensity may improve mobility and the self-perception of mobility in T2DM patients.

Regarding the lack of significant alterations in the executive function, maximal walking speed, and transfer capacity observed in T2DM after the 6-month MCEP, some investigations support our findings and demonstrate that T2DM patients present an impaired adaptability to physical stress (i.e., skeletal geometry) [39]. In addition, evidence demonstrates that T2DM patients present marked alterations in the cellular and physiological functioning of different tissues (e.g., brain, skeletal muscle) with a key role in the adaptive response to physical exercise [14–19].

Improvements in the cognitive function after ET, for example, are product of several mechanisms elicited by each session of exercise, such as increase in blood flow [40, 41]. However, investigations with humans [16, 18] and animal models [17] have demonstrated that T2DM is associated with a decreased diameter of cerebral perforating and middle cerebral arteries, followed by an impaired cerebral blood flow, which would impair the increase in cerebral blood flow in response to a physical stimulus.

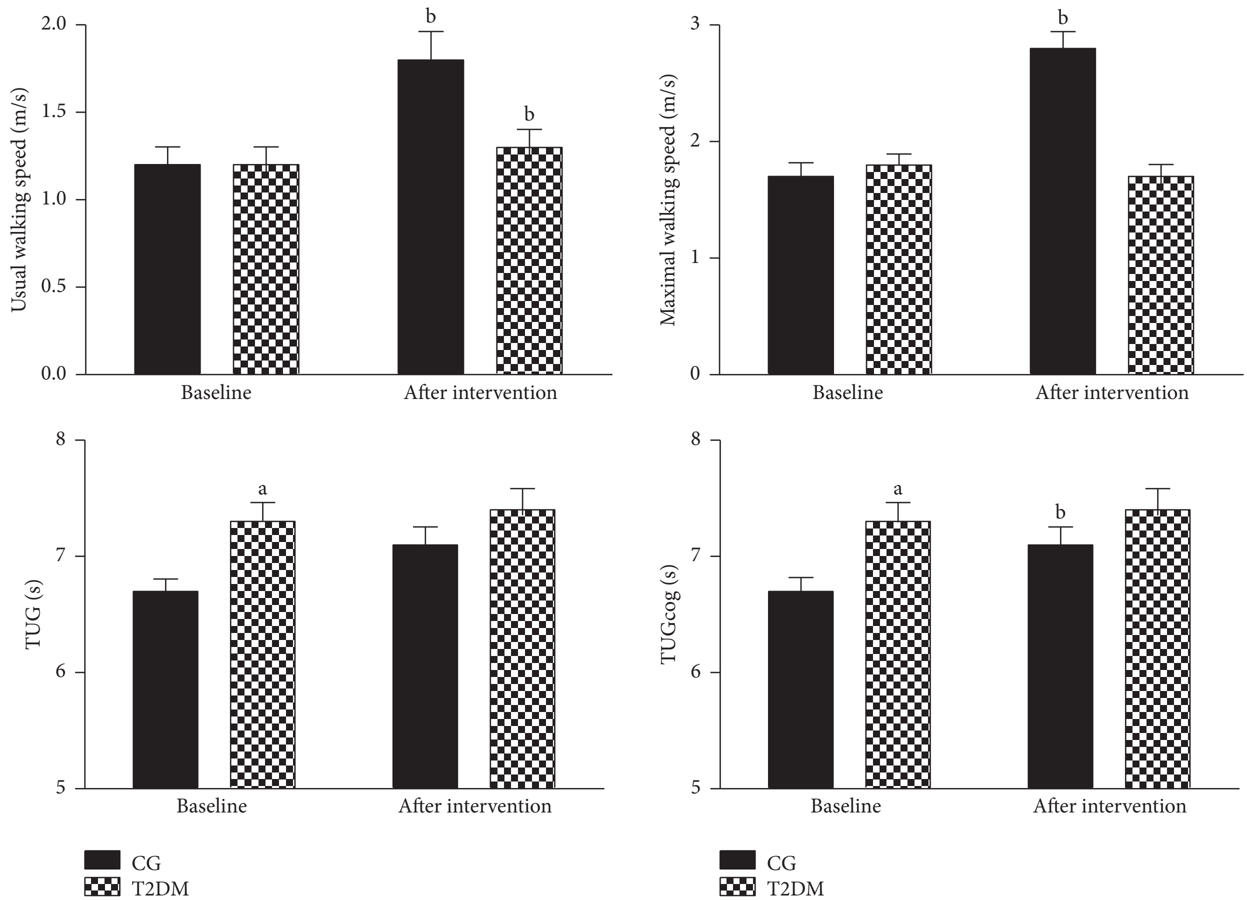

Figure 2: Functional and cognitive parameters. CG = control group; T2DM = Type II diabetes mellitus; TUG = Timed "Up and Go"; ES = effect size; $^{a}P < 0.05$ versus CG; $^{b}P < 0.05$ versus baseline.

Furthermore, regarding the neuromuscular apparatus, Allen et al. [14, 15] observed that T2DM patients with diabetic peripheral neuropathy presented a small number of motor units in the lower limbs. In addition, the findings indicate an altered protein metabolism, in favor of protein breakdown, due to insulin resistance in T2DM patients [19]. Interestingly, improvements in muscle strength and power in response to ET occur as a product of muscle hypertrophy [22–24] and/or neuromuscular adaptations (e.g., increased neural recruitment) [22, 23, 42].

Therefore, these investigations suggest that our MCEP was not fully sufficient to counteract the *negative* environment (e.g., reactive oxygen species, inflammation, hyperglycemia, and insulin resistance) responsible for the impaired adaptability in response to the physical stimulus present in T2DM patients. Thus, since maximal walking speed, TUG, and TUGcog performances involve a larger number of physical capabilities (e.g., muscle strength and power, attention, and inhibition) and physiological structures than usual walking speed, these tests were not altered in response to the MCEP.

Lastly, the current study evaluated the hemodynamic parameters of older T2DM patients. At baseline, our findings suggest that volunteers were in a *prehypertensive* state, while the CG group presented *normal* blood pressure values. These findings are consistent with existing knowledge, because the prevalence of high blood pressure values is around 80% in T2DM patients, contributing substantially to the high cardiovascular risk observed in these patients [12, 43].

The MCEP was able to elicit a marked decrease in blood pressure values of T2DM patients. Other studies have observed a reduction in blood pressure values after MCEP in T2DM patients, and different magnitudes of change in SBP and DBP may be observed among the studies [28]. In fact, in the experiment performed by Baptista et al. (2017) [28], volunteers showed 15 mmHg decrease in SBP, while the patients of the present study demonstrated 4.5 mmHg decrease. On the other hand, a larger decrease in DBP was observed in the current trial (−10 mmHg) when compared to the abovementioned study (−6 mmHg) [28].

The inconsistencies among these findings could be a function of the differences in the design of the MCEP (e.g., frequency, volume, duration, and intensity), as well as the initial state of the volunteers. Accordingly, it is not possible to indicate the crucial factor that influenced the different declines observed in blood pressure values. However, it is worth mentioning that in the trial of Baptista et al. (2017) [28] hypertensive patients were included in the sample, which limit the comparisons, since patients with high blood pressure values present larger reductions in these parameters after different regimes of ET, including multicomponent exercise [27], than patients with low blood pressure values. Moreover, Baptista et al. (2017) [28] evaluated blood pressure through a nonblinded method, which is associated with a measurement bias.

Some limitations of the current study should be mentioned and addressed in future studies to a better understanding about the effects of MCEP in T2DM patients, such as the lack of information regarding the educational level of the volunteers, blood analyses of the participants, evaluation of other cognitive domains, other designs of multicomponent exercise, and a sedentary CG.

10. Conclusions

Data of the current study indicate that a 6-month MCEP may improve mobility and reduce blood pressure in T2DM patients. However, maximal walking speed, transfer capacity, and executive function were only improved in CG, indicating that T2DM may present impaired adaptability in response to physical stimulus.

Disclosure

The authors alone are responsible for the content and writing of the paper.

Conflicts of Interest

The authors report no conflicts of interest.

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Research Article

Evidence-Based Cutoff Threshold Values from Receiver Operating Characteristic Curve Analysis for Knee Osteoarthritis in the 50-Year-Old Korean Population: Analysis of Big Data from the National Health Insurance Sharing Service

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We aimed to investigate the characteristics of patients with osteoarthritis (OA), using the data of all Koreans registered in the National Health Insurance Sharing Service Database (NHISS DB), and to provide ideal alternative cutoff thresholds for alleviating OA symptoms. Patients with OA (codes M17 and M17.1–M17.9 in the Korean Standard Classification of Disease and Causes of Death) were analyzed using SAS software. Optimal cutoff thresholds were determined using receiver operating characteristic curve analysis. The 50-year age group was the most OA pathogenic group (among 40~70 years, $n = 2088$). All exercise types affected the change of body mass index ($p < 0.05$) and the sex difference in blood pressure (BP) ($p < 0.01$). All types of exercise positively affected the loss of waist circumference and the balance test (standing time on one leg in seconds) ($p < 0.01$). The cutoff threshold for the time in seconds from standing up from a chair to walking 3 m and returning to the same chair was 8.25 (80% sensitivity and 100% specificity). By using the exercise modalities, categorized multiple variables, and the cutoff threshold, an optimal alternative exercise program can be designed for alleviating OA symptoms in the 50-year age group.

1. Introduction

According to the database (DB) of the Health Insurance Review and Assessment Service, the proportion of patients with diseases of the musculoskeletal system was 50% in 2003 and 71% in 2013. In particular, knee diseases were the 10th most common cause of hospitalization, involving costs of about 2500 USD per person and ranking second in terms of total medical expenses (http://www.hira.or.kr). In addition, medical treatments take an average of 8 days to complete. Furthermore, the number of patients with OA increases steadily and OA pathogenesis shows a pattern of occurring even in younger age groups, which necessitates the establishment of prognostic and treatment programs for knee OA.

Several trials to identify multiple causes of knee OA have been performed to establish individualized and specific treatments for curing OA symptoms [1, 2].

As many cases have an unspecified etiology (causality; i.e., OA has multiple causes such as knee anterior cruciate ligament, meniscus damage, and quadriceps muscle weakness), providing individualized solutions for OA is difficult [3–5]. Because the causality between knee damage and OA cannot be clearly identified and it is difficult to find solutions for OA (many factors lead to aggravation of knee OA), prevention of OA is considered the ideal option [6]. To reach a reasonable solution to this issue, understanding the various characteristics of OA from diverse aspects is important to determine related factors affecting the pathogenesis of the

Table 1: Characteristics of the NHISS DB-based population older than 40 years.

Parameters	Values	
	Men	Women
Total analyzed population	279,125	235,740
Average age (years)	56.66	58.36
Follow-up years (years)	2002–2013	
BMI (kg/m^2)	23.99	23.99
Total cholesterol (mg/dL)	196.47	203.08
SGOT_AST (U/L)	28.36	24.66
SGPT_ALT (U/L)	29.11	21.72
Gamma_GTP (U/L)	52.04	22.86

The total analyzed population from the NHISS DB showed sex differences in demographic characteristics. NHISS DB, National Health Insurance Sharing Service database; BMI, body mass index; SGOT_AST, serum glutamic oxaloacetic transaminase and aspartate aminotransferase; SGPT_ALT, serum glutamic pyruvic transaminase and alanine aminotransaminase; Gamma_GTP, gamma glutamyl transpeptidase.

disease and to decide appropriate optimal cutoff threshold points for improving prognostic programs (e.g., exercise prescriptions).

Big data analysis of health information is possible, as health-care providers mandatorily register their patient's injury or disease information through the National Health Insurance Sharing Service (NHISS) for reimbursement of medical service costs in Korea. The NHISS DB provides standardized health and medical information from unilateral medical check records of the entire Korean population. This DB was electronically organized, digitalized, and formatted from 2002 to 2013.

To address the above-mentioned issues and provide beneficial information about patients with OA for ameliorating OA symptoms from various aspects by using NHISS big data, we first set the following research objectives.

In this study, we aimed to examine the most prevalent ages of patients with OA among the elderly Korean population and characterize various features of OA according to four different exercise types, in order to provide evidence-based proper cutoff points for ameliorating OA pathogenesis. We examined three hypotheses in this study, as follows:

(1) There would be specific age ranges of pathogenic OA in the elderly Korean population.

(2) Variables related to comprehensive and physical function will show the overall characteristics of OA in relation to different exercise modalities.

(3) There are appropriate cutoff thresholds for variables of pathogenic OA, and these can provide beneficial information for designing a reasonable prognostic program for improving OA symptoms.

2. Materials and Methods

2.1. Study Design. This study is a retrospective cohort study of data from the NHISS DB. Korean Standard Classification of Disease and Causes of Death- (KSCDCD-) designated OA-related codes (M17 and M17.1–17.9) were used to identify patients with OA aged > 40 years from the NHISS DB. These patients were categorized into four age groups with increments of 10 years (40–49, 50–59, 60–69, and 70–79 years) to examine which age groups have a high risk of OA. The demographic, exercise, and functional test characteristics of each age group were subsequently investigated. The flow of the study is described in Figure 1.

2.2. Data Source and Subject Population. A total of 514,866 patients (approximately 10% of the whole population aged >40 years from the NIHSS DB pool) were randomly selected from patients registered in the NHISS. After the age of 40 years, Korean adults mandatorily need to undergo life cycle-based health checks, and the NHISS DB stores their data including exercise information and basic physiological health screening data (Table 1). An individualized design based on the NHISS data of patients aged > 40 years was used because OA-related symptoms with clinical evidence were observed at this age [7]. Patients with OA codes M17 and M17.1–M17.9 in the KSCDCD (http://kssc.kostat.go.kr/ksscNew_web/index.jsp) were extracted by using SAS software (Table 2). The KSCDCD defines M17 and M17.1 to M17.9 as indicating arthrosis of the knee. The study was approved by the institutional review board of Yonsei University (1040917-201603-HRBR-152-01E).

2.3. Categorization of Variables. Nineteen variables were divided into three categories. The first category comprised four exercise-related variables (Exerci_Freq_RSPS_CD: frequency of moderate-intensity exercise per week, Mov20_Wek_Freq_ID: frequency of 20 min intensive exercise per week, Mov30_Wek_Freq_ID: frequency of 30 min moderate-intensity exercise per week, and WLK30_Wek_Freq_ID: frequency of 30 min walking per week). The second category comprised 10 comprehensive variables including sex difference, body mass index (BMI, kg/m^2), high blood pressure (BP_high, mm Hg), low blood pressure (BP_LWST, mm Hg), total cholesterol (TOT_CHOLE, mg/dL), serum glutamic oxaloacetic transaminase and aspartate aminotransferase (SGOT_AST, U/L), serum glutamic pyruvic transaminase and alanine aminotransaminase (SGPT_ALT, U/L), gamma glutamyl transpeptidase (Gamma_GTP, U/L), disease history (HCHK_PMH_CD2), and waist circumference (WAIST, cm). The third category comprised physical function-related variables such as lower-limb function test results for 66-year-old

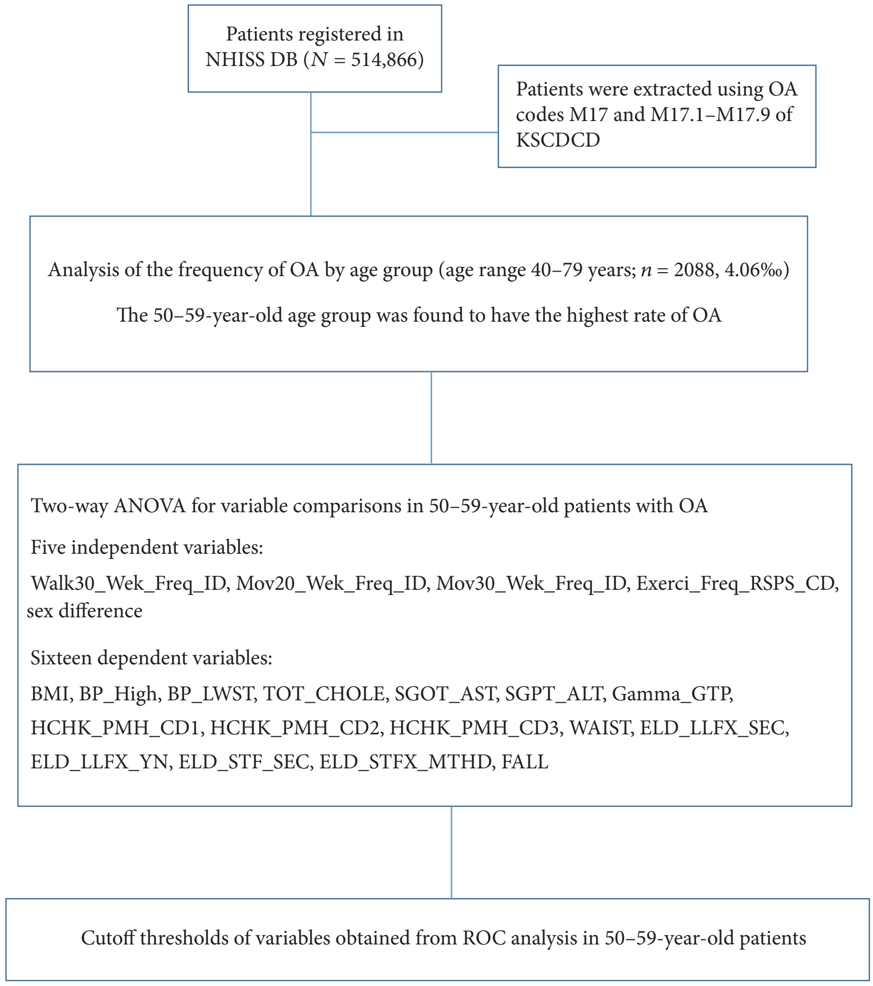

Figure 1: Diagram of the study design. A total of 514,866 patients enlisted in the NHISS were extracted. Patients with OA from the NHISS DB were subtracted by using KSCDCD-provided OA codes (M17, M17.1, M17.2, M17.3, M17.4, M17.5, M17.6, M17.7, M17.8, and M17.9), and patients with OA in this stage were those registered in the NHISS with a one-time diagnosis of OA. The age range of patients used to analyze the most OA pathogenic group was from 40 to 70 years. The effect of 4 independent variables (Walk30_Wek_Freq_ID, Mov20_Wek_Freq_ID, Mov30_Wek_ID, and Exerci_Freq_RSPS_ID) on 16 dependent variables (BMI, BP_High, BP_LWST, TOT_CHOLE, SGOT_AST, SGPT_ALT, Gamma_GTP, HCHK_PMH_CD2, WAIST, ELD_LLFX_SEC, ELD_LLFX_YN, STF_SEC, ELD_STFX_MTHD, and FALL) were verified by using univariate analysis of variance. Variables with statistical significance were selected and cutoff thresholds for optimal points were provided by using ROC curve analysis in 50-year-old patients with OA. OA, osteoarthritis; NHISS, National Health Insurance Sharing Service; KSCDCD, Korean Standard Classification of Disease and Causes of Death; Exerci_Freq_RSPS_CD, number of dates with exercise; Walk30_Wek_Freq_ID, number of dates with >30 min walking exercise in a week; Mov20_Wek_Freq_ID, number of dates with 20 min intensive exercise in a week; Mov30_Wek_Freq_ID, number of dates with 30 min moderate exercise in a week; BMI, body mass index; BP_High, maximal systolic blood pressure; BP_LWST, lowest diastolic blood pressure; ELD_LLFX_SEC, lower-extremity function assessing the time taken for walking 3 m away and back (only for 66 year olds); ELD_STFX_MTHD, balance test only for 66 year olds by taking the time of standing up with eyes closed or eyes opened; SGOT_AST, serum glutamic oxaloacetic transaminase and aspartate aminotransferase; SGPT_ALT, serum glutamate-pyruvate transaminase and alanine aminotransferase; TOT_CHOLE, total cholesterol.

subjects (ELD_LLFX_SEC: time in seconds from standing up from a chair to walking 3 m and returning to the same chair and ELD_LLFX_YN: presence or absence of gait disability described as 1 or 2, respectively), balance test for 66-year-old subjects (ELD_STF_SEC: time of standing on one leg in seconds and ELD_STFX_MTHD: time in seconds of standing on one leg with eyes closed or open), and falls (FALL, fall injury within 6 months). The above-described variables were used to examine the second hypothesis and to provide ideal cutoff thresholds of statically examined variables of OA (hypothesis (3)) in the most OA pathogenic age group (hypothesis (1)).

2.4. Statistical Analysis. All data are presented as mean ± standard deviation. In the most OA pathogenic group, reciprocal effects and interactions were investigated by analyzing the established independent and dependent variables to understand the characteristics of OA. Statistically

Table 2: Characteristics of the NHISS DB-derived population with OA.

Parameters	Values	
	Men	Women
Total patients with OA	723	1365
Average age (years)	54.51	54.73
BMI (kg/m^2)	24.42	25.50
Total cholesterol (mg/dL)	199.84	211.37
SGOT_AST (U/L)	31.06	25.81
SGPT_ALT (U/L)	29.97	23.83
Gamma_GTP (U/L)	63.85	23.21

Patients with KSCDCD-derived codes M17 and M17.1–M17.9 were extracted from the NHISS DB. NHISS DB, National Health Insurance Sharing Service database; KSCDCD, Korean Standard Classification of Disease and Causes of Death; OA, osteoarthritis; BMI, body mass index; SGOT_AST, serum glutamic oxaloacetic transaminase and aspartate aminotransferase; SGPT_ALT, serum glutamic pyruvic transaminase and alanine aminotransaminase; Gamma_GTP, gamma glutamyl transpeptidase.

well-defined variables were then selected to provide the optimal cutoff thresholds in the most OA pathogenic patient group. As described in the *Categorization of Variables* section, the four exercise types were indicated as independent variables, and the 10 comprehensive and 5 physical function-related variables were considered dependent variables. Each of the four exercise types was tested for its effectiveness and interaction with the 15 dependent variables by using two-way univariate analysis of variance (ANOVA) in the 50-year OA group (to verify hypothesis (2)). By using logistic regression between patients with and without OA in the 50-year age group, risk factors according to the existence of OA were found and these variables were analyzed by using receiver operating characteristic (ROC) curve analysis to determine the cutoff points for the optimal threshold for avoiding OA pathogenesis (to examine hypothesis (3)). SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS version 18.0 were used for all statistical analyses. A value of $p < 0.05$ was considered to indicate a statistically significant difference in all analyses.

3. Results

3.1. Subject Characteristics. All Koreans are mandatorily registered in the NHISS for their health check. A total of 514,886 randomly selected subjects from the NHISS DB pool were used to represent the entire population aged > 40 years, which was estimated to comprise about 5 million Koreans. By using the provided NHISS DB, sex-different demographic characteristics were identified and the values (men versus women) were as follows: total analyzed population, 279,125 versus 235,740; average age, 56.66 versus 58.36 years; BMI, 23.99 versus 23.99 kg/m^2; TOT_CHOLE, 196.47 versus 203.08 mg/dL; SGOT_AST, 28.36 versus 24.66 U/L; SGPT_ALT, 29.11 versus 21.72 U/L; and Gamma_GTP, 52.04 versus 22.86 U/L (Table 1). The KSCDCD-derived codes indicating knee OA were M17 and M17.1–M17.9. The number of extracted patients with knee OA was 2088 (men versus women: 723 versus 1365), which means the number comprising single patients who had only one medical prescription for knee OA during 2002–2013. The values of average age, BMI, TOT_CHOLE, SGOT_AST, SGPT_ALT, and Gamma_GTP in patients with OA showed sex differences (Table 2).

3.2. Pathogenesis of OA in Each Age Group. The subjects, aged from their 40s to 70s, were divided into four age groups with increments of 10 years (40–49, 50–59, 60–69, and 70–79 years). The linear function graph was verified to comparatively investigate the frequency of OA pathogenesis in each group (Figure 2). The angle of the graph for the 40–49- and 50–59-year age groups was 7.4° and 8.9°, respectively, and these groups showed an increasing OA pathogenesis pattern; however, the 60–69-year (angle, −3.6°) and 70–79-year (angle, −17.7°) age groups showed reversely decreasing values to patient numbers. Thus, we clarified our first hypothesis based on the observation that OA pathogenesis occurred most frequently in the 50-year age group.

3.3. Four Independent Variables (Exercise Modalities) on Comprehensive Variables. A sex difference was observed only in Walk30_Wek_Freq_ID according to age difference within 50~59-year age group ($p < 0.01$). All exercise types significantly affected the change of BMI; however, Walk30 showed a sex difference ($p < 0.05$). The interaction between sex difference and different exercise types was effective in changing BMI ($p < 0.01$). Sex difference affected BP in all exercise types ($p < 0.01$); however, exercise frequency did not seem to affect the change of BP in all exercise types. The four exercise types seemed more related to hypertension, cardiopathy, stroke, diabetes, cancer, and others than to tuberculosis, hepatitis, and hepatism in HCHK_PMH_CD2. Higher frequencies of exercise did not seem to affect the change of disease history; however, it depended more on the type of exercise ($p < 0.01$).

Male patients with OA aged 50~59 years had higher values of SGOT_AST and SGPT_ALT than female patients with OA. Higher frequency of exercise showed lower values of SGOT_AST and SGPT_ALT. Significant differences of sex and exercise type and interactions between sex difference and exercise type were found in SGOT_AST and SGPT_ALT ($p < 0.01$). The highest value of SGOT_AST was seen with the least frequency of male exercise. TOT_CHOLE in men

Table 3: Logistic regression and ROC curve analyses for patients with OA.

Parameter	OR	AUC	p value	Cutoff values	Sensitivity (%)	Specificity (%)
Sex	1.973	0.559	<0.01	N/A	N/A	N/A
Age (years)	0.895	0.265	<0.01	N/A	N/A	N/A
SGOT_AST (U/L)	1.014	0.463	<0.01	18.75	88%	85%
ELD_STF_SEC (s)	0.189	0.022	<0.01	14.75	75%	100%
Fall	0.963	0.895	<0.01	N/A	N/A	N/A
ELD_LLFX_SEC (s)	0.478	0.861	<0.01	8.25	80%	100%

Variables with significant p values were selected via logistic regression analysis, and then other factors such as AUC, p value, and sensitivity and specificity of the cutoff points were considered to finally select the cutoff threshold values of the significant variables. ROC, receiver operating characteristic; OA, osteoarthritis; OR, odds ratio; AUC, area under the curve; N/A, not applicable; SGOT_AST, serum glutamic oxaloacetic transaminase and aspartate aminotransferase; ELD_STF_SEC, standing time on one leg in seconds; ELD_LLFX_SEC, time in seconds from standing up from a chair to walking 3 m and returning to the same chair.

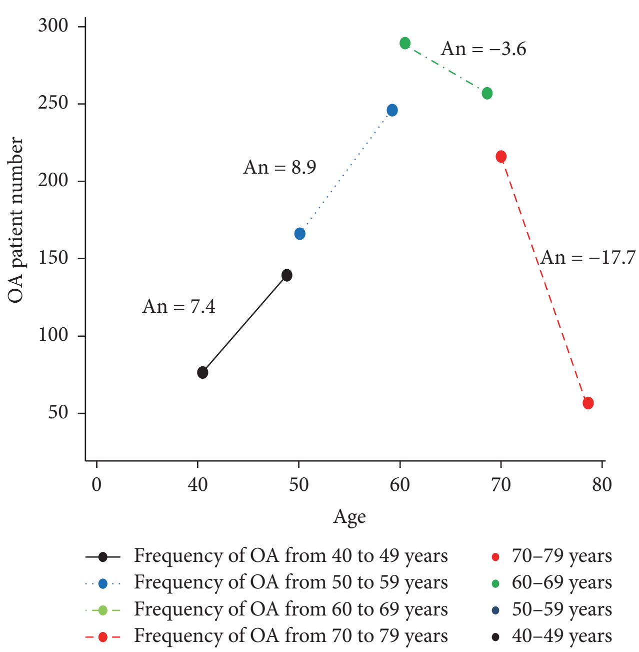

Figure 2: Pathogenesis of OA in each age group. Carefully extracted patients with OA who had only one hospital visit and OA prescription record in the NHISS from 2002 to 2013 were categorized into four age groups with increments of 10 years (40–49, 50–59, 60–69, and 70–79 years). Each angle from the linear functional graph in each age group was calculated to determine the increase or decrease of OA pathogenesis in patients. From this figure, the 50-year age group was selected and further investigated because the maximum OA occurrence was observed in this age group (An, 8.9). Compared with the 40- and 50-year age groups, the number of patients older than 60 years with OA pathogenesis unexpectedly decreased. OA, osteoarthritis; An, angle.

was lower than that in women ($p < 0.01$). Only Exerci_Freq had no relation to TOT_CHOLE ($p < 0.01$). For improving TOT_CHOLE, Mov20 or Mov30, not Exerci_Freq, may be a better option. Figure 3(b) shows that daily Exerci_Freq for improving TOT_CHOLE was more effective in men. All types of exercise significantly affected the changes of WAIST ($p < 0.01$).

Figures 3(a) and 3(b) show representative variables among 10 variables that had clearly common patterns according to the relationship to sex difference in Exerci_Freq.

3.4. Physical Function-Related Variables according to Independent Variables (Four Exercise Types). All exercise types affected the changes in ELD_LLFX_SEC ($p < 0.01$), with patterns showing that daily exercise seemed to decrease the time in ELD_LLFX_SEC (Figure 3(c)). In ELD_LLFX_YN (presence or absence of gait disability), patients with OA with gait disability did not exercise at all, whereas all patients with OA without gait disability performed exercise. Sex difference was seen in all types of exercise ($p < 0.01$) except Mov20_Wek_freq. The balance test ELD_STF_SEC was affected by all exercise types ($p < 0.01$). Another balance test, ELD_STFX_MTHD, showed a significant difference in the effect of all exercise types ($p < 0.05$). Sex difference, exercise type, and the interaction between sex difference and exercise type had significant differences in FALL ($p < 0.01$). Figure 3(d) shows that female patients with less exercise experienced falls more frequently, and this difference showed a decreasing tendency as the women exercised more (Figure 3(d)). A clear difference was observed between the daily exercise and less exercise groups (Figure 3(d)).

Panels (c) and (d) of Figure 3 represent similar patterns of each variable in the four exercise types.

We thus examined hypothesis (2) and concluded that there are specific high-risk dependent variables with the effect of exercise modalities in the incidence of OA.

3.5. Which Variables Affect OA Pathogenesis and What Are the Evidence-Based Optimal Cutoff Points of the Variables for Preventing and Alleviating OA Symptoms? Randomly selected patients without OA registered in the NHISS were compared with patients with OA for logistic regression analysis. Among the variables, we found that FALL ($p < 0.05$) and ELD-LLFX-SEC ($p < 0.01$) significantly affected the pathogenesis of OA (Table 3). For 50-year-old patients with OA, ROC curve analysis provided ideal cutoff values for ELD_LLFX_SEC as 8.25 s (80% sensitivity and 100% specificity, area under the curve 0.861) (Figure 4). FALL did not have a meaning for the cutoff value because the responses for FALL were 1 (no experience of falls) or 2 (with experience of falls).

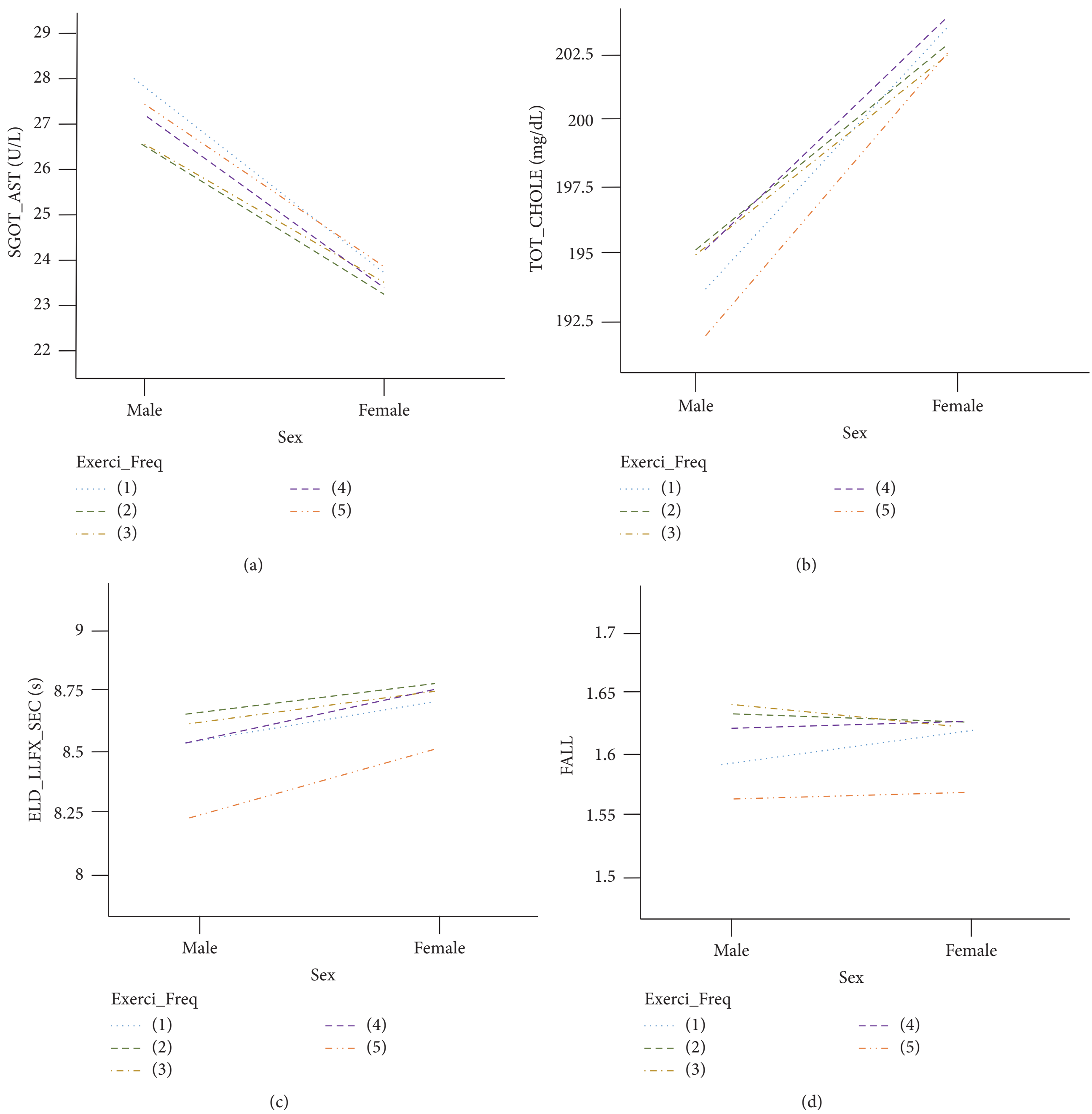

FIGURE 3: Comprehensive and physical function-related variables according to Exerci_Freq in 50-year-old patients with OA. Among 15 variables, (a) SGOT_AST (U/L), (b) TOT_CHOLE (mg/dL), (c) ELD_LLFX_SEC (s), and (d) FALL were representatively selected, as these variables had definite and similar patterns in Exerci_Freq among the four exercise types (Mov20_Wek, frequency of 20 min intensive exercise per week; Exerci_Freq, frequency of moderate-intensity exercise per week; Move30_Freq, frequency of 30 min moderate-intensity exercise per week; Walk30_Wek, frequency of 30 min walking per week). (1) do not exercise at all; (2) exercise 1-2 times per week; (3) exercise 3-4 times per week; (4) exercise 5-6 times per week; (5) almost daily exercise.

Hypothesis (3) was also clearly examined by using these results.

4. Discussion

We obtained the following OA-related results from patients registered in the NHISS by clustering the retrospective cohort of Koreans aged > 40 years.

(1) OA pathogenesis was found most frequently in the 50-year age group.

(2) The four analyzed exercise types affected the change of BMI ($p < 0.05$) and affected BP with a sex difference ($p < 0.01$); however, exercise frequency did not affect the change of BP. Exercise type and exercise frequency were important for SGOT and SGPT. Only

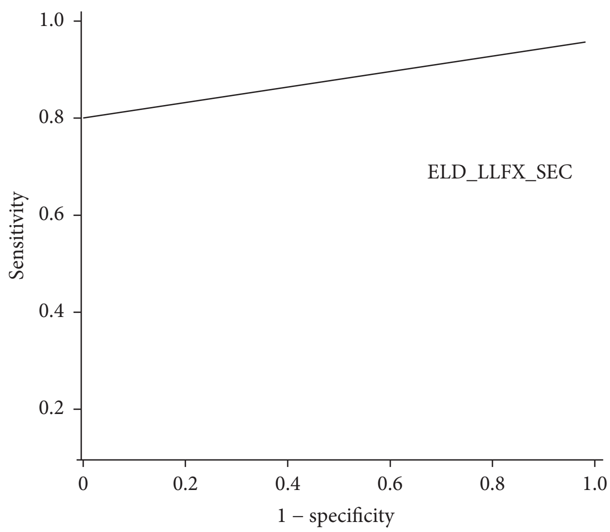

Figure 4: Graph of the ROC curve for the 50–59-year-old Korean population with knee OA. ROC curve analysis of ELD_LLFX_SEC (s) provided the optimal threshold value of 8.25 s, with area under the curve value of 0.861, sensitivity of 80%, and specificity of 100% ($p < 0.01$). ROC, receiver operating characteristic; OA, osteoarthritis; ELD_LLFX_SEC, time in seconds for standing up from a chair, walking 3 m, and returning to the same chair.

Exerci_Freq did not affect the change of cholesterol ($p < 0.01$), and all exercise types affected loss of WAIST ($p < 0.01$). All types of exercise positively affected the balance test result ($p < 0.01$).

(3) The optimal cutoff threshold for ELD_LLFX_SEC was 8.25 s (80% sensitivity and 100% specificity).

4.1. Big Data Analysis as a Useful Tool. NHISS is a worldwide unprecedented DB because all Korean citizens are mandatorily registered in this DB. Therefore, the entire medical history of the whole Korean population can be traced at any time [8].

Use of the NHISS DB overcomes the flaws of previous data sources such as private information and the limited contents of large-scale DBs. This DB allows researchers to access cross-sectional, retrospective, and prospective studies of each individualized patient derived from the DB cohort.

By using the large-scale NHISS DB, we were able to extract patients with OA according to the study design, and we were able to compare different age groups in terms of the pathogenicity of OA. In this study, we found that OA pathogenesis occurred most frequently in the 50-year age group among the randomly selected Koreans with OA aged > 40 years ($n = 2088$; nonoverlapping patients with only one prescription for OA) from the total cohort of 514,866 patients in the NHISS DB. Interestingly, the 60- and 70-year age groups were oppositely different from the 40- and 50-year age groups. The number of patients with OA in the 60–70-year age groups unexpectedly declined, and we presumed that patients in these age groups easily neglect visiting the hospital or have a higher mortality rate than the younger age groups, which affected our results. We believe that this DB will be useful in promoting national health and welfare.

4.2. Individualized Exercise Prescription for Reducing the Incidence of OA. A specific exercise prescriptive program based on these data can be designed. BP, cholesterol, and HCHK_PMH showed a pattern that is more related to the specific intensity, time, and frequency of exercise. The results showed that tailor-made exercise prescriptions are possible, and thus this study evidences that the DB can be an indispensable tool for improving the symptoms of OA. Our results comprehensively include microlevel to macrolevel data, from blood tests to physical function tests. Most modernized countries have emerging issues about experiences of falls in the aging society [9]. In Korea, 13% of 828 urban and 32% of 2295 rural elderly dwellers experienced falls in 1 year [9, 10]. The socioeconomic cost from fall injuries was calculated to be 343,614,988,000 Korean won [11]. To relieve this socioeconomic and individual burden, a more specially individualized exercise prescription can be an ideal option. According to this study, falls more often occurred in 50-year-old women with OA than in 50-year-old men with OA; thus, performing any kind of exercise on a daily basis can be an ideal option for improving fall symptoms in patients with OA.

4.3. Optimal Cutoff Threshold for OA Pathogenesis. The finding that OA occurred most frequently in the 50-year age group was used in further analysis to identify factors influencing the pathogenesis of the disease. We found that FALL and ELD_LLFX_SEC ($p < 0.01$) were associated with the occurrence of OA in the 50-year age group, and we suggest that this is associated with the muscle strength of the lower limb [12] (Table 3).

The results of four static and dynamic physically functional tests were examined in this study. Interestingly, only ELD_LLFX_SEC was significantly associated with the 50-year age group of patients with OA but not the three other similar functional tests ($p < 0.01$). This suggests that physically dynamic weight bearing load (ELD_LLFX_SEC) rather than static weight bearing load (ELD_STF_SEC; ELD_STFX_MTHD) beneficially suppresses damage on the knee joints [13]. According to the provided cutoff value, an immediate lower-limb strengthening exercise program should be developed to improve OA symptoms [14].

In conclusion, we obtained the following multifaceted results from the large-scale analysis of the NHISS DB, which can help in developing evidence-based OA preventive methods such as individualized exercise prescription programs.

(1) Pathogenic OA was found most frequently in the 50-year age group.

(2) All four exercise types investigated affected the change of BMI ($p < 0.05$) and had a sex-different effect on BP ($p < 0.01$); however, exercise frequency did not affect the change of BP. Exercise type and exercise frequency were important for SGOT and SGPT. Exerci_Freq only did not affect the change of cholesterol ($p < 0.01$), and all exercise types affected loss of WAIST ($p < 0.01$). All types of exercise positively affected the balance test ($p < 0.01$).

(3) The optimal cutoff threshold for SGOT_AST and ELD_STF_SEC was 18.75 (88% sensitivity and 85% specificity) and 14.75 (75% sensitivity and 100% specificity), respectively.

This large-scale DB study may be indispensable in describing the risk factors affecting the aggravation of knee damage, for example, from anterior cruciate ligament to OA, and may lead to the development of standard and individualized prognostic OA interventions in the most OA pathogenic period of life.

Conflicts of Interest

The authors have no conflicts of interest.

Acknowledgments

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Review Article

Comparison of the Effectiveness of Whole Body Vibration in Stroke Patients: A Meta-Analysis

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Objectives. The goals of this study were to assess the effectiveness of WBV (whole body vibration) training through an analysis of effect sizes, identify advantages of WBV training, and suggest other effective treatment methods. *Methods*. Four databases, namely, EMBASE, PubMed, EBSCO, and Web of Science, were used to collect articles on vibration. Keywords such as "vibration" and "stroke" were used in the search for published articles. Consequently, eleven studies were selected in the second screening using meta-analyses. *Results*. The total effect size of patients with dementia in the studies was 0.25, which was small. The effect size of spasticity was the greatest at 1.24 (high), followed by metabolism at 0.99 (high), balance, muscle strength, gait, and circulation in the decreasing order of effect size. *Conclusions*. The effect sizes for muscle strength and balance and gait function, all of which play an important role in performance of daily activities, were small. In contrast, effect sizes for bone metabolism and spasticity were moderate. This suggests that WBV training may provide a safe, alternative treatment method for improving the symptoms of stroke in patients.

1. Introduction

Stroke rehabilitation is a process through which patients with disabilities as a result of stroke manage to resume activities of daily living and reestablish their normal lifestyle through a learning process. It also aims to assist patients in gaining better understanding of their condition, adapting to difficulties they experience due to their disabilities, and preventing secondary complications [1]. Typical disabilities that follow stroke include muscle weakness, abnormal muscle stress, and dystonia. These disabilities not only limit daily activities but also affect the balancing ability and gait function [2].

To a large extent, research has been conducted with the aim of resolving these stroke-related problems. Recently, whole body vibration (WBV) has been heavily researched as a way to improve muscle function, muscle strength, and gait function in stroke patients [3, 4]. WBV training involves standing or making vigorous movements on a vibration platform placed on a static surface. In previous studies, WBV training was suggested as a potential method to improve physical functions. It was also suggested that WBV improves muscle function and balance by increasing muscle strength.

Therapies that involve WBV exercises have been on the rise recently; however, only a few studies have compared WBV therapy with other treatment modalities. Therefore, this study aims to compare the effects of WBV treatment using meta-analysis. Further, the purpose of this study is to assess the effectiveness of WBV training through an analysis of effect sizes, identify advantages of WBV training, and suggest other effective treatment methods.

2. Material and Method

2.1. Research Question. The purpose of this systemic review was determined according to PICO (patient, intervention, comparison, and outcome). In this review, the patient (P) was defined as a person having "stroke." The intervention (I) was defined in the experimental group that underwent WBV training (static activities and vigorous exercise). The experimental group was compared (C) to the control group

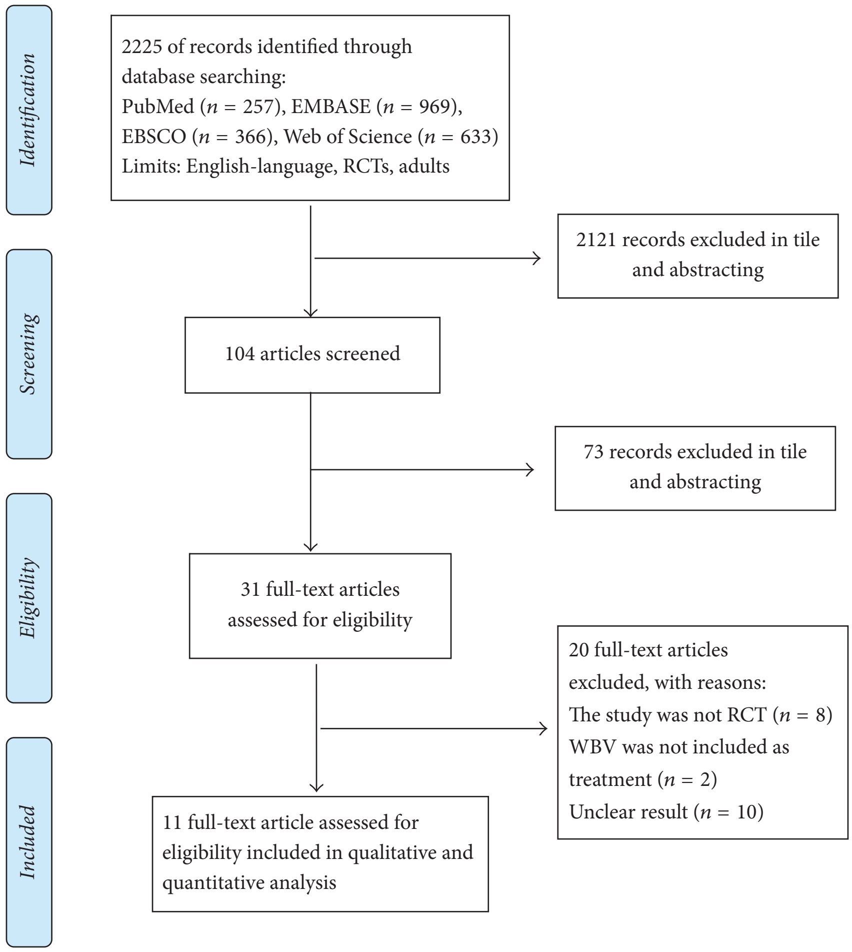

Figure 1: Flow diagram of studies included.

that did not undergo WBV training. The outcome (O) was defined as changes in motor functions and body structure. This study investigated effect sizes of WBV training on different variables and determined the ones on which WBV had the greatest effect.

2.2. Selection and Collection of Articles to Be Analyzed. Articles related to WBV were searched for in 5 databases including EMBASE, PubMed, EBSCO, and Web of Science for inclusion in the meta-analysis. The criteria for selecting a dissertation were as follows: studies involving clinical diagnosis of stroke and its treatment in a randomized controlled clinical trial. The language was limited to English. "Vibration" and "stroke" were used as keywords in order to minimize the number of articles that would be missed when searching solely with the keyword, "WBV." Using these keywords, a total of 2225 studies were initially selected, after which we excluded the ones that did not report sufficient statistics. The exclusion criteria were reviewed by examining the title and abstract of the papers with respect to the subject, while the main text and the theory of research were excluded from the analysis. We also excluded research that was difficult to classify after reviewing the design methods of each analyzed study. Of the 2225 initially selected articles, 2121 were excluded. Upon reviewing the titles and abstracts of the selected studies, 73 were further excluded and 31 were selected based on the research topic. Within these, 20 studies were excluded owing to the following reasons: eight studies were not randomized controlled trials, two articles did not investigate general vibration training, and 10 papers showed ambiguous results that did not provide sufficient statistical data in relation to the meta-analysis. Finally, 11 studies were selected and the characteristics of PRISMA flow chart were summarized (Figure 1, Table 1). The selected studies analyzed the treatment effects of WBV in stroke patients. The number of patients used in the final analysis was 4,413. A detailed description of the included individual studies is presented in Table 1. A review of the methodologies used in the selected articles revealed that most of them used a one-group pretest-posttest design (Table 2).

2.3. Data Processing. With the agreement of all members of the research team, the author names, published year, publication type, research model, study participants, assessment tools, program type, and program effectiveness were recorded for data coding. A physical therapist and a meta-analysis specialist performed the coding. Conflicts in opinions were resolved through negotiation and opinions of a physiotherapy

Table 1: Characteristic of included trials.

Study	Number of participants analyzed (E/C)	Mean age (E/C)	Start REH intervention (E/C)	Duration of prog.	Time
Brogardh et al. 2012 [5]	16/15	61.3 ± 8.5/63.9 ± 5.8	37.4/33.1 m	2/week ∗ 6	45 min
Chan et al. 2012 [6]	15/15	56.07 ± 11.04/54.93 ± 7.45	30.4/38.87 m	One session	
Choi et al. 2014 [7]	15/15	62.8 ± 9/65.1 ± 15.7	13/12.6	5/w ∗ 4	15 min
Lau et al. 2012 [8]	41/41	57.3 ± 11.3/57.4 ± 11.1	4.6/5.3 y	3/w ∗ 8	
Liao et al. 2016 [9]	28/28	59.8 ± 9.1/60.8 ± 8.3	8.5/9.0 y	3/w ∗ 10	
Marin et al. 2013 [10]	11/9	62.3 ± 10.6/64.4 ± 7.6	4.3/4.3 y	12 w (17 sessions)	12 min
Pang et al. 2013 [11]	38/38	57.3 ± 11.3/57.4 ± 11.1	4.6/5.3 y	3/w ∗ 8	
Tankisheva et al. 2014 [12]	6/7	57.4 ± 13/65.3 ± 3.7	7.71/5.28 y	3/w ∗ 6	
Tihanyi et al. 2007 [13]	8/8	58.2 ± 9.4	27.2 ± 10.4 d	One session	30 min
van Nes et al. 2006 [14]	27/26	59.7 ± 12.3/62.6 ± 7.6	38.9/34.2 d	5/w ∗ 6	
Yule et al. 2016 [15]	4/2	50.5 ± 14.5/39 ± 2	6 m–5 y	3/w ∗ 4	15 min

professor. The credibility and consistency of people involved in coding were not calculated.

2.4. Data Extraction. A CMA software specialized in meta-analysis was used for data analysis. In order to interpret the effect sizes obtained from the meta-analysis, Cohen and Wolf's standard was used. According to Cohen [16], an effect is small if it is less than 0.2, moderate if it is 0.5, and large if it is greater than 0.8.

2.5. Quality Assessment. Using the PEDro database's method of analysis, a quality assessment of randomized controlled trial articles was performed. The PEDro scale determines the scientific validity of clinical trials (9-10 = excellent, 6–8 = good, 4–6 = fair, and <4 = poor). Studies of excellent or good qualities with a sample size greater than or equal to 50 were considered as level 1 evidence [17] (Table 3).

3. Results

3.1. Homogeneity Test and Total Effect Size. Assuming that results of each study were based on one homogeneous population, a homogeneity test with a fixed-effects model was performed. The Q value was 18.02, verifying that the studies were performed on homogeneous population. Considering each subject's result as one unit and using a random effects model, a "standardized mean difference" effect size (d) was calculated. The obtained total effect size of WBV was 0.25, and the 95% confidence interval was 0.17~0.32 (Table 4, Figure 2). Since the effect size of WBV on stroke was close to 0.2, it was interpreted that WBV has a "small effect size."

3.2. Publication Bias Assessment. Publication biases were assessed to validate the results of meta-analysis using three different methods. A type of sensitivity analysis was performed using Duval and Tweedie's [18] trim-and-fill method. Since the correction values of articles and the observed values were identical, it was difficult to conclude if publication bias was present (Table 5).

3.3. Effect Size according to Treatment Effectiveness. As presented in Table 5, the effect size of spasticity was the largest at 1.24, followed by bone metabolism at 0.99, balance, muscle strength, gait, and cardiac function, in decreasing order of effect size (Table 6).

3.4. Effect Size at Different Vibration Frequencies. Vibration frequencies below 20 Hz were considered low frequencies and those over 30 Hz were considered high frequencies. The effect size was 0.25 at high frequency and 0.24 at low frequency; therefore, there was no significant difference in the effect sizes between high and low frequency (Figure 3).

3.5. Effect Size according to the Time Lapse after the Onset of Stroke. The effect size was 0.26 when time lapse after the onset of stroke was over a year (chronic) and 0.19 when the time lapse was under one year (acute/subacute). The effect size of acute/subacute stroke was close to 0.2, which signifies a small effect size. In contrast, the effect size was relatively large for chronic stroke (Figure 4).

3.6. Effect Size according to the Treatment Period. The effect size was 0.42 for one session and 0.4 for four weeks of therapy; both effect sizes were moderate (Figure 5).

3.7. Effect Size according to the Number of Treatments per Week. The effect size was 0.45 for one session and the effect size for the other times was 0.2 (Figure 6).

3.8. Changes per Published Year. Research on WBV for stroke patients started recently, and the number of studies is gradually increasing every year (Figure 7).

4. Discussion

This study was conducted to investigate the effectiveness of WBV through a meta-analysis of numerous studies on WBV therapy that were published recently. According to Lee et al. [2], muscle dystrophy, muscle tone, and loss of sensation in

Table 2: Review of the studies.

Study	Outcome measures	Type of intervention	control	frequency	amplitude
Brogardh et al. 2012 [5]	Muscle tone: MAS Balance: BBS Muscle strength measurements Gait performance: TUG, 10 MGS, 6 MWT Participation: SIS	Standing barefoot on the platforms in a static position with the knee flexed 45° 60°	vibrating platform with an amplitude of 0.2 mm	25	3.75
Chan et al. 2012 [6]	Ankle spasticity: MAS, deep tendon reflex, VAS Gait performance: TUG, 10 MWT, cadence Foot pressure	Positioned on the platform in a semisquatting position with buttock support and were kept in an upright position with even weight distribution on both feet	same procedure, No WBV	12	4
Choi et al. 2014 [7]	Static sitting balance: COP Dynamic sitting balance: MFRT	Task oriented training + WBV (1) Sitting alone at a table and correcting body alignment (2) Reaching in different directions for objects located beyond arm's length using the nonparetic side (3) Reaching in different directions for objects located beyond arm's length using the paretic side (4) A bilateral reaching task	task oriented training	15–22	0–5.8
Lau et al. 2012 [8]	Balance: BBS Dynamic postural control: LOS Muscle strength measurements (70°) Gait performance: 10 MWT, 6 MWT Fall-related self-efficacy ABC	Side-to-side weight shift, semisquat, forward and backward weight shift, forward lunge, standing on one leg, deep squat	same platform, No WBV	20–30	0.44–0.6
Liao et al. 2016 [9]	Muscle tone: MAS Balance: Mini BESTest Gait performance: TUG, 6 MWT Fall-related self-efficacy ABC	Dynamic weight shift side to side, dynamic deep squat, dynamic forward and backward weight shift, static semisquat	same platform, No WBV	20	1
Marin et al. 2013 [10]	Balance: BBS Muscle strength: thickness of RF, VL, MG in both legs Maximum isometric knee extension strength	Standing on a vibration platform with knee flexion of 30°	same position, No WBV	5–21	4–6
Pang et al. 2013 [11]	Bone turnover markers Spasticity: MAS, VAS Muscle strength: knee peak power	Side-to-side weight shift, semisquat, forward and backward, weight shift, forward lunge, standing on one leg, deep squat	same platform, No WBV	20–30	0.44–0.6

Table 2: Continued.

Study	Outcome measures	Type of intervention	control	frequency	amplitude
Tankisheva et al. 2014 [12]	Muscle tone: MAS Muscle strength measurements: isokinetic knee extension in both legs (60°/s) Isokinetic knee flexion in both legs (60°/s) Isometric knee extension in both legs Isometric knee flexion in both legs Isokinetic knee extension in nonparetic leg (240°/s) Isokinetic knee flexion in nonparetic leg (240°/s) SOT Equilibrium scores	Standing on their toes, knee flexion of 50–60, knee flexion of 90°, wide-stance squat, one-legged squat	No	35, 40	1.7, 2, 5
Tihanyi et al. 2007 [13]	EMG: Maximum isometric knee extension torque Maximum eccentric knee extension torque Rate of torque development Maximal voluntary eccentric torque at 60° of knee flexion Coactivation quotient of BF during Isometric knee extension Coactivation quotient of BF during eccentric knee extension	Standing the platform with knees slightly flexed at 40° and shifting body mass to the paretic leg	same platform, No WBV	20	5
van Nes et al. 2006 [14]	Balance: BBS BI Rivermead Mobility Index Trunk Control Test FAC Motricity Index Somatosensory threshold of affected leg	Standing on the platform with knees slightly flexed	Exercise therapy on music	30	
Yule et al. 2016 [15]	Pulse wave velocity Carotid to radial PTT Arterial stiffness Heart rate Blood pressure Augmentation index	Static squat stance with 70° knee flexion	No	22–26	

MAS: Modified Ashworth Scale, BBS: Berg Balance Scale, TUG: Timed Up & Go, SIS: Stroke Impact Scale, 10 MGS: 10 miters' gait speed, 6 MWT: six-minute walk test, COP: Center of Pressure; MFRT: Modified Functional Reach Test, LOS: Limit of Stability, 10 MWT: 10 miters' walk test, ABC: activities-specific balance confidence scale.

Table 3: Quality assessment.

	Brogardh et al. (2012)	Chan et al. (2012)	Choi et al. (2014)	Lau et al. (2012)	Liao et al. (2016)	Marin et al. (2013)	Pang et al. (2013)	Tankisheva et al. (2014)	Tihanyi et al. (2007)	van Nes et al. (2006)	Yule et al. (2016)
Eligibility criteria	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not Yet
Random allocation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not Yet
Concealed allocation	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not Yet
Baseline comparability	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not Yet
Blinded subjects	Yes	Yes	No	No	No	No	No	No	No	No	Not Yet
Blinded therapists	Yes	No	No	No	No	No	No	No	No	No	Not Yet
Blinded assessors	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	Not Yet
Adequate follow-up	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not Yet
Intention-to-treat analysis	Yes	No	Yes	Yes	Yes	Yes	Yes	No	No	Yes	Not Yet
Between-group comparisons	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not Yet
Point estimators and variability	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not Yet
Total PEDro score	9	8	6	8	8	8	8	7	6	8	Not Yet
Sample size ≥ 50	No	No	No	Yes	No	No	Yes	No	Yes	Yes	No
Level of evidence	2	2	2	1	2	2	1	2	1	1	2

Table 4: Homogeneity test and the total effect size.

N	Q-value	p	I^2	Point estimate	95% CI	Standard error
11	18.02	0.00	44.5	0.25	0.17–0.32	0.04

Table 5: Trim-and-fill publication bias assessment.

	Studies trimmed	Point estimate	95% CI		Q-value
			Lower limit	Upper limit	
Observed values	-	0.25	0.17	0.32	18.02
Adjusted values	0	0.25	0.1	0.32	18.02

Table 6: Effect size according to treatment effectiveness.

Group	Number of studies	Point estimate	Standard error	95% CI
Balance	19	0.28	0.08	0.12–0.43
Muscle strength	40	0.16	0.05	0.07–0.25
Gait function	15	0.09	0.07	−0.06–0.24
Spasticity	3	1.24	0.23	0.76–1.7
Bone metabolism	2	0.99	0.18	0.65–1.35
Cardiac function	3	0.2	0.4	−0.59–0.99
Total	82	0.22	0.04	0.16–0.29

Study name	Hedges' g	Standard error	Variance	Lower limit	Upper limit	Z-value	p value
Brogardh et al. 2012 [5]	0.274	0.125	0.016	0.029	0.519	2.188	0.029
Chan et al. 2012 [6]	0.633	0.154	0.024	0.332	0.935	4.115	0.000
Choi et al. 2014 [7]	0.433	0.161	0.026	0.118	0.749	2.692	0.007
Lau et al. 2012 [8]	0.138	0.098	0.010	−0.054	0.330	1.405	0.160
Liao et al. 2016 [9]	0.130	0.080	0.006	−0.026	0.286	1.635	0.102
Marin et al. 2013 [10]	0.156	0.193	0.037	−0.222	0.534	0.809	0.419
Pang et al. 2013 [11]	0.349	0.096	0.009	0.161	0.538	3.627	0.000
Tankisheva et al. 2014 [12]	0.513	0.154	0.024	0.212	0.814	3.337	0.001
Tihanyi et al. 2007 [13]	0.106	0.212	0.045	−0.309	0.521	0.499	0.618
van Nes et al. 2006 [14]	0.070	0.121	0.015	−0.167	0.307	0.578	0.564
Yule et al. 2016 [15]	0.200	0.402	0.161	−0.587	0.987	0.498	0.619
	0.247	0.038	0.001	0.171	0.322	6.432	0.000

Statistics for each study

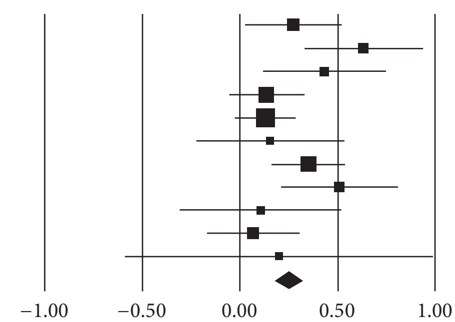

Figure 2: Homogeneity test.

−20 Hz/30 Hz−	Study name	Hedges' g	Standard error	Variance	Lower limit	Upper limit	Z-value	p value
20 Hz	Brogardh et al. 2012 [5]	0.274	0.125	0.016	0.029	0.519	2.188	0.029
	Chan et al. 2012 [6]	0.633	0.154	0.024	0.332	0.935	4.115	0.000
	Choi et al. 2014 [7]	0.433	0.161	0.026	0.118	0.749	2.692	0.007
	Liao et al. 2016 [9]	0.130	0.080	0.006	−0.026	0.286	1.635	0.102
	Marin et al. 2013 [10]	0.156	0.193	0.037	−0.222	0.534	0.809	0.419
	Tihanyi et al. 2007 [13]	0.106	0.212	0.045	−0.309	0.521	0.499	0.618
		0.250	0.053	0.003	0.146	0.355	4.695	0.000
30 Hz	Lau et al. 2012 [8]	0.138	0.098	0.010	−0.054	0.330	1.405	0.160
	Pang et al. 2013 [11]	0.349	0.096	0.009	0.161	0.538	3.627	0.000
	Tankisheva et al. 2014 [12]	0.513	0.154	0.024	0.212	0.814	3.337	0.001
	van Nes et al. 2006 [14]	0.070	0.121	0.015	−0.167	0.307	0.578	0.564
	Yule et al. 2016 [15]	0.200	0.402	0.161	−0.587	0.987	0.498	0.619
		0.243	0.055	0.003	0.135	0.351	4.399	0.000
		0.247	0.038	0.001	0.171	0.322	6.432	0.000

Statistics for each study

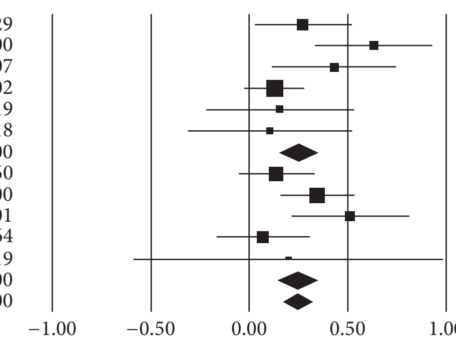

Figure 3: Effect size at different vibration frequencies.

Subacute/chronic	Study name	Hedges' g	Standard error	Variance	Lower limit	Upper limit	Z-value	p value
Subacute	Choi et al. 2014 [7]	0.433	0.161	0.026	0.118	0.749	2.692	0.007
	Tihanyi et al. 2007 [13]	0.106	0.212	0.045	−0.309	0.521	0.499	0.618
	van Nes et al. 2006 [14]	0.070	0.121	0.015	−0.167	0.307	0.578	0.564
	Yule et al. 2016 [15]	0.200	0.402	0.161	−0.587	0.987	0.498	0.619
		0.186	0.086	0.007	0.017	0.354	2.157	0.031
Chronic	Brogardh et al. 2012 [5]	0.274	0.125	0.016	0.029	0.519	2.188	0.029
	Chan et al. 2012 [6]	0.633	0.154	0.024	0.332	0.935	4.115	0.000
	Lau et al. 2012 [8]	0.138	0.098	0.010	−0.054	0.330	1.405	0.160
	Liao et al. 2016 [9]	0.130	0.080	0.006	−0.026	0.286	1.635	0.102
	Marin et al. 2013 [10]	0.156	0.193	0.037	−0.222	0.534	0.809	0.419
	Pang et al. 2013 [11]	0.349	0.096	0.009	0.161	0.538	3.627	0.000
	Tankisheva et al. 2014 [12]	0.513	0.154	0.024	0.212	0.814	3.337	0.001
		0.262	0.043	0.002	0.178	0.346	6.112	0.000
		0.247	0.038	0.001	0.171	0.322	6.432	0.000

Statistics for each study

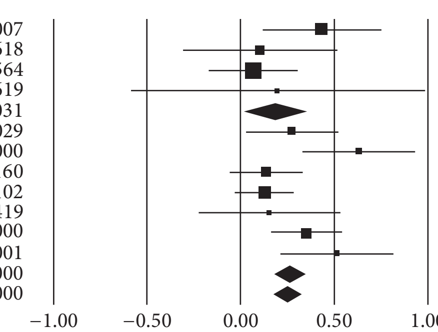

Figure 4: Effect size according to the time lapse after the onset of stroke.

the aftermath of stroke affect the ability to function and walk. In this study, we analyzed the magnitude of these effects on muscle strength, locomotion, muscular dystrophy, and balance and analyzed the effects of bone density and circulation in order to prevent secondary complications. Previous meta-analyses have investigated the effects of WBV on balance, gait function, and limb movement [19], activity and participation after stroke [20], muscle strength, proprioceptive sense, and

Duration	Study name	Hedges' g	Standard error	Variance	Lower limit	Upper limit	Z-value	p value
One session	Chan et al. 2012 [6]	0.633	0.154	0.024	0.332	0.935	4.115	0.000
	Tihanyi et al. 2007 [13]	0.106	0.212	0.045	−0.309	0.521	0.499	0.618
		0.415	0.172	0.029	0.079	0.752	2.420	0.016
4 wks	Choi et al. 2014 [7]	0.433	0.161	0.026	0.118	0.749	2.692	0.007
	Yule et al. 2016 [15]	0.200	0.402	0.161	−0.587	0.987	0.498	0.619
		0.382	0.202	0.041	−0.014	0.779	1.889	0.059
6 wks	Brogardh et al. 2012 [5]	0.274	0.125	0.016	0.029	0.519	2.188	0.029
	Tankisheva et al. 2014 [12]	0.513	0.154	0.024	0.212	0.814	3.337	0.001
	van Nes et al. 2006 [14]	0.070	0.121	0.015	−0.167	0.307	0.578	0.564
		0.271	0.121	0.015	0.033	0.509	2.235	0.025
8 wks	Lau et al. 2012 [8]	0.138	0.098	0.010	−0.054	0.330	1.405	0.160
	Pang et al. 2013 [11]	0.349	0.096	0.009	0.161	0.538	3.627	0.000
		0.244	0.134	0.018	−0.019	0.507	1.820	0.069
10 wks	Liao et al. 2016 [9]	0.130	0.080	0.006	−0.026	0.286	1.635	0.102
		0.130	0.181	0.033	−0.255	0.485	0.718	0.473
12 wks	Marin et al. 2013 [10]	0.156	0.193	0.037	−0.222	0.534	0.809	0.419
		0.156	0.253	0.064	−0.339	0.651	0.618	0.537
Total		0.271	0.073	0.005	0.128	0.414	3.716	0.000

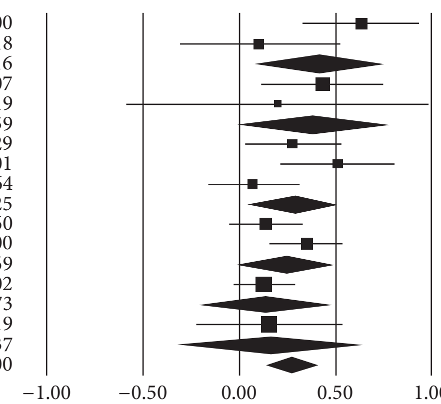

Figure 5: Effect size according to the treatment period.

Times/wk	Study name	Hedges' g	Standard error	Variance	Lower limit	Upper limit	Z-value	p value
1 session	Chan et al. 2012 [6]	0.633	0.154	0.024	0.332	0.935	4.115	0.000
	Tihanyi et al. 2007 [13]	0.106	0.212	0.045	−0.309	0.521	0.499	0.618
		0.451	0.124	0.015	0.207	0.695	3.623	0.000
2 times	Brogardh et al. 2012 [5]	0.274	0.125	0.016	0.029	0.519	2.188	0.029
	Marin et al. 2013 [10]	0.156	0.193	0.037	−0.222	0.534	0.809	0.419
		0.239	0.105	0.011	0.033	0.445	2.276	0.023
3 times	Lau et al. 2012 [8]	0.138	0.098	0.010	−0.054	0.330	1.405	0.160
	Liao et al. 2016 [9]	0.130	0.080	0.006	−0.026	0.286	1.635	0.102
	Pang et al. 2013 [11]	0.349	0.096	0.009	0.161	0.538	3.627	0.000
	Tankisheva et al. 2014 [12]	0.513	0.154	0.024	0.212	0.814	3.337	0.001
	Yule et al. 2016 [15]	0.200	0.402	0.161	−0.587	0.987	0.498	0.619
		0.228	0.049	0.002	0.132	0.324	4.670	0.000
5 times	Choi et al. 2014 [7]	0.433	0.161	0.026	0.118	0.749	2.692	0.007
	van Nes et al. 2006 [14]	0.070	0.121	0.015	−0.167	0.307	0.578	0.564
		0.201	0.097	0.009	0.012	0.391	2.080	0.038
		0.247	0.038	0.001	0.171	0.322	6.432	0.000

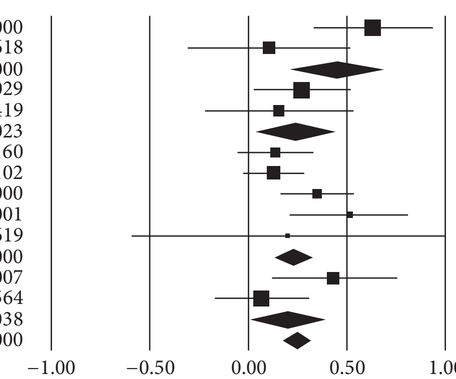

Figure 6: Effect size according to the number of treatments per week.

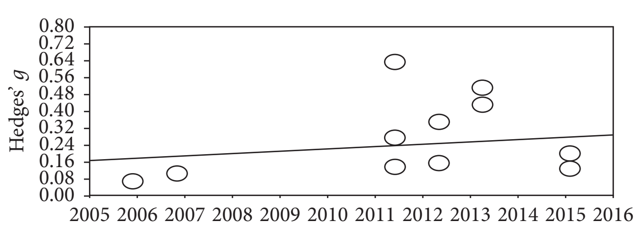

Figure 7: Changes per published year.

quality of life [21], and muscle stress [22]. However, in a meta-analysis by Lu et al. [23], WBV did not have significant effects on muscle strength, balance, and gait function. Further, this suggests a need for investigations based on the therapeutic efficacy of WBV in stroke patients.

In our meta-analysis, the total effect size was 0.25, which signifies a small effect size. However, when we evaluated the therapeutic efficacy of WBV for stroke symptoms, the effect size for spasticity was the largest at 1.24, followed by bone turn over test at 0.99, balance, muscle strength, gait function, and circulation in the decreasing order of effect size. Evaluation of spasticity comprised MAS, ATR, and so forth; muscle strength was isometric and isometric exercise was also evaluated. The evaluation comprised TUG, 10 MWT, and so forth, and the balance was between BBS, MFRT, and so forth. The goal was to measure bone metabolism using CTx and BAP, while cardiac function was evaluated by measuring HR and BP. According to the results of this study, WBV was more effective for spasticity that affects gait function than for gait function itself and muscle strength. This is consistent with the results of a study by Chan et al. [6], who reported that WBV reduced ankle plantarflexion spasticity in chronic stroke patients and therefore would be useful in gait function improvement. Moreover, they reported that WBV did improve gait function and would improve movements and movement speed. Another previous study also reported that a reduction in ankle plantarflexion spasticity affects gait function, limb movement, and movement speed [24, 25].

Even if bone metabolism does not affect gait function and risk of falls, it may prevent secondary physical problems that occur upon falling among stroke patients. Pang et al. [11] used a bone turnover test to evaluate the effects on bone mineral density. While no significant differences in the effects between the experimental and control groups were noted, it was suggested that the treatment period be extended or the therapeutic intensity be increased. Garnero et al. [26] also reported that the level of bone turnover could be useful for osteoporosis risk assessment. Considering that the majority of stroke patients are at an advanced age and have a high risk of falls due to the reduced control of their bodies, it is expected that WBV may be an effective treatment for bone weakening.

While Lau et al. [8] reported that WBV had no effect on risk of falls or motor functions, their study focused on self-efficacy of falls, which is related to balance, postural control, mobility, and muscle strength and balance. Although it cannot be definitively concluded that WBV directly improves motor functions and thereby prevents falls, WBV may certainly prevent secondary problems that occur in patients who had strokes due to an accidental fall. In this study, the effect size was small for balance, gait function, and muscle strength.

With regard to balance and muscle strength, Tihanyi et al. [13] reported that WBV was effective in increasing voluntary muscle strength, which further helped balancing and gait function. Lau et al. [8] reported that WBV eliminated risk of falls and enhanced motor functions in stroke patients during leg exercises. Regarding balance, van Nes et al. [14] reported improvements in performance of activities of daily life and balance in the WBV group compared to controls after a 12-week program. As reported by Choi et al. [7], WBV improved sitting balance and was suggested as an effective training method to improve balance. It was also reported that WBV was helpful for stimulation of the vestibular system, posture improvement, and posture correction [27] as well as postural sway enhancement [28].

However, WBV in our analysis had a small effect compared to these individual studies. The results of our study are consistent with those of Brogardh et al. [5], in which WBV had a small effect on balance and gait function improvement. They are also consistent with the results obtained by Marin et al. [10], in which there was no significant difference in muscle strength and balance between the WBV and control groups.

Similarly, Yule et al. [15] concluded that WBV does not effectively improve physical functions related to muscle strength and balance that are related to walking and activities of daily life; however, they suggested that WBV is a safe method to improve spasticity, which is related to safety and sitting balance. Likewise, Liao et al. [9] and Tankisheva et al. [12] reported that WBV is a safe therapy that can be used to improve physical functions, structure, activity, and muscle gain. Since WBV safely reduces spasticity and has an effect on bone mineral density, it may be expected to prevent secondary problems caused by accidental falls. Although these analyses compared the effects of vibration frequencies, there was no difference in the magnitude of effects according to frequency. Further, there were no significant differences in the amount of effects caused by the period of stroke; however, it appeared somewhat higher in the chronic period. This implies that WBV is therapeutic for stroke when considered in terms of spontaneous recovery. There was no difference in the effectiveness on the basis of number of sessions and weeks of treatment. Because our meta-analysis studies lacked a sufficiently large number of studies, we need to further evaluate studies on WBV for stroke. A small sample size was used in this study to establish indisputable evidence. In future, a higher number of studies on effectiveness according to the timing of stroke are required.

5. Conclusion

This study investigated effect sizes of WBV training therapy for stroke patients through a meta-analysis. The number of analyzed articles was perhaps too small because studies that included subjects without a diagnosis of stroke were excluded, several studies investigated the effects of intervention qualitatively, and several others were nonrandomized controlled studies or did not have control groups.

The purpose of our study was to verify the efficacy of WBV training as a novel approach to stroke treatment and suggest more effective treatment methods. Effect sizes from WBV studies with a pretest-posttest design and a control group were obtained, and the total effect size was small. The effect sizes for muscle strength and balance and gait function, all of which play an important role in performance of daily activities were small. In contrast, effect sizes for bone metabolism and spasticity were moderate. WBV training is a safe therapeutic method for improving symptoms in stroke patients.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Research Article

The Reliability and Validity of a Modified Squat Test to Predict Cardiopulmonary Fitness in Healthy Older Men

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Background. Shortcomings are noted in currently available cardiopulmonary field tests for the older adult and thus relevant research is still ongoing. *Purpose*. The purpose of this study was to investigate the reliability and validity of a modified squat test and to establish a regression model for predicting aerobic fitness in the older adult. *Methods*. Twenty-five healthy men aged 60 to 75 years completed this study. Each subject performed two modified squat tests with a prototype testing equipment and a maximal exercise test to determine maximal oxygen consumption. Recovery heart rates (HR) (0~30, 60~90, and 120~150 seconds) were measured following the modified squat tests. The fitness indexes included the sum of recovery HR, recovery HR index, age-adjusted recovery HR index, and immediate HR. *Results*. The results revealed that the age-adjusted recovery HR index fitness had the highest intraclass correlation coefficients (ICC) of 0.9 and Pearson's correlation coefficients of 0.71, which suggested the modified squat test can reasonably assess cardiopulmonary fitness for the older adult. The regression equation for estimating aerobic power was $\dot{V}O_2$max = 16.781 + 16.732 × (age-adjusted recovery HR index) + 0.02467 × (physical activity level). *Conclusion*. The modified squat test is a valid and reliable field test and thus can be an option to assess the cardiopulmonary fitness level of healthy older men in clinics or communities.

1. Introduction

Cardiopulmonary fitness, which is most accurately presented by maximal oxygen uptake ($\dot{V}O_2$max), is related to mortality in older adults. Laboratory maximal exercise tests with a treadmill or an ergometer can precisely evaluate $\dot{V}O_2$max, which is not always accessible due to expensive equipment and trained personnel being required [1, 2]. For practical purposes, field tests are developed and used to measure cardiopulmonary fitness. Based on the characteristics of the older adult, the common test modes of field tests are stepping and walking tests.

A three-minute stepping test is widely used to predict cardiopulmonary fitness in that heart rate (HR) responses immediately or during recovery after the stepping test are recorded and calculated. Different stepping frequency, bench height, test duration, the number of stages, and the scoring method have been developed for particular populations. For example, Petrella et al. [3] established a self-paced step test for the community-dwelling older adult, which is implemented at 40 cm height and requires stepping 20 times at different paces. A high correlation coefficient of 0.75~0.94 is found between the observed and the predicted maximal oxygen consumption ($\dot{V}O_2$max). Though the self-paced step test appears to accurately estimate cardiopulmonary fitness in older adults, it is argued that stepping movements might cause orthopedics problems in knees as well as increase the fall risk to mobility-limited older adults [4]. Rikli et al. [5, 6]

developed a two-minute self-paced test involving stepping in place, which is safer for the older adult. However, the relationship between this two-minute step-in-place test and maximal oxygen consumption is not established.

The walking test employs functional movements in nature and is easy to conduct. Particularly, the walking test is much safer than the stepping test and thus is more commonly used in senior people. Six-minute walking test and Rockport fitness walking test can reasonably predict cardiopulmonary fitness in the elderly [7, 8] while shortcomings are noted. Numerical studies have demonstrated that the 6 min walking test is not appropriate to evaluate changes in cardiorespiratory fitness in healthy older men who received endurance training for 24 weeks [9–12]. Moreover, a spacious walkway is needed. Therefore, research on developing new field tests of cardiopulmonary fitness for the older adult is still ongoing.

Inoue and Nakao developed a cardiopulmonary fitness test, a squat test, that is simple to administer in a confined space with minimum apparatus [13]. Participants should repeat squatting 30 times per min by bending of the legs until the hips meet with the heels. A significant correlation ($r = 0.92$ for women, $r = 0.82$ for men, $p < .001$) between $\dot{V}O_2$max and the fitness index of the squat test has been found in young adults. Considering difficulties to fully squat down in the older adult and the heavy loading of the knee joint during the squatting activity due to the nature of the movement, we modified the original squat test from full squatting to half-squatting in order to minimize possible injuries to knee joints. The purpose of this study was to evaluate the reliability and validity of the modified squat test and to construct a model for the estimation of aerobic fitness based on the modified squat test performance.

2. Method

2.1. Participants. Thirty-three healthy older subjects between the ages of 60 and 75 years participated in this study. Exclusion criteria included cardiovascular disease, metabolic disease, pulmonary disease, mental problems, and severe orthopedic diseases of the lower extremity. Informed consent was obtained from all participants. To assess potential risks of performing a maximal exercise test, the Physical Activity Readiness Questionnaire (PAR-Q) was administered and the resting 12-lead EKG was conducted and screened by a cardiologist. Before testing, body weight, height, body fat (TANITA, Taiwan), and Physical Activity Scale for the Elderly (PASE) score were recorded.

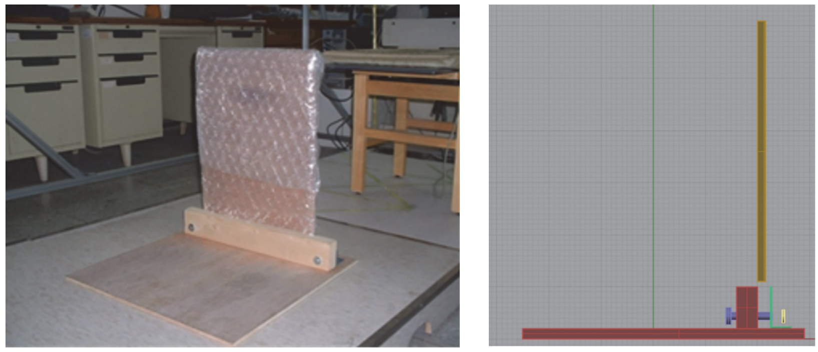
2.2. Experimental Protocol. All participants had to complete a maximal exercise test and two modified squat tests. The subject performed the first modified squat test, followed by the second modified squat test with oxygen consumption measured and then a maximal exercise test. An adequate rest was provided between the tests in order to allow heart rate and blood pressure to be returned to the level of baseline, which was defined as within 5 beats/minutes for heart rate and 5 mmHg for blood pressure.

Table 1: Cornell-Modified Bruce Protocol.

Stage	Min	Speed (mph)	Grade (%)
0.0	2	1.7	0
0.5	4	1.7	5
1.0	6	1.7	10
1.5	8	2.1	11
2.0	10	2.5	12
2.5	12	3.0	13
3.0	14	3.4	14
3.5	16	3.8	15
4.0	18	4.2	16
4.5	20	4.6	17
5.0	22	5.0	18

2.3. Maximal Exercise Test. Aerobic capacity was measured by performing a treadmill exercise test using the Cornell-modified Bruce treadmill exercise protocol (Table 1). The protocol, which was used to determine the cardiopulmonary fitness of the elderly, consists of 2-min stages, beginning with 0 stage at 1.7 mph and 0% grade, gradually increasing intensity to stage 5 of the Bruce protocol [14, 15]. The 12–lead EKG was monitored during the test as well as the recovery stage. Heart rate was recorded every minute, and blood pressure and Borg's rating of perceived exertion (RPE) on a scale of 6–20 were assessed every 2 minutes. Respiratory gas samples were analyzed breath-by-breath using a portable metabolic system (K4b^2, COSMED, Rome, Italy). The test was terminated based on American College of Sports Medicine (ACSM) guidelines for conducting a maximal exercise test [16, 17], with the age-predicted maximum heart rate calculated as $(208 - 0.7 \times \text{age})$ [18] and respiratory exchange ratio (RER) adjusted for 1.00 [19]. Aerobic power ($\dot{V}O_2$max), HR_{max}, maximal blood pressure, rating of perceived exertion (RPE) based on a 6–20 points' Borg Scale, and the time of the exercise test were obtained.

2.4. Modified Squat Test. A custom-made lightweight equipment platform (Figure 1(a)) was developed to conduct the modified squat test. The vertical part of the testing equipment (Figure 1(b)) could be detached from the horizontal part so that the equipment could be easily carried. When performing the modified squat test, the subject started at a standing position with his elbows 90° flexed at the sides of the waist (Figure 2(a)), followed by squatting down to 45° knee flexion with both arms pushed out at the same time (Figure 2(b)), and then returned to the starting position (Figure 2(a)). The subject repeated the above-mentioned sequences at a rate of 104 cycles/min for 3 minutes, using a metronome. Recovery heart rates (HR) (0~30, 60~90, and 120~150 seconds) were counted following the modified squat test with using a stethoscope. Blood pressure and RPE were recorded at the end of the test. To compare with previous studies, we calculated several fitness indexes including immediate HR, the sum of recovery HR, and recovery HR index $(18000/((HR_{0\sim30} + HR_{60\sim90} + HR_{120\sim150}) \times 2))$. In addition, we developed a new index calculated as (recovery HR index/age). The indexes obtained from the modified squat test were determined as follows.



(a) (b)

Figure 1: Custom-made lightweight equipment. (a) Assembled testing device. (b) A diagram from a lateral view showing the upright part of the device can be detached from the horizontal part.

(a) (b)

Figure 2: Movements of the modified squat test. (a) Starting position. (b) Ending position.

2.4.1. Immediate HR. After the termination of the modified squat test, heart rate measured from Polar was recorded immediately.

2.4.2. The Sum of Recovery HR. When the modified squat test was finished, cumulative heart beats were counted during 0~30, 60~90, and 120~150 seconds. The total number of recovery pulse counts was calculated as the sum of recovery HR.

2.4.3. Recovery HR Index. The fitness index was revised from the equation of Harvard step test [20]:

$$\text{Recovery HR index} = \frac{\text{test duration of modified squat test (second)} \times 100}{(\text{the sum of recovery HR}) \times 2}. \quad (1)$$

2.4.4. Age-Adjusted Recovery Heart Rate. The fitness index was calculated according to the following equation:

$$\text{Age-adjusted recovery heart rate} = \frac{\text{recovery HR index}}{\text{age}}. \quad (2)$$

2.5. Statistical Analysis. Test-retest reliability for the modified squat test was established by determining the intraclass correlation coefficient (ICC). The ICC values greater than 0.75 were considered as good reliability, those between 0.5 and 0.75 as moderate reliability, and those below 0.5 as poor reliability [21]. Pearson correlation analysis was used to evaluate the correlation between the fitness indexes of the modified squat test and the maximal exercise test performance. Correlation coefficients (r) higher than 0.6 were defined as high correlations, those between 0.3 and 0.6 as moderate correlations, and those

Table 2: Physical characteristics and baseline physiological parameters for the subject ($N = 25$).

	Mean	SD
Age (years)	65.16	4.90
Weight (kg)	66.11	8.58
Height (cm)	166.52	5.21
BMI (kg/m^2)	23.81	2.59
Body fat (%)	20.57	5.73
Heart rate rest (beats/min)	73.80	11.69
Systolic blood pressure (mmHg)	128	14.59
Diastolic blood pressure (mmHg)	81.28	9.34
Physical Activity Scale for the Elderly	137.07	64.81

SD: standard deviation.

Table 3: Physiological responses to maximal exercise test ($N = 25$).

	Mean	SD
$\dot{V}O_2$max (ml/kg/min)	35.82	4.44
RER	1.05	0.11
Time to exhaustion (min)	12.80	2.00
HRmax (beats/min)	165.12	8.25
Systolic blood pressure (mmHg)	196.75	18.88
Diastolic blood pressure (mmHg)	88.00	10.49
RPE	17.28	1.24

SD: standard deviation.

under 0.3 as poor correlations [21]. To predict $\dot{V}O_2$max from the best fitness index, a stepwise multiple regression analysis was performed with physical activity level and physiological and anthropometric data (age, resting HR, height, weight, BMI, and percent of body fat) as independent variables.

3. Results

3.1. Participant Characteristics. Thirty-three male participants aged 60 to 75 years were recruited. Eight of these participants did not complete the maximal exercise test due to cardiac and/or balance problems and were excluded for data analysis. The baseline characteristics of the remaining 25 participants analyzed are presented in Table 2.

3.2. Maximal Graded Exercise Test. Physiological responses of the participant to the maximal exercise test are shown in Table 3. Twenty-five subjects completed the maximal exercise test without any abnormal ECGs or complications. The $\dot{V}O_2$ and RER at baseline were 4.86 ± 1.03 (ml/kg/min) and 0.76 ± 0.10, respectively. The $\dot{V}O_2$ and RER at maximal efforts reached 35.82 ± 4.44 (ml/kg/min) and 1.05 ± 0.11, respectively. The time to volitional exhaustion was within an optimal exercise time of 8 to 12 minutes as suggested by ACSM.

3.3. The Modified Squat Test. Table 4 presents the result of the two modified squat tests. As shown in Table 4, the intensity for the modified squat test was 20.72 ± 3.60 ml/kg/min, corresponding to $58.22 \pm 10.00\%$ of $\dot{V}O_2$max and $80.98 \pm 10.92\%$ of age-predicted maximal HR.

3.4. Reliability of Squat Test. All the modified squat test fitness indexes showed high test-retest reliabilities, with ICC values ranging from 0.77 to 0.90. As shown in Table 5, age-adjusted recovery HR index had the highest ICC value (0.90) among the four squat test indexes.

3.5. Validity of the Modified Squat Test. As shown in Table 6, a significant negative correlation was seen between the sum of recovery HR and $\dot{V}O_2$max, whereas significant positive correlations between the recovery HR index and age-adjusted recovery index and $\dot{V}O_2$max were found. Age-adjusted recovery HR index had the highest correlation with $\dot{V}O_2$max.

3.6. Prediction of $\dot{V}O_2$max Equation. Table 7 presents the result of the stepwise multiple regression analysis for prediction of $\dot{V}O_2$max. Age-adjusted recovery HR index and physical activity level were strongly correlated with $\dot{V}O_2$max and accounted for 63% of the variance. The prediction equation for $\dot{V}O_2$max from the modified squat test was

$$\begin{aligned}\dot{V}O_2\text{max} = {} & 16.781 + 16.732 \\ & \times (\text{Age-adjusted recovery HR index}) \\ & + 0.02467 \times (\text{physical activity level}).\end{aligned} \tag{3}$$

4. Discussion

Cardiopulmonary fitness is associated with risks of cardiovascular diseases [22–24]. With aging, maximal oxygen consumption declines at the rate of 1% per year [25]. Regular exercise has been considered to be a safe and effective strategy to delay the aging process. Evaluation of cardiopulmonary fitness is essential to assure that a safe exercise prescription is implemented for older people [26]. Considering the nature of physical characteristics of older individuals, we modified a squat test, which was originally designed for young healthy adults.

4.1. Reliability. The ICC analyses on the fitness indexes (the immediate HR, sum of recovery HR, recovery HR index, and age-adjusted recovery HR index) of the modified squat test revealed that the ICCs ranged from 0.77 to 0.90, suggesting high reliabilities according to the definition of reliability level proposed by Portney and Watkins [21]. Age-adjusted recovery HR index had the highest ICC among the four modified squat test fitness indexes, showing the best reliability. On the contrary, the immediate HR yielded the lowest ICC value (0.77). The older adult has greater variations in physiological responses to an exercise and slower adaptations to an exercise, which contributes to the lower ICC seen in the immediate HR fitness index.

Petrella et al. investigated the validity of the self-paced step test in older adults while the reliability was not conducted [3]. Kervio et al. assessed the reliability of the 6-minute walk test in 12 healthy old individuals [27]. In their study, six trials of the 6-minute walk test were performed. However, only the coefficient of variation (CV) instead of ICCs was reported. Fenstermaker et al. investigated the test-retest ICC reliability of the Rockport walking test on the fitness indexes of walking

Table 4: Parameters of the modified squat test ($N = 25$).

	S1	S2
Immediate HR (beats/min)	131.40 ± 17.85	134.04 ± 18.63
Recovery HR_0–30 s (beats)	51.16 ± 9.59	58.36 ± 9.63
Recovery HR_60–90 s (beats)	47.80 ± 8.27	48.60 ± 9.57
Recovery HR_120–150 s (beats)	44.84 ± 8.01	45.96 ± 9.17
Sum of recovery HR (beats)	149.80 ± 24.79	152.92 ± 27.45
Recovery HR index	61.92 ± 11.81	60.70 ± 10.85
Age-adjusted recovery HR index	0.96 ± 0.21	0.94 ± 0.18
$\dot{V}O_2$ (ml/kg/min)	—	20.72 ± 3.60
Percentage of $\dot{V}O_2$max (%)	—	58.22 ± 10.00
Percentage of age-predicted HR_{max} (%)	80.93 ± 10.88	82.53 ± 11.05
SBP (mmHg)	167.11 ± 17.27	164.27 ± 22.48
DBP (mmHg)	95.78 ± 8.21	88.18 ± 11.43
RPE	12.20 ± 1.44	12.48 ± 1.81

S1: the first modified squat test; S2: the second modified squat test with oxygen consumption measurement; —: not available.

Table 5: Test-retest reliability of the modified squat test ($N = 25$).

Index	Immediate HR (beats)	Sum of recovery HR (beats)	Recovery HR index	Age-adjusted recovery HR index
ICC	0.77	0.88	0.87	0.90

Table 6: Correlations between the squat test indexes and $\dot{V}O_2$max ($n = 25$).

	S1	S2
Immediate HR (beats/min)	-0.52^{**}	-0.51^{*}
Sum of recovery HR (beats)	-0.64^{**}	-0.60^{**}
Recovery HR index	0.68^{**}	0.64^{**}
Age-adjusted recovery HR index	0.70^{**}	0.71^{**}

$^{**}p < .001$; $^{*}p < .05$; S1: the first modified squat test; S2: the second modified squat test with oxygen consumption measurement.

Table 7: The regression model for the modified squat test to predict $\dot{V}O_2$max.

	Regression coefficient (B)	SE	Standardized regression coefficients (β)	p value
Age-adjusted recovery HR index	16.732	3.149	0.497	.000
Physical activity level	0.02467	0.009	0.130	.000
Constant	16.781	3.203		.011
R^2	0.63			
Adjusted R^2	0.59			

SE: standard error; R^2: coefficient of determination.

time, HR, and estimated $\dot{V}O_2$max [9]. The ICC values of Rockport walking fitness indexes ranged from 0.67 to 0.71. In our study, a high ICC of 0.90 for age-adjusted recovery HR index suggests that the reliability of the modified squat test is comparable or superior to the above-mentioned fitness tests.

4.2. Validity. Previous studies have developed several aerobic fitness tests for old individuals. Rikli and Jones investigated the validity of the 6 min walk test in older individuals by correlating the treadmill performance time reaching 85% of

Though those commonly seen aerobic fitness tests have acceptable validity, there are some shortcomings. For example, the 6 min walk test needs a spacious testing environment. The self-paced step test used a step with 40 cm height, which may predispose older individuals to increased risk of falls during testing. In our study, moderate to high correlations between fitness indexes and $\dot{V}O_2$max, with the highest correlation of 0.7 seen in age-adjusted recovery HR index, suggested the modified squat test is a valid fitness test in the older individual and comparable to or even superior to other fitness field tests reported in previous studies. The modified squat test is convenient, has low cost, is safe to administer, and requires limited space and thus may be another option for assessing aerobic fitness for old healthy individuals.

Recovery HR after exercise has been found to be correlated with the fitness level and mortality in old individuals

[28, 29]. The immediate HR fitness index had the worst validity among the fitness indexes. One contributory factor might be due to the aged autonomic nervous system. Immediate HR recovery is primarily a function of reactivation of the parasympathetic nervous system, while later recovery of HR is associated with gradual withdrawal of the sympathetic nervous system [30, 31]. Aging results in slower adaptations of the autonomic nervous system to the termination of exercise [32, 33]. In other words, it takes longer for older adults to recover their HR to the baseline. Therefore, fitness indexes using several recovery HRs would be more representative of the fitness level of the older individual.

4.3. Prediction of Equation. Kervio et al. reported that predicted $\dot{V}O_2$max equation for older individuals from the 6-minute walk test parameters (distance, heart rate) and anthropometric value (age, weight, and height) accounted for 94% of the variance in $\dot{V}O_2$max, with a small subject number of 12 [27]. In the self-paced step test, stepping time, heart rate, age, BMI, and O_2 pulse were significantly associated with $\dot{V}O_2$max and were chosen to establish the predictive formula, which can explain 72% to 86% of variance [3]. The correlation of the predicted $\dot{V}O_2$max of the self-paced step test and the measured $\dot{V}O_2$max was from 0.88 and 0.90 for low-fitness men and women and 0.83 and 0.94 for high-fitness men and women. In our study, the age-adjusted recovery HR fitness index had the highest validity among four fitness indexes calculated and thus was chosen to develop a prediction equation for aerobic power of the older individual. Factors which might affect $\dot{V}O_2$max value such as age, resting HR, height, weight, body fat, and physical activity were taken into account for regression analysis to establish the prediction of $\dot{V}O_2$max. The predicted $\dot{V}O_2$max using this model was highly correlated ($r = 0.79$) with measured $\dot{V}O_2$max from the maximal exercise test. The predictive model based on age-adjusted recovery HR and physical activity explained 63% of the variances in $\dot{V}O_2$max. The variance explained by the prediction equation in our study appears to be lower than those in the 6 min walk test and the self-paced step test. However, only 12 subjects were recruited to develop the prediction equation from the 6 min walk test in Kervio et al. study. In the prediction model for the self-paced step test, O_2 pulse was used as one of predictive parameters. Petrella et al. indicated that O_2 pulse from the self-paced step test was strongly associated with $\dot{V}O_2$max and improved the percentage variance to be explained in the prediction of $\dot{V}O_2$max [3]. For clinical practice purposes, we did not include O_2 pulse in our model, which might contribute to the discrepancy. In addition, previous research stated that body composition, such as BMI, weight, or body fat, is a factor in the predictive equation of $\dot{V}O_2$max [3, 9, 27]. However, in our study, body composition was excluded in the regression analyses. A small sample size and homogeneous body fat in our subjects might be contributory factors.

4.4. Suggestions for Future Applications of the Modified Squat Test. The exercise intensity for the modified squat test is approximately 60% of $\dot{V}O_2$max and 81% of age-predicted maximal HR, corresponding to a moderate exercise workload. No discomfort or injuries during the testing were reported. The modified squat test is submaximal while appearing to be able to elicit substantiate physiological exercise responses to allow one's maximal aerobic power to be assessed safely and accurately. Moreover, it is interesting to note that most of the subjects expressed that they would practice the modified squat test as an exercise afterwards, suggesting the continuous movement of the modified squat test might potentially be developed as an interesting form of exercise. To serve this purpose, the prototype testing device used in this study should be further developed to provide adjustments of exercise workloads as well as feedback of exercise intensity. The prototype testing device could be manufactured with sensors monitoring HR and with a device indicating different rates of half-squatting. In addition, an electronic goniometer could well be integrated into the testing system to indicate the appropriate angle of squatting.

There are several limitations in this study. First, the sample size of this study was small. In addition, most of the subjects tended to be young older adults (aged < 70 years). Therefore, a larger sample size with individuals aged 70 years and beyond is required in future studies to enhance the application of the $\dot{V}O_2$max prediction equation determined from the modified squat test. Second, the subjects of this study were all males. Whether the modified squat test is valid for healthy older females still needs to be confirmed.

5. Conclusions

The results reveal that the modified squat test is valid and reliable and can be an option for evaluating the fitness level in healthy elderly men in clinics or communities. The best index is age-adjusted recovery heart rate. The predicted equation for $\dot{V}O_2$max is 16.781 + 16.732 × age-adjusted recovery HR + 0.02467 × physical activity level (score of PASE questionnaire).

Conflicts of Interest

The authors declare no conflicts of interest.

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Clinical Study

Unilateral Arm Crank Exercise Test for Assessing Cardiorespiratory Fitness in Individuals with Hemiparetic Stroke

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Cardiorespiratory fitness assessment with leg cycle exercise testing may be influenced by motor impairments in the paretic lower extremity. Hence, this study examined the usefulness of a unilateral arm crank exercise test to assess cardiorespiratory fitness in individuals with stroke, including sixteen individuals with hemiparetic stroke (mean ± SD age, 56.4 ± 7.5 years) and 12 age- and sex-matched healthy controls. Participants performed the unilateral arm crank and leg cycle exercise tests to measure oxygen consumption ($\dot{V}O_2$) and heart rate at peak exercise. The $\dot{V}O_2$ at peak exercise during the unilateral arm crank exercise test was significantly lower in the stroke group than in the control group ($p < 0.001$). In the stroke group, the heart rate at peak exercise during the unilateral arm crank exercise test did not significantly correlate with the Brunnstrom recovery stages of the lower extremity ($p = 0.137$), whereas there was a significant correlation during the leg cycle exercise test (rho = 0.775, $p < 0.001$). The unilateral arm crank exercise test can detect the deterioration of cardiorespiratory fitness independently of lower extremity motor impairment severity in individuals with hemiparetic stroke. This study is registered with UMIN000014733.

1. Introduction

Cardiorespiratory fitness in individuals with stroke is reduced to 26–87% of that in age- and sex-matched healthy persons [1]. Even independently ambulant and community dwelling individuals with stroke have reduced cardiorespiratory fitness as compared to nonstroke individuals [2]. Cardiorespiratory fitness reduction is potentially related to walking disability [3, 4], limitations in activities of daily living [5–7], and an increased risk of further cardiovascular disease [8] in individuals with stroke. In addition, cardiorespiratory fitness is associated with better cognitive performance, greater grey matter volume, and greater integrity of the white matter in individuals with stroke [9]. Therefore, the assessment of cardiorespiratory fitness is essential for identifying physical deconditioning, predicting prognosis, and assessing the effects of therapeutic exercise in stroke rehabilitation [10, 11].

Oxygen consumption ($\dot{V}O_2$) at peak exercise measured during the leg cycle exercise test is commonly used to assess cardiorespiratory fitness in individuals with hemiparetic stroke [12–16]. However, with this approach, motor impairments in the paretic lower extremity may limit exercise test performance [13–15]. Considering the possibility that the reduced $\dot{V}O_2$ at peak exercise in individuals with hemiparetic stroke reflects motor impairments in the paretic lower extremity, development of a cardiorespiratory fitness assessment that is not influenced by motor impairments is required [17].

An arm crank ergometer can be used for assessing cardiorespiratory fitness, particularly in individuals with motor impairments in the paretic lower extremity, such as in spinal cord injury [18]. However, the conventional bilateral arm crank ergometer is not suitable for individuals with hemiparetic stroke, because of the limitations associated with hemiparesis. Here, a unilateral arm crank exercise test was employed as a unique strategy [19, 20]. Unilateral arm crank exercise testing with the nonparetic arm in individuals with stroke is potentially useful to assess cardiorespiratory fitness independently of lower extremity motor impairment severity. However, there are no reports that have compared cardiorespiratory fitness in individuals with stroke and healthy adults using the unilateral arm crank exercise test. In addition, no study has directly examined the relationship between heart rate at peak exercise during the unilateral arm crank exercise test and motor impairments of the paretic lower extremity. This study aimed to examine the usefulness of a unique exercise test performed with the nonparetic arm for assessing cardiorespiratory fitness in individuals with hemiparetic stroke. We hypothesized that the unilateral arm crank exercise test can detect the deterioration of cardiorespiratory fitness in individuals with hemiparetic stroke. We also hypothesized that unilateral arm crank exercise testing with the nonparetic arm can assess cardiorespiratory fitness independently of the lower extremity motor impairment severity in individuals with hemiparetic stroke.

2. Methods

2.1. Study Design. This study used a cross-sectional observational design. The study protocol was approved by the appropriate ethics committee. All participants provided written informed consent prior to study enrollment. The study was conducted according to the Declaration of Helsinki of 1964, as revised in 2013.

2.2. Participants. Sixteen individuals with hemiparetic stroke participated in this study. A group of 12 healthy volunteers matched for age and sex participated as controls. Participants with stroke were recruited from a convalescent rehabilitation hospital between November 2014 and November 2015. Control participants were recruited from a local community. The inclusion criteria in participants with stroke were as follows: age 40–80 years, being within 180 days after first-ever stroke, ability to remain seated independently for 30 min without any support, and a Mini-Mental State Examination score [21] of 24 or more. The inclusion criteria in control participants were as follows: age 40–80 years, a Mini-Mental State Examination score of 24 or more, and no involvement in regular exercise more than twice a week. The exclusion criteria in both participants with stroke and control participants were as follows: limited range of motion and/or pain that could affect the exercise test, unstable medical conditions, such as unstable angina, uncontrolled hypertension, or tachycardia, use of beta-blockers, and any comorbid neurological disorder.

2.3. Exercise Testing. All participants performed the unilateral arm crank and leg cycle exercise tests on different days, but within 7 days. The order of the two tests was randomly determined for each participant to remove order bias. Both tests were performed on an ergometer (Strength Ergo 240, Mitsubishi Electric Engineering Co., Tokyo) that can be precisely load-controlled (coefficient of variation, 5%) over a wide range of pedaling resistance (0–400 W). Participants were instructed not to eat food for 3 h and to avoid caffeine and vigorous physical activity for at least 6 and 24 h, respectively, before the tests [22].

For the unilateral arm crank exercise test, the rotational axis of the ergometer was set at the height of participant's shoulder [23] and at a distance where the participant's elbow was in a slightly bent position with maximal reach (Figure 1(a)). The resistance was set at 10 W for the first 3 min of exercise testing and gradually increased by $5\ W{\cdot}min^{-1}$ in both the stroke and control groups [23].

For the leg cycle exercise test, the distance from the seat edge to pedal axis was adjusted so that the participant's knee flexion angle was 20° when extended maximally (Figure 1(b)). The backrest was set at 20° reclined from the vertical position. For participants with stroke, additional strapping was attached to secure the paretic foot to the pedal as needed. The resistance was set at 10 W for the first 3 min of exercise testing and was gradually increased by $10\ W{\cdot}min^{-1}$ in both groups [15].

Control participants were instructed to maintain a target cadence of 50 rpm throughout the exercise in both tests [15, 23]. Each participant with stroke was instructed to maintain a speed at which they could perform the test comfortably at 10 W (37 ± 7 rpm in the unilateral arm crank exercise test and 46 ± 7 rpm in the leg cycle exercise test) throughout each test, because some participants could not maintain a cadence of 50 rpm, even at 10 W.

Criteria for termination of either exercise test included one of the following: the participant reached 85% of the age-predicted maximal heart rate (220 minus age) [24], the participant was unable to maintain a target cadence, or the participant appeared to be in distress as defined in the termination criteria established by the American College of Sports Medicine [22].

An expired gas analyzer (Aerosonic AT-1100, ANIMA Corp., Tokyo) and a heart rate monitor (Polar WearLink, Polar Electro Japan Inc., Tokyo) were used to measure the expired gas and heart rate, respectively, during the exercise

(a) (b)

Figure 1: Experimental setup of the unilateral arm crank exercise test (a) and the leg cycle exercise test (b).

tests. Expired gas and heart rate were measured simultaneously on a breath-by-breath basis. The expired gas data were smoothed with a 30 s moving average to minimize breath-to-breath variability in determining the $\dot{V}O_2$ values at peak exercise [14, 25]. The $\dot{V}O_2$, heart rate, respiratory exchange ratio, minute ventilation, the ventilatory equivalents of oxygen and carbon dioxide, and the end-tidal oxygen and carbon dioxide at peak exercise were defined as the highest values achieved during exercise testing [14]. The heart rate at peak exercise is an important determining factor for the $\dot{V}O_2$ at peak exercise and is an indicator of the degree of effort [24]. The respiratory exchange ratio is defined as the ratio between carbon dioxide output ($\dot{V}CO_2$) and $\dot{V}O_2$ and is also an indicator of exercise effort [24]. Work rate at peak exercise was defined as the highest work rate maintained for at least 30 s [24]. Participants provided their ratings of perceived exertion (6 = no exertion at all, 20 = maximal exertion) [26] at the end of the test. Participants who discontinued exercise testing because of their inability to maintain a target cadence were requested to report the reason (i.e., either general fatigue or limb muscle fatigue). A 3-lead electrocardiogram (BSM-2401, Nihon Kohden Corp., Tokyo) was used to monitor cardiac activity throughout the tests and during the recovery phase. Blood pressure was obtained every minute from the paretic arm in the stroke group and the nondominant arm in the control group using an automated system (Tango, Sun Tech Medical Inc., NC).

The ventilatory threshold was determined using a combination of the following criteria: (1) the point where the ventilatory equivalent of oxygen reaches its minimum or starts to increase, without an increase in the ventilatory equivalent of carbon dioxide; (2) the point at which the end-tidal oxygen fraction reaches a minimum or starts to increase, without a decline in the end-tidal carbon dioxide fraction; (3) the point of deflection of $\dot{V}CO_2$ versus $\dot{V}O_2$ (V-slope method) [27]. The first two criteria were prioritized in case the three criteria presented different results [28]. The ventilatory threshold was determined as the averages from two independent raters (CO and DK), when the difference in the $\dot{V}O_2$ values of the corresponding points as determined by the two raters was less than 100 mL·min^{-1} [29]. In case of any discrepancy, a third experienced rater (KO) judged the point, and the ventilatory threshold was taken as the average of the two closest values [28]. The $\dot{V}O_2$ at the ventilatory threshold was used as a submaximal index of exercise capacity [24].

2.4. Motor Impairment Assessment. The Brunnstrom recovery stages [30] consisted of six categories: stage I, flaccid; stage II, synergy pattern development with minimal voluntary movement; stage III, voluntary synergistic movement; stage IV, some movements deviating from synergy; stage V, independent movement apart from the basic synergic pattern; and stage VI, isolated voluntary joint movements.

2.5. Statistical Analysis. Participant characteristics between the stroke and control groups were compared using unpaired t-test for continuous variables and Fisher's exact test for dichotomous variables, respectively. The $\dot{V}O_2$ differences between the stroke and control groups in each test were examined using the unpaired t-test to determine if the tests could detect the $\dot{V}O_2$ reduction in individuals with stroke. The Spearman rank correlation coefficient was used to examine whether the heart rate and $\dot{V}O_2$ at peak exercise correlated with motor impairments in the paretic lower extremity. Furthermore, heart rate, respiratory exchange ratio, minute ventilation, the ventilatory equivalents of oxygen and carbon dioxide, the end-tidal oxygen and carbon dioxide, work rate, systolic and diastolic blood pressures, ratings of perceived exertion, and $\dot{V}O_2$ at the ventilatory threshold were compared between stroke and control groups using the unpaired t-test or the Mann–Whitney U test, depending on the type of variable. To identify whether maximal effort was achieved during the exercise test, we set the following criteria [24]: (1) the exercise test was terminated when achieving 85% of the age-predicted maximal heart rate and (2) the respiratory exchange ratio at peak exercise was 1.10 or more. The number of participants who met a criterion for maximal effort was compared between groups using Fisher's exact test. Statistical analyses were performed using the Statistical Package for the Social Sciences software version 21.0 (International Business Machines Corp., NY). Any p values < 0.05 were considered statistically significant.

Table 1: Participant characteristics.

Variable	Stroke (n = 16)	Control (n = 12)	95% CI	p value
Age (years), mean ± SD	56.4 ± 7.3	58.3 ± 7.8	−7.7, 4.1	0.535
Sex, n (%)				
Men	11 (68.8)	4 (33.3)	NA	0.125
Women	5 (31.2)	8 (66.7)		
Height (m), mean ± SD	1.66 ± 0.09	1.61 ± 0.11	−0.03, 0.12	0.206
Weight (kg), mean ± SD	60.3 ± 10.7	59.7 ± 12.1	−8.2, 9.6	0.877
Body mass index (kg/m^2), mean ± SD	21.9 ± 2.9	22.9 ± 2.9	−3.2, 1.3	0.406
Antihypertensive medications, n (%)				
Angiotensin-converting enzyme inhibitor	3 (18.8)	0 (0.0)	NA	<0.001
Angiotensin II receptor blocker	5 (31.2)	0 (0.0)		
Calcium channel blocker	11 (68.8)	0 (0.0)		
Comorbidities, n (%)				
Hypertension	14 (87.5)	0 (0.0)	NA	<0.001
Diabetes mellitus	5 (31.2)	0 (0.0)		
Hyperlipidemia	3 (18.8)	0 (0.0)		
Type of stroke, n (%)				
Ischemic	5 (31.2)	NA		
Hemorrhagic	11 (68.8)			
Side affected by stroke, n (%)				
Right	6 (37.5)	NA		
Left	10 (62.5)			
Time since stroke (days), mean ± SD	101 ± 39	NA		
Brunnstrom recovery stages of lower extremity, n (%)				
II	3 (18.7)	NA		
III	4 (25.0)			
IV	3 (18.7)			
V	3 (18.7)			
VI	3 (18.7)			

95% CI: 95% confidence interval of the difference between the means (stroke group − control group), NA: not applicable.

3. Results

Of the 90 individuals who met the inclusion criteria, 74 were excluded based on the exclusion criteria; consequently, 16 individuals with stroke participated in the study. Table 1 shows the characteristics of the 16 participants. There were no significant differences in age, sex, height, weight, and body mass index between the stroke and control groups ($p > 0.05$).

No significant adverse events occurred during or after either exercise test in both the stroke and control groups. Measurement values at peak exercise in each group during the unilateral arm crank and leg cycle exercise tests are shown in Tables 2 and 3, respectively. The mean $\dot{V}O_2$ at peak exercise during the unilateral arm crank exercise test in the stroke group was significantly reduced to 73.0% (mean difference = −3.7; 95% confidence interval [CI] = −5.6, −1.7; $p < 0.001$) of that in the control group. In the leg cycle exercise test, the mean $\dot{V}O_2$ at peak exercise in the stroke group was also reduced to 66.3% (mean difference = −6.5; 95% CI = −9.8, −3.2; $p < 0.001$) of that in the control group. Results showed that the unilateral arm crank exercise test, as well as the leg cycle exercise test, detected the deterioration of cardiorespiratory fitness in participants with hemiparetic stroke compared with healthy controls.

The heart rate and $\dot{V}O_2$ at peak exercise during the unilateral arm crank exercise test did not correlate with the Brunnstrom recovery stages of the lower extremity (rho = 0.388, 95% CI = −0.133, 0.741, and p = 0.137; rho = 0.417, 95% CI = −0.099, 0.756, and p = 0.108, resp.) (Figure 2), whereas those during the leg cycle exercise test correlated significantly (rho = 0.775, 95% CI = 0.454, 0.918, and $p < 0.001$; rho = 0.781, 95% CI = 0.466, 0.920, and $p < 0.001$, resp.) (Figure 3).

The heart rate and respiratory exchange ratio at peak exercise during the unilateral arm crank exercise test were not significantly different between the stroke and control groups (mean difference = −4, 95% CI = −14, 6, and p = 0.428; mean difference = 0.13, 95% CI = −0.03, 0.30, and p = 0.102, resp.). Six participants with hemiparetic stroke

Table 2: Comparisons of various parameters at peak exercise in participants with stroke and healthy controls in the unilateral arm crank exercise test.

Variable	Unilateral arm crank exercise test			
	Stroke (n = 16)	Control (n = 12)	95% CI	p value
$\dot{V}O_2$ ($mL\cdot kg^{-1}\cdot min^{-1}$), mean ± SD	10.0 ± 2.6	13.7 ± 2.1	−5.6, −1.7	<0.001
Heart rate (bpm), mean ± SD	125 ± 14	129 ± 11	−14, 6	0.428
Respiratory exchange ratio, mean ± SD	1.28 ± 0.25	1.15 ± 0.13	−0.03, 0.30	0.102
Minute ventilation ($L\cdot min^{-1}$), mean ± SD	28.2 ± 9.0	29.5 ± 9.1	−8.4, 5.8	0.715
Ventilatory equivalent of oxygen, mean ± SD	48.1 ± 14.7	35.2 ± 3.6	3.9, 21.9	0.007
Ventilatory equivalent of carbon dioxide, mean ± SD	39.9 ± 9.0	33.3 ± 3.5	0.9, 12.2	0.024
End-tidal oxygen fraction (%), mean ± SD	17.1 ± 1.0	16.1 ± 0.5	0.3, 1.6	0.006
End-tidal carbon dioxide fraction (%), mean ± SD	5.01 ± 0.66	5.32 ± 0.51	−0.76, 0.14	0.166
Work rate (W), mean ± SD	34.1 ± 22.7	36.9 ± 7.4	−17.0, 11.3	0.702
Systolic blood pressure (mmHg), mean ± SD	177 ± 17	192 ± 18	−29, −1	0.043
Diastolic blood pressure (mmHg), mean ± SD	102 ± 13	105 ± 13	−17, 11	0.484
Ratings of perceived exertion, median (IQR)	15 (14, 17)	15 (13, 17)	NA	0.504
$\dot{V}O_2$ at the ventilatory threshold ($mL\cdot kg^{-1}\cdot min^{-1}$), mean ± SD	7.4 ± 1.2	10.2 ± 1.6	−3.8, −1.7	<0.001
Number of participants who terminated exercise test when achieving 85% of the age-predicted maximal heart rate, n (%)	6 (37.5)	5 (41.7)	NA	0.999
Number of participants who achieved the respiratory exchange ratio at peak exercise of 1.10 or more, n (%)	14 (87.5)	7 (58.3)	NA	0.103
Termination reasons prior to achieving 85% of the age-predicted maximal heart rate, n (%)				
General fatigue	3 (18.8)	0 (0.0)		
Arm muscle fatigue	5 (31.2)	4 (33.3)		
Diastolic blood pressure > 115 mmHg	2 (12.5)	3 (25.0)		

95% CI: 95% confidence interval of the difference between the means (stroke group − control group), IQR: interquartile range, NA: not applicable.

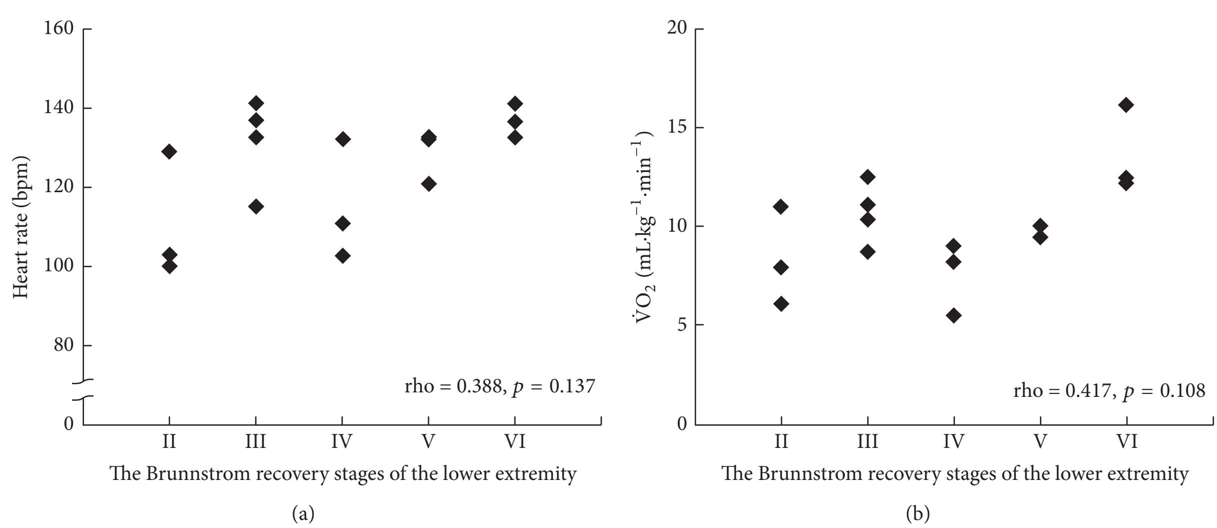

Figure 2: Correlations between heart rate and the Brunnstrom recovery stages of the lower extremity (a) and that between $\dot{V}O_2$ and the Brunnstrom recovery stages of the lower extremity (b) as measured during the unilateral arm crank exercise test.

Table 3: Comparisons of various parameters at peak exercise in participants with stroke and healthy controls in the leg cycle exercise test.

Variable	Leg cycle exercise test			
	Stroke (n = 16)	Control (n = 12)	95% CI	p value
$\dot{V}O_2$ (mL·kg^{-1}·min^{-1}), mean ± SD	13.0 ± 4.6	19.6 ± 3.6	−9.8, −3.2	<0.001
Heart rate (bpm), mean ± SD	117 ± 20	138 ± 7	−32, −8	0.003
Respiratory exchange ratio, mean ± SD	1.15 ± 0.18	1.10 ± 0.12	−0.06, 0.18	0.336
Minute ventilation (L·min^{-1}), mean ± SD	29.6 ± 13.1	36.7 ± 11.8	−17.0, 2.7	0.150
Ventilatory equivalent of oxygen, mean ± SD	38.3 ± 7.2	31.5 ± 5.0	1.8, 11.8	0.009
Ventilatory equivalent of carbon dioxide, mean ± SD	36.0 ± 7.4	29.9 ± 3.7	1.4, 11.0	0.014
End-tidal oxygen fraction (%), mean ± SD	16.4 ± 1.1	15.5 ± 0.9	0.1, 1.7	0.028
End-tidal carbon dioxide fraction (%), mean ± SD	5.51 ± 0.75	5.99 ± 0.62	−1.0, 0.1	0.081
Work rate (W), mean ± SD	55.0 ± 34.6	92.4 ± 9.2	−60.4, −14.5	0.004
Systolic blood pressure (mmHg), mean ± SD	164 ± 24	187 ± 16	−38, −7	0.009
Diastolic blood pressure (mmHg), mean ± SD	88 ± 14	93 ± 16	−17, 6	0.363
Ratings of perceived exertion, median (IQR)	13 (13, 15)	13 (13, 15)	NA	0.923
$\dot{V}O_2$ at the ventilatory threshold (mL·kg^{-1}·min^{-1}), mean ± SD	9.5 ± 2.2	14.7 ± 2.6	−7.1, −3.4	<0.001
Number of participants who terminated exercise test when achieving 85% of the age-predicted maximal heart rate, n (%)	6 (37.5)	12 (100.0)	NA	<0.001
Number of participants who achieved the respiratory exchange ratio at peak exercise of 1.10 or more, n (%)	9 (56.3)	8 (66.7)	NA	0.705
Termination reasons prior to achieving 85% of the age-predicted maximal heart rate, n (%)				
General fatigue	4 (25.0)	0 (0.0)		
Leg muscle fatigue	5 (31.2)	0 (0.0)		
Diastolic blood pressure > 115 mmHg	0 (0.0)	0 (0.0)		
Ankle clonus	1 (6.3)	0 (0.0)		

95% CI: 95% confidence interval of the difference between the means (stroke group − control group), IQR: interquartile range, NA: not applicable.

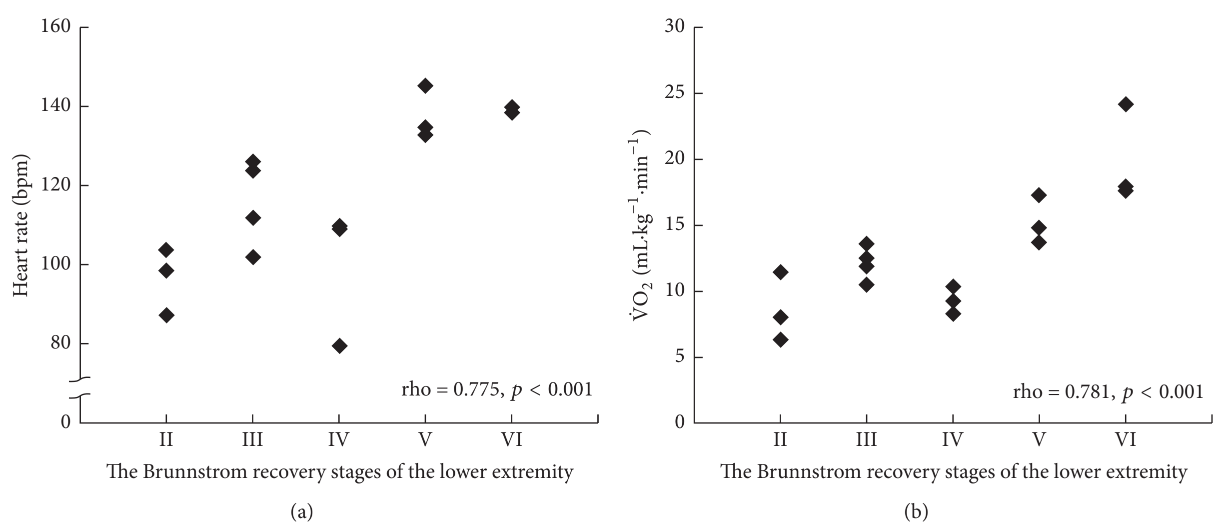

Figure 3: Correlations between heart rate and the Brunnstrom recovery stages of the lower extremity (a) and that between $\dot{V}O_2$ and the Brunnstrom recovery stages of the lower extremity (b) as measured during the leg cycle exercise test.

(37.5%) and 5 control participants (41.7%) achieved 85% of the age-predicted maximal heart rate during the exercise test ($p = 0.999$). The respiratory exchange ratio at peak exercise of 1.10 or more was observed in 14 participants with hemiparetic stroke (87.5%) and in 7 control participants (58.3%) ($p = 0.103$). In addition, the work rate at peak exercise during the unilateral arm crank exercise was also not significantly different between the groups (mean difference = −2.8; 95% CI = −17.0, 11.3; $p = 0.702$). These results showed that both the stroke and control groups could achieve the same exercise intensity level during the unilateral arm crank exercise test. The ventilatory equivalents of oxygen and carbon dioxide at peak exercise during the unilateral arm crank exercise test were significantly higher in the stroke group than in the control group (mean difference = 12.9, 95% CI = 3.9, 21.9, and $p = 0.007$; mean difference = 6.6, 95% CI = 0.9, 12.2, and $p = 0.024$, resp.). The end-tidal oxygen fraction at peak exercise during the unilateral arm crank exercise test was also significantly higher in the stroke group than in the control group (mean difference = 1.0; 95% CI = 0.3, 1.6; $p = 0.006$). The ventilatory threshold was identifiable in all participants during the unilateral arm crank exercise test. The $\dot{V}O_2$ at the ventilatory threshold was significantly lower in the stroke group than in the control group (mean difference = −2.8; 95% CI = −3.8, −1.7; $p < 0.001$).

The heart rate at peak exercise during the leg cycle exercise test was significantly lower in the stroke group than in the control group (mean difference = −21; 95% CI = −32, −8; $p = 0.003$), whereas there was no significant difference in the respiratory exchange ratio at peak exercise between the groups (mean difference = 0.05; 95% CI = −0.06, 0.18; $p = 0.336$). Six participants with hemiparetic stroke (37.5%) and all the control participants (100.0%) achieved 85% of the age-predicted maximal heart rate during the exercise test ($p < 0.001$). Only 3 participants with hemiparetic stroke reached 85% of the age-predicted maximal heart rate in both the unilateral arm crank and leg cycle exercise tests. The respiratory exchange ratio at peak exercise of 1.10 or more was observed in 9 participants with hemiparetic stroke (56.3%) and in 8 control participants (66.7%) ($p = 0.705$). Nine participants with hemiparetic stroke reached the respiratory exchange ratio at peak exercise of 1.10 or more in both exercise tests. The work rate at peak exercise during the leg cycle exercise was significantly lower in the stroke group than in the control group (mean difference = −37.4; 95% CI = −60.4, −14.5; $p = 0.004$). The ventilatory equivalents of oxygen and carbon dioxide at peak exercise during the leg cycle exercise test were significantly higher in the stroke group than in the control group (mean difference = 6.8, 95% CI = 1.8, 11.8, and $p = 0.009$; mean difference = 6.1, 95% CI = 1.4, 11.0, and $p = 0.014$, resp.). The end-tidal oxygen fraction at peak exercise during the leg cycle exercise test was also significantly higher in the stroke group than in the control group (mean difference = 0.9; 95% CI = 0.1, 1.7; $p = 0.028$). The ventilatory threshold was identifiable in all participants during the leg cycle exercise test. The $\dot{V}O_2$ at the ventilatory threshold was significantly lower in the stroke group compared with the control group (mean difference = −5.2; 95% CI = −7.1, −3.4; $p < 0.001$).

4. Discussion

This is the first study to evaluate the usefulness of unilateral arm crank exercise test for assessing cardiorespiratory fitness in individuals with hemiparetic stroke. All participants completed the unilateral arm crank exercise test using their nonparetic arm without any adverse events. The $\dot{V}O_2$ at peak exercise and the $\dot{V}O_2$ at the ventilatory threshold during the unilateral arm crank exercise test were significantly reduced in the stroke group compared with the control group. Moreover, the heart rate at peak exercise during the unilateral arm crank exercise test did not correlate with the Brunnstrom recovery stages of the lower extremity. These results suggest that the unilateral arm crank exercise test can detect the deterioration of cardiorespiratory fitness independently of the lower extremity motor impairment severity in individuals with hemiparetic stroke.

Tang et al. [15] reported that motor impairments in the paretic lower extremity may limit exercise test performance during the leg cycle exercise test. In this study, all control participants and only 37.5% ($n = 6$) of the participants with hemiparetic stroke achieved 85% of the age-predicted maximal heart rate during the leg cycle exercise test. In addition to heart rate, there was a significant correlation between the $\dot{V}O_2$ at peak exercise and the Brunnstrom recovery stages of the lower extremity during the leg cycle exercise test. Furthermore, both the heart rate and $\dot{V}O_2$ at peak exercise during the leg cycle exercise test were significantly lower in the stroke group than in the control group. These results indicate that the Brunnstrom recovery stages of lower extremity scores may be a covariate in exploring the differences between individuals with stroke and healthy adults using the leg cycle exercise test. Conversely, there was no significant correlation between the $\dot{V}O_2$ at peak exercise and the Brunnstrom recovery stages of the lower extremity during the unilateral arm crank exercise test. These findings suggest that assessment of cardiorespiratory fitness using the unilateral arm crank exercise test can be applied to individuals with stroke independently of motor impairment severity in the paretic lower extremity. Additionally, compared with the control group, the stroke group exhibited a reduction in the $\dot{V}O_2$ at peak exercise during the unilateral arm crank exercise test but no difference in the heart rate. Considering that $\dot{V}O_2$ is the product of heart rate, stroke volume, and arterial-venous oxygen difference [24], the reduced $\dot{V}O_2$ at peak exercise in participants with stroke observed during the unilateral arm crank exercise test may represent the decline in the stroke volume and/or arterial-venous oxygen difference at peak exercise.

A few concerns with the unilateral arm crank exercise test were identified in this study. In both the stroke and control groups, over 50.0% ($n = 10$ in the stroke group and $n = 7$ in the control group) of the participants had difficulty achieving 85% of the age-predicted maximal heart rate during the unilateral arm crank exercise. Five out of 16 participants with hemiparetic stroke (31.3%) and 4 out of 12 control participants (33.3%) discontinued the unilateral arm crank exercise because of arm muscle fatigue, which could be attributed to the greater recruitment of metabolically inefficient type II muscle fibers during unilateral arm cranking [31]. Moreover, a few participants had a diastolic blood pressure greater than 115 mmHg during the unilateral arm exercise test. di Blasio et al. [32] suggested that small muscle mass exercises, such as arm cranking, generate increased intramuscular pressure, which reduces muscular perfusion and increases resistance to blood circulation. Thus, the protocol in the present study might result in an overload on their arm muscle rather than the cardiorespiratory function. Despite concerns regarding local fatigue, as stated above, a respiratory exchange ratio at peak exercise of 1.10 or more was observed in 14 participants with hemiparetic stroke (87.5%) and in 7 control participants (58.3%) during the unilateral arm crank exercise test in the present study. It has previously been reported that a respiratory exchange ratio of 1.10 or more is generally an indication of excellent participant effort during exercise tests [24]. Therefore, the results may support consideration that the unilateral arm crank exercise test can detect the $\dot{V}O_2$ response at maximal effort. Although further studies are required to determine more appropriate protocols (e.g., target cadence, increments in exercise intensity, or target heart rate) for the unilateral arm crank exercise test, it should be noted that the present feasibility study is the first to show the usefulness of a unilateral arm crank exercise test for assessing cardiorespiratory fitness in individuals with hemiparetic stroke, as it could detect a decline in cardiorespiratory fitness independently of lower extremity motor impairment severity in individuals with stroke.

In both the unilateral arm crank and leg cycle exercise tests, there was no significant difference in the minute ventilation at peak exercise between the stroke and control groups, although the $\dot{V}O_2$ at peak exercise was significantly lower in the stroke group than in the control group. In addition, the ventilation equivalents of oxygen and carbon dioxide, and the end-tidal oxygen fraction at peak exercise, were significantly higher in the stroke group than in the control group. Therefore, ventilatory efficiency may be compromised in individuals with hemiparetic stroke during the unilateral arm crank and leg cycle exercise tests. Moreover, Sisante et al. [33] have reported that individuals with subacute stroke have low ventilatory efficiency when cardiorespiratory exercise testing was performed using a recumbent stepper. The unilateral arm crank exercise test also provides useful information on ventilatory efficiency as well as on deterioration in cardiorespiratory fitness in individuals with hemiparetic stroke.

This study had several limitations. First, it included a relatively small sample of individuals with subacute stroke; therefore, generalization of the findings should be made with caution. Second, normative values for the cardiorespiratory fitness assessment using the unilateral arm crank exercise test remain unclear. Establishing standard values and minimal detectable change in variables measured during the unilateral arm crank exercise test in healthy adults and individuals with stroke is necessary. Finally, previous studies showed that a total-body recumbent stepper exercise test [33–35], a nonparetic leg cycle exercise test [36, 37], and a robotics-assisted tilt table exercise test [28, 38] may be useful for assessing cardiorespiratory fitness in individuals with hemiparetic stroke. In future studies, evaluating the advantages of a unilateral arm crank exercise test over these exercise tests for assessing cardiorespiratory fitness in individuals with hemiparetic stroke is warranted.

5. Conclusions

This study suggests that the unilateral arm crank exercise test can detect cardiorespiratory fitness deterioration in individuals with hemiparetic stroke. The test could also assess cardiorespiratory fitness independently of lower extremity motor impairment severity in individuals with hemiparetic stroke. Therefore, the unilateral arm crank exercise test may be useful for assessing cardiorespiratory fitness in individuals with hemiparetic stroke.

Disclosure

Part of the manuscript was presented as an abstract in the Asian Confederation for Physical Therapy 2016 Congress. The funding source had no involvement with the study design, collection, analysis, and interpretation of data, writing of the report, and the decision to submit the article for publication.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article. The authors have read and approved the submitted manuscript.

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Research Article

Measurement of Gender Differences of Gastrocnemius Muscle and Tendon Using Sonomyography during Calf Raises: A Pilot Study

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Skeletal muscles are essential to the gender-specific characteristics of human movements. Sonomyography, a new signal for quantifying muscle activation, is of great benefit to understand muscle function through monitoring the real-time muscle architectural changes. The purpose of this pilot study was to investigate gender differences in the architectural changes of gastronomies muscle and tendon by using sonomyography during performing two-legged calf raising exercises. A motion analysis system was developed to extract sonomyography from ultrasound images together with kinematic and kinetic measurements. Tiny fascicle length changes among seven male subjects were observed at the initial part of calf raising, whereas the fascicle of seven female subjects shortened immediately. This result suggested that men would generate higher mechanical power output of plantar flexors to regulate their heavier body mass. In addition, the larger regression coefficient between the fascicle length and muscle force for the male subjects implied that higher muscle stiffness for the men was required in demand of maintaining their heavier body economically. The findings from the current study suggested that the body mass might play a factor in the gender difference in structural changes of muscle and tendon during motion. The sonomyography may provide valuable information in the understanding of the gender difference in human movements.

1. Introduction

Skeletal muscles are important human tissues to regulate force generation and control body motions as biological motors [1]. The force generation capabilities of skeletal muscles have been studied for decades to understand the gender-specific characteristics of human movements [2–5]. Several studies reported that men produced greater absolute strength than women [2–4]. The difference was significant even after adjusting for body weight, body mass index (BMI), the cross-sectional area of muscle, or fiber size. Men also had a greater rate of force development compared with women during maximum voluntary contraction (MVC), suggesting their faster force generation abilities [5]. These gender differences can be attributed to many factors, including architectural characteristics of muscle, muscle fiber type, muscle biomechanical characteristics, and neural activity during muscle contractions [6–8].

Muscle architecture, primarily represented by the geometric layout of fascicles within the muscle, such as fascicle length (FL) and pennation angle (PA), is closely related to the muscle function [9, 10]. Muscle imaging has become a promising field of research to recognize the biological and bioelectrical characteristics of muscles through checking the muscle architectural change. As a low cost, widely available, and radiation-free imaging modality, ultrasound imaging has been used in muscle imaging for examining the static changes of FL and PA in response to contraction [10], aging [11], physical training [12], and fatigue [13]. Ultrasound imaging has also been applied to investigate the contribution of muscle architectural difference to gender-specific characteristics in force generation capabilities [14–20]. Males tended to have larger PA in comparison with females [15–17, 19], though the differences in some muscles were not significant [15, 16]. And men compared with women had significantly larger optimal PA for generating maximal force during MVC [20]. Muscles with greater PA allow more fibers to be arranged in parallel within a given cross-sectional area, suggesting a higher force generation potential [18]. These observations can partly explain the difference in force-generating capability between the genders. However, there is a controversy regarding the FL between the sexes in previous literature [14–17]. It is still unclear whether the FL would contribute to the gender-specific characteristics of force generation.

Recently, sonomyography (SMG), representing the real-time change of muscle architecture obtained using ultrasound imaging, was proposed as a noninvasive option for measuring the muscle activation to comprehend the characteristics of human movements in vivo [21]. SMG has been demonstrated to be a very useful and reliable research tool to evaluate how muscle operates during motion [22–26] and diagnosis and rehabilitation assessment in vivo [27–30]. SMG is of great benefit to the understanding of human movements by measuring muscle activation through the real-time muscle architectural changes, though the application of SMG requires extra efforts which demand further considerations of various issues including the synchronization between the ultrasound scanner and the motion analysis system, ultrasound probe placement, and ultrasound data collection and processing. However, there is still a lack of report about using SMG for examining the gender-specific characteristics of muscle architectural change, such as fascicle-shortening range. Moreover, the architectural changes of muscle were facilitated by the tendon elasticity for efficient movement performance [24]. Although previous studies have revealed gender differences in the stiffness of joint, muscle, and tendon [16, 31], the interaction between muscle and tendon tissue has not been investigated using SMG for the gender-specific utilization of tendon elasticity in mechanical demands during movement.

The purpose of this pilot study was to apply SMG to examine the gender-specific architectural changes of the gastrocnemius (GM) muscle and its tendon during performing the two-legged standing calf-raise exercise. The plantar flexor plays an essential role in different functional tasks, such as walking, running, and hopping [22, 32, 33]. The calf-raise exercise has been proven to be capable of accessing the strength and power in the plantar flexors [34]. Also, the muscle activity in the GM and soleus during walking was similar to that in the calf raise [35]. We, therefore, chose to study the standing calf raises exercise to understand the contribution of gender-specific architectural changes of GM muscle to the plantar flexor. In this study, we developed a human motion analysis system with SMG, which consisted of an ultrasound scanner with custom-designed flat probe and software to collect the ultrasound images, a vision-based motion capture system to measure the kinematic and kinetic data, a custom-built device to synchronize the measurements of the ultrasound scanner and motion capture system, and a

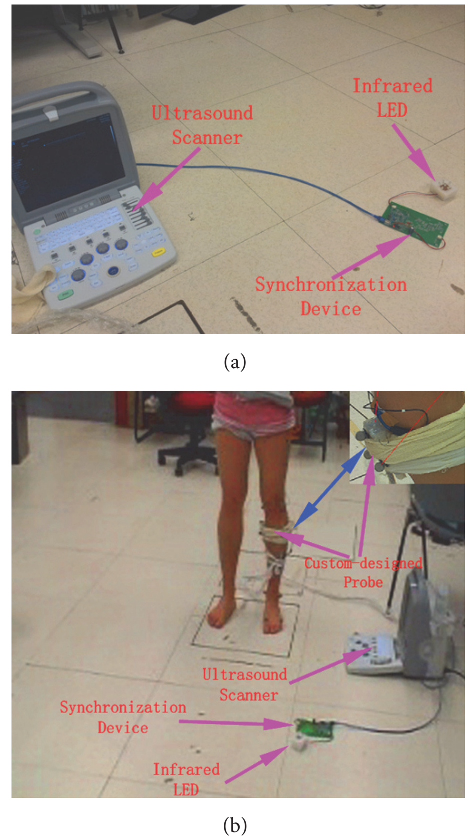

Figure 1: The ultrasound scanner with custom-designed probe and synchronization device: (a) the custom-designed synchronization device; (b) the custom-designed probe was attached on the muscle belly of GM.

custom-designed platform to process and analyze the data. We hypothesize that this newly developed motion analysis system could capture and quantity muscle architectural change during motion and that there exist gender-specific differences in the architectural changes of GM muscle and tendon during calf-raise exercises.

2. Materials and Methods

2.1. Motion Analysis System with SMG. The developed motion analysis system mainly consisted of three parts: motion capture system, portable ultrasound instruments with the custom-designed flat probe, and a custom-built synchronization device (Figure 1). In this study, a vision-based motion capture system (VICON MX system, VICON Corp., California, USA) was used for accurate kinematic measurements with eight cameras sampled at 100 Hz. A force sensing platform (ATMI OR6 Series, Advanced Mechanical Technology Inc., Massachusetts, USA) was deployed to measure the gravity reaction force (GRF) for the kinetic analysis. The raw force and moment signal were sampled at 1 kHz and transmitted to the motion capture system. Moreover, the GRF together with the kinematic data was stored in the VICON MX system for further processing. As shown in

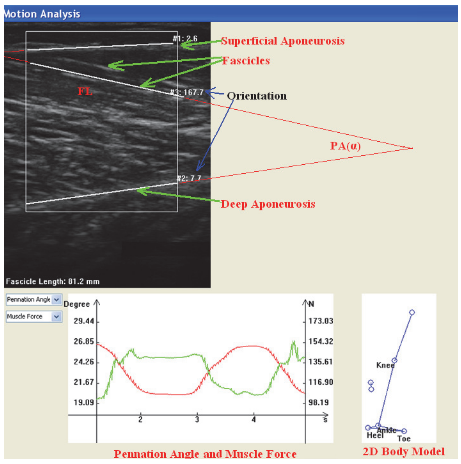

Figure 2: The FL and PA as defined in GM ultrasound image on the interface of custom-designed data analysis platform.

Figure 1, a portable ultrasound scanner (SIUI1100, Shantou Institute of Ultrasonic Instruments Co., Ltd., Guangdong, China) together with a custom-designed probe of 38 mm in width and 5–10 MHz in frequency was adopted as SMG measurement instrument. The custom-designed flat probe enclosed with silicone was used to make the attachment steadfast and avoid the probe tilt during motion. A custom-built control circuit board with the infrared LED was connected to the ultrasound scanner through universal serial bus (USB) communication (Figure 1), and the infrared LED on the circuit board was used to synchronize the data acquisition of the motion capture system and the ultrasound scanner. Custom-designed software programmed using Visual Studio (Microsoft Corporation, Washington, USA) was integrated on the ultrasound scanner for controlling the synchronization device and capturing ultrasound images directly from the ultrasound scanner. During the data acquisition, the infrared LED on the circuit was switched on by the custom-designed software, which can be recognized as the external synchronization signal to the motion capture system. Simultaneously, the ultrasound images were directly stored on the ultrasound scanner (21 frames/s), which avoided the additional time-delay and possible artifacts if using extra video capture card. The time index of each image was recorded for better alignment between the measurements of motion capture system and ultrasound scanner.

After the data acquisition, the data stored in the motion capture system was picked out to synchronize with ultrasound data by using the signal indicated by the infrared LED. And the selected data together with ultrasound images was then exported into the custom-designed data analysis program developed with Visual Studio (Microsoft Corporation, Washington, USA) and visualization tool OpenGL for data processing and analysis. The kinematic analysis, such as joint angle change, was achieved through calculating the spatial data of the human body, while the SMG, including FL and PA (Figure 2), was automatically derived from the ultrasound images. Some automated approaches had been developed to extract the SMG from ultrasound images [25, 26, 36–40]. In the current system, the automatic extraction of SMG was achieved by applying a number of our previously developed image processing techniques [25, 26, 39, 40]. Moreover, the GRF with kinematic data and SMG could be used to calculate tendon and muscle force through inverse dynamics [41], thus allowing the estimation of muscle force-length relationship.

2.2. Experimental Protocol. Fourteen healthy normal subjects (seven male and seven female) with no history of musculoskeletal injury were recruited from the authors' institute and participated in the study. Exclusion criteria were musculoskeletal disorders in the lower limb that prevented participation in typical activities greater than 1 day, current pain in the lower limb or trunk, or being engaged in some regular exercise (physical activity at least 3 times per week). The mean body weight and BMI of the subjects were 52.3 (6.4) kg and 20.1 (2.7) kg/m^2 for the women (age: 29.0 (4.0) years) and 77.2 (10.5) kg and 24.8 (3.2) kg/m^2 for the men (age: 34.7 (6.8) years). The institutional ethical committee approved this study, and all subjects gave written informed consent prior to participation in the experiment.

The reflective markers were attached to the subject's left leg with medical proof fabric on the basis of the uOttawa marker set because this enhanced version of the Plug-in-Gait marker set could increase the reproducibility of joint kinematics and kinetics during motion [42]. These reflective markers were placed over the lower lateral surface of the thigh, the lateral and medial epicondyle of the knee, the lower shank, the lateral and medial malleolus, heel, and the first and fifth metatarsal head, respectively. As the measurements along the mid-sagittal axis were found to be representative for the fascicle measurements both at rest and in the contracted state [10], the custom-designed flat probe was secured steadfastly on the mid-belly of GM with the bandage. The orientation of probe was carefully adjusted to visualize the fascicles from deep to superficial aponeuroses. Enough ultrasound gel was also applied on the region of measurement to fill the gap between the probe and the skin so as to reduce the artificial effect in ultrasound images caused by motion. Before data acquisition, the subjects were instructed to perform the two-legged calf raises freely in the laboratory to facilitate adaptation to the speed, heel height, and the laboratory environment. During data collection, the subject stood on the force platform and repeatedly raised up on their tiptoes with their body in an upright posture. The subjects were instructed to rise onto their toes as high as possible and followed a rhythm of 1 Hz produced with an electronic metronome. The subjects raised and lowered their heels each for approximately 1 second, which was similar to the previous studies [35, 43]. The examination was repeated three times with a rest of 1 minute between two consequent trials, and each trial lasted for about 20~30 seconds.

2.3. Data Analysis. The architectural changes in the muscle and tendon were analyzed together with the ankle plantar-flexion angle. The plantar-flexion angles of the ankle were calculated by the obtained spatial data of the reflective markers. The length of GM muscle-tendon unit (MTU),

L_{MTU}, was estimated from the joint angular data and the shank length with the model of Hawkins and Hull [44]. As shown in Figure 2, PA was defined as the angle of fascicle to deep aponeurosis, and FL was defined as the length along the fascicular path from the superficial to deep aponeuroses. In cases in which the fascicle extended off the ultrasound image, the length of the fascicle was estimated by extrapolating both the visible path of fascicle and the aponeuroses in the image linearly. According to the definitions, the PA (α) and FL (L_{Fas}) of GM were automatically extracted from the B-Mode images by applying a number of image processing techniques [25, 26, 39, 40]. The FL and PA obtained with the automatic methods were visually examined for guaranteeing the measurements of muscle architecture. Finally, the Achilles tendon length was calculated by using the MTU length (L_{MTU}), the FL (L_{Fas}), and the PA (α):

$$L_{\mathrm{Ach}} = L_{\mathrm{MTU}} - L_{\mathrm{mus}} = L_{\mathrm{MTU}} - L_{\mathrm{Fas}} \cdot \cos(\alpha). \quad (1)$$

The joint torque can be calculated with the GRF and kinematic data through inverse dynamics [41]. Because the moment arm length of Achilles tendon, M_{A}, has been reported to be a function of ankle joint angles [45], the Achilles tendon force was estimated from the ankle joint torque T_{Ankle} and the moment arm length of Achilles tendon:

$$F_{\mathrm{Ten}} = \frac{T_{\mathrm{Ankle}}}{M_{\mathrm{A}}}. \quad (2)$$

The relative contribution of force developed by the GM to the Achilles tendon force was assumed to be equal to the relative physiological cross-sectional area (PCSA) of the GM within all plantar flexors [23]. The GM PCSA takes up 15.4% of the total PCSA among all plantar flexors [32]. The GM muscle force can then be calculated with

$$F_{\mathrm{GM}} = \frac{(0.154 * F_{\mathrm{Ten}})}{\cos(\alpha)}. \quad (3)$$

The regression coefficient (slope) of the muscle force-length was then calculated as the recruited muscle stiffness in calf raises. Moreover, as the range of plantar-flexion ankle angle in humans has significant variations in the activities of daily life [46, 47] and the ankle plantar-flexion range is usually below 25° during walking [48, 49], the changes of muscle and tendon within 25° plantar-flexion ankle angle were examined between the male and female subjects.

2.4. Statistical Analysis. Values were presented as mean (SD). One-way analysis of variance (ANOVA) was used to test the effect of gender on the height, body mass, BMI, muscle force, tendon force, FL, PA, and tendon length, respectively. The linear regression analysis was employed to describe the relationship between the FL and muscle force and between the tendon length and tendon force. Pearson product-moment correlations (r) were calculated to measure the correlation. Student's paired t-test was applied to check the differences between the male and female groups for the changes in FL, PA, and tendon length. Moreover, the regression coefficient (slope) and area of force-length relationships between the male and female subjects were examined with Student's paired t-test. The linear regressions analysis was also implemented to verify the relationship between the slope and body mass for both genders. In each test, the level of significance was accepted if $P < 0.05$. As well, Cohen's d effect size was calculated as an indicator of the magnitude of the difference between groups, considering large effect sizes as clinically relevant differences (i.e., $|d| > 0.8$) [50].

3. Results

During calf-raise exercises, the FL ranged from 74.7 (6.7) mm to 35.0 (6.7) mm, while the range of PA was from 18.3 (2.8)° to 36.8 (6.4)°. And the average difference in tendon length was 26.1 mm. The FL of the females and males was 73.0 (5.3) mm and 76.4 (7.9) mm at rest (Cohen's $d = 0.51$), while the PA was 17.4 (2.2)° and 19.2 (3.2)° (Cohen's $d = 0.66$), respectively. Although the PA and length of fascicle and tendon were larger in males, these gender differences were not significant (all $P > 0.05$). In contrast, compared with the female subjects, the peak plantar flexor moment and force of their counterparts were significantly larger (torque: male = 48.6 (8.6) Nm, female = 30.6 (5.5) Nm, Cohen's $d = 2.5$; force: male = 911.1 (163.9) N, female = 581.5 (111) N, Cohen's $d = 2.35$; all $P < 0.001$).

The length change of fascicle and tendon was almost the same between the genders when the plantar-flexion angle was changed by 25° (Table 1), while the change of PA for the men was 3° larger ($P = 0.06$, Cohen's $d = 1.12$). As shown in Figure 3, the difference in PA between the males and females became larger with the change of plantar-flexion angle. This suggests that more fibers would be arranged in parallel within a given CSA for men when performing the calf raises exercises. The pattern of fascicle change was also observed to be different, particularly in the initial part of calf raises, though the range of FL was almost the same between the genders (Figure 4). The FL of men was kept nearly constant at the initial part of calf raises, while the fascicle of women shortened by 2.3 mm. This would contribute to the significant difference in peak plantar flexor moment and force that was required to support their different body mass for both genders (all $P < 0.001$).

Figure 5 shows the force-length relationships of the GM muscle and tendon within the plantar-flexion angle change of 25° for both the males and females. The areas made by force-length relationships were significantly larger for men for both the muscle and tendon (muscle: $P = 0.041$, Cohen's $d = 1.22$, Figure 5(a); tendon: $P = 0.049$, Cohen's $d = 1.17$, Figure 5(b)). This implied that more mechanical energy was generated and dissipated by men when performing the calf raises exercises. The tendon length was not significantly linearly correlated with the tendon force during the plantar-flexion exercises ($r = 0.37$ (0.19)). On the other hand, the linear correlation between the FL and muscle force was significant for both the genders (male: $r = 0.87$ (0.04), all $P < 0.001$; female: $r = 0.86$ (0.07), all $P < 0.001$). Figure 6 shows the typical correlation between the FL and muscle force for one male and one female subject during experiments. Moreover, although the difference in the slope

Table 1: The architectural changes of muscle and tendon within the plantar-flexion ankle angle change of 25°.

	Female	Male	Total
Fascicle length (mm)			
Change ($P = 0.51$, *Cohen's* $d = 0.36$)	24.2 (4.1)	25.4 (2.3)	24.8 (3.2)
Pennation angle (°)			
Change ($P = 0.06$, *Cohen's* $d = 1.12$)	8.0 (2.2)	11.2 (3.4)	9.6 (3.2)
Tendon length (mm)			
Change ($P = 0.39$, *Cohen's* $d = 0.19$)	10.7 (3.3)	11.2 (1.7)	10.9 (2.5)

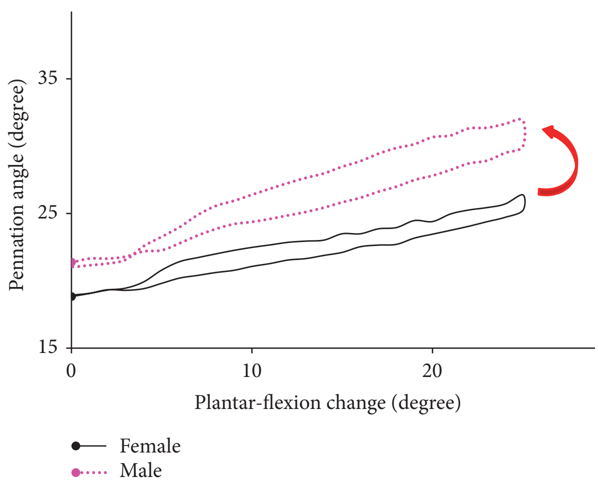

Figure 3: The average pennation angle change for seven male subjects and seven female subjects within the plantar-flexion angle change of 25°. The arrow in red indicates the direction of raising and lowering subjects' heels.

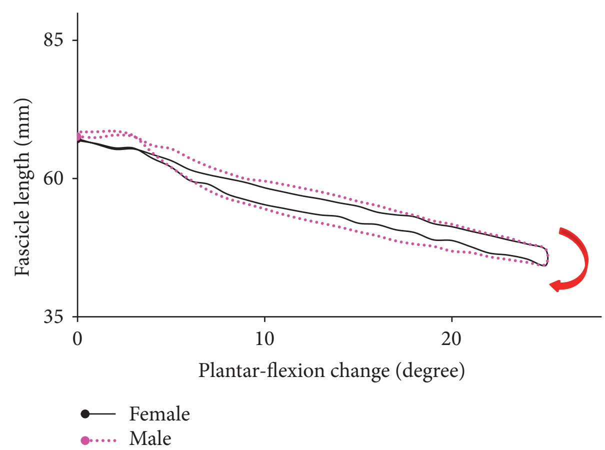

Figure 4: The average fascicle length change for seven male subjects and seven female subjects within the plantar-flexion angle change of 25°. The arrow in red indicates the direction of raising and lowering subjects' heels.

of the relationship was not significant ($P = 0.12$), the regression coefficient (slope) of the males (slope = 1.28 (0.34) N/mm) was larger than that of the females (slope = 0.96 (0.37) N/mm). Also, large effect size (Cohen's $d = 0.90$) was found for the regression coefficient. After normalizing to the body weight, there is almost no difference in the slope between the genders (male: normalized slope = 0.017 (0.04); female: normalized slope = 0.018 (0.05); $P = 0.62$, Cohen's $d = 0.02$). Furthermore, the slope was highly correlated with their body mass for the females ($r = 0.90$), whereas there is a weak linear correlation between the body weight and slope for the males ($r = 0.38$). When only using the slope of the male subjects with BMI less than 25 kg/m^2, the linear correlation became more correlated ($r = 0.82$).

4. Discussion

We have investigated the effect of gender on the architectural changes of GM muscle and tendon undergoing the cyclic two-legged calf raises exercises. The main finding of this study was that the pattern of GM fascicle change was different at the initial part of calf raises between the men and women (Figure 3), though no significant difference in the length change of GM fascicle and tendon was observed between them. It has been reported that body weight and physique emerged as a significant predictor of muscle strength of the ankle plantar flexors between the genders [3, 51] and might be affecting the gait pattern [52, 53] and muscle endurance [54]. Since the male participants in this study were approximately 25 kg heavier than the female participants, the difference in GM fascicle change can be partly attributed to the body weight difference between the genders. In addition, a greater regression coefficient between the FL and muscle force (female: 0.96 (0.37) N/mm; male: 1.28 (0.34) N/mm) was observed for the males in calf raises, implying that higher muscle stiffness for the men was recruited for supporting the body weight economically.

The changes of fascicles were observed to be different between the genders (Figure 3). The fascicle of the female subjects shortened immediately at the initial part of calf raises, while that of the male subjects kept nearly constant. As both the raising and lowering portions took approximately 1 second during calf raises, this result inferred that shortening velocity of the males was slower than that of the females at the initial part of calf raises under the same ankle angular speed. A lower shortening velocity would be beneficial for the mechanical power output at the initial part of calf raises

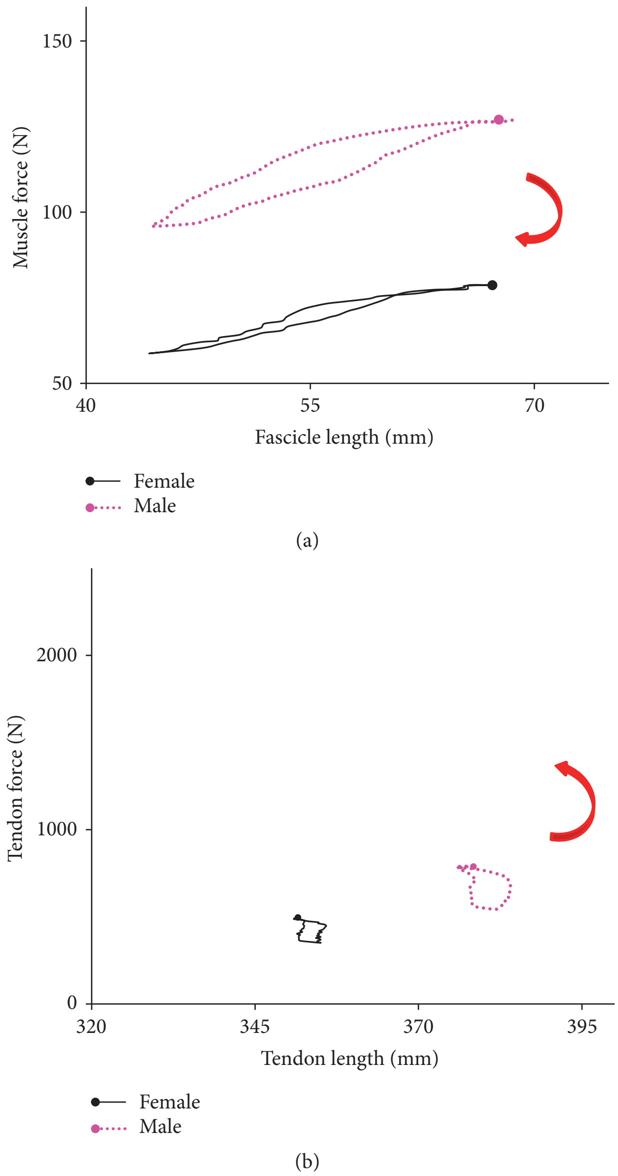

Figure 5: The force-length relationships of muscle and tendon. Average of seven male subjects and seven female subjects within the plantar-flexion angle change of 25°: (a) the relationship between muscle force and fascicle length; (b) the relationship between tendon force and tendon length. The arrows in red indicate the direction of raising and lowering subjects' heels.

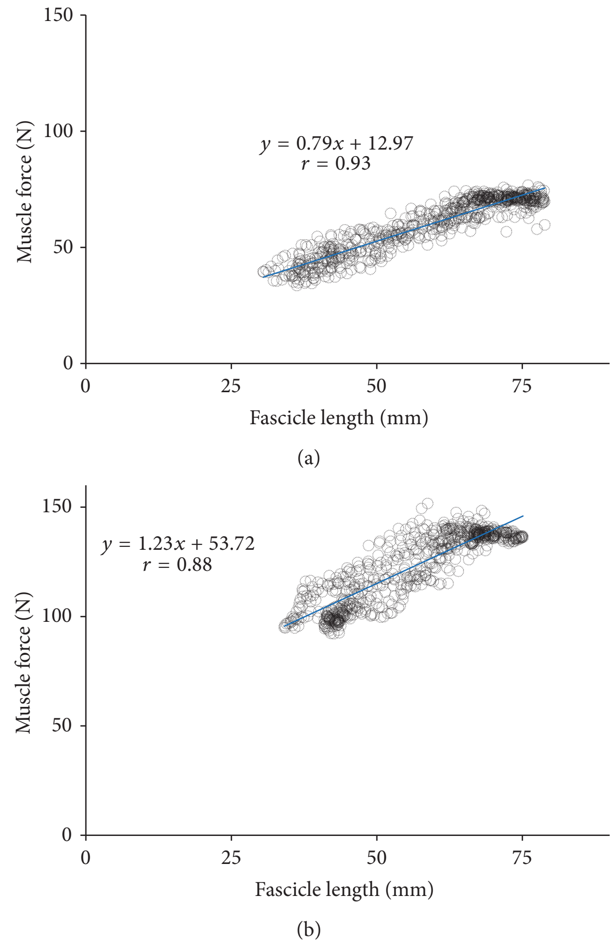

Figure 6: The cross-correlation between fascicle length and muscle force during calf raises: (a) the cross-correlation between fascicle length and muscle force for one typical female subject; (b) the cross-correlation between fascicle length and muscle force for one typical male subject.

because it operated around the plateau region of the force-length curve. According to a previous study in gait analysis, fascicle shortening at the time of peak force production was shifted to much slower velocities when switching from a walking gait to a running gait at the same speed, resulting in a substantial increase in peak muscle force and an increase in GM power output [22]. In the squat jump, the counter-movement jump, and drop jump, the fascicles also worked in the relatively low-shortening velocity region, especially in the late push-off phase, which enables the fascicles to generate relatively high force according to the force-velocity relationship [23, 24]. Our findings together with the previous results suggest that the GM muscle of men produces high forces at a relatively optimal level with small amounts of work and high efficiency at the initial part of calf raises. Since the body weight and fat-free mass have been reported to be one of the important contributors to jump performance and strength at all lower limb joints [3, 15], this difference in fascicle changes might be attributed to the heavier body mass of men. The acceleration of the leg into the swing and forward kinetic energy of the trunk were mainly dependent on the ankle plantar flexor work in the stance phase of walking [22, 33]. And an increase of vertical velocity of the mass center of the body during the late push-off phase required a high mechanical power output of plantar flexors [23]. Therefore, the little change of FL at the initial part of calf raises would enable the muscle to operate near its highest force region, serving to generate higher mechanical power output of plantar flexors to support the heavier body weight of men.

The fascicle and tendon exhibited the viscosity behavior during the repeated two-legged calf-raise exercises in the present study (Figure 5). The MTU exhibited viscoelastic properties for efficiently utilizing the outcome of muscle contraction during human movement [24, 55], which can be ascribed to the elasticity of cross-bridge, the actin, and possibly the myosin filaments. The viscoelastic characteristics of MTU play a significant role in stretch-shortening cycles in which an eccentric action is immediately followed by a concentric action of working muscles. Tendon acted as an energy storing spring by springing in the cyclic plantar flexion, to contribute a considerable amount of energy to the total mechanical work performed [23]. The area within the tendon force-length curve, that is, hysteresis, was the energy loss mainly due to converting mechanical work into heat, while the area under the descending limb of the force-length curve represented the energy recovered from tendon [56, 57]. Although higher mechanical power output for the men (Figure 5(a), $P = 0.041$) was generated during calf-raise exercises, the significantly larger hysteresis area of the tendon force-length curve in the male subjects that indicated more energy was dissipated in the cyclic calf raises exercises (Figure 5(b), $P = 0.049$). This observation of greater hysteresis in males was in agreement with the finding of a previous investigation reported by Kubo et al. [56]. This can partly explain the muscle endurance difference between the genders when performing stretch-shortening cycle exercise [5, 51].

The tendon was elongated slightly under the lower Achilles tendon force. When tendons were forcibly stretched, they responded in a nonlinear fashion, with an initial curvilinear toe region followed by an approximately linear region [58]. The elongation of the tendon increased in a curvilinear pattern, implying that in vivo tendons may exhibit creep [59]. During walking, the elongation of triceps surae elastic structures can reach up to 4%, which operates in the toe region of tendons [1]. An interesting finding of this study was that no significant linear correlation was observed between the tendon force and tendon length, which may suggest that the tendons operated in the curvilinear toe region during calf-raise exercises. On the other hand, the muscle force was significantly correlated with the FL. The regression coefficient (slope) of the muscle force-length relationship for the men compared with the women was larger, while the slope of the men became almost the same as that of the women after normalized to the body weight. Some previous studies showed that both the passive and active muscle stiffness in women was lower than that in men [6, 60, 61]. Muscle stiffness difference between genders was likely to be attributed to a gender difference in the viscoelastic properties of the muscle [61]. It has been reported that the muscular system of males was more efficient in resisting changes in its length [6], implying stiffer muscle involved in contraction. Therefore, the larger slope of the male subjects in this study may suggest stiffer muscle recruited in calf raises. Moreover, muscle mass and body weight could further explain the majority of the gender effect in leg stiffness and muscle stiffness [16, 31, 60, 62]. Male subjects recruited higher leg stiffness to drive their heavier body mass than the lighter female subjects during performing functional tasks [31, 62]. As active muscle stiffness contributed to leg stiffness [31], the larger slope observed in the male subjects may imply that males recruited stiffer muscle to support the heavier body weight of men economically in calf raises. Body mass was also an important contributor to the between-subject difference in stiffness [16], which can explain the strong correlation between the body weight and slope for the females ($r = 0.90$) in the present study. However, the slope was not highly correlated with the body mass for the males ($r = 0.38$). Body fat has been demonstrated to be significantly positively correlated with BMI [63, 64]. The BMI of 25 kg/m^2 in men and 23 kg/m^2 in women has been suggested as diagnostic screening cut-offs for obesity [64]. Thus, the observed nonsignificant correlation between the body weight and slope might be partly attributed to the higher BMI in the males in this study (male: 24.8 (3.2) kg/m^2; female: 20.1 (2.7) kg/m^2). When only using the slopes for the male subject with BMI less than 25 kg/m^2, the correlation became more correlated ($r = 0.82$). Further study is required to explore the influence of body mass and body fat in more detail by recruiting more subjects.

The changes and values of FL and PA measured with the proposed method were consistent with the previous reports [9, 10, 58, 65]. In this experiment, the mean FL at rest was 74.7 mm and was reduced to 35.0 mm during calf raises, while the range of average PA was from 18.3° to 36.8°. The average length of GM fascicle for healthy subjects was 78 mm as the knee was fully extended and the ankle reached 15° dorsiflexions [65]. With the knee fully extended and the ankle fixed at its neutral position, the fascicles reportedly shortened to 30~34 mm during MVC, while the PA increased to 35~40° [58]. Both the PA and FL in the males were found to be larger than those of the females in this study, though the differences were not significant ($P = 0.23$ and $P = 0.37$, resp.). Greater PA in males is well agreed in previous literature [15–17, 19, 20]. However, there are contradictive results regarding the FL in different genders [14, 15, 17, 19]. Alegre et al. [15] reported longer fascicles of GM muscle in men. In contrast, women were reported to have larger FL in GM muscle [14, 17]. Previous studies found that training can induce the necessary adaptation of fascicle geometry [12, 66]. The gender-specific difference in GM fascicle depended on the training or regular exercise mode [19]. The habit of routine exercise might contribute to the variance in FL in both genders. Thus, the gender might not be the primary determinant of GM fascicle length. In future, more subjects should be recruited to validate this assumption.

It should be noted in this study that the slope of the force-length relationship was not the actual muscle stiffness. The torque that was subtracted by the torque of relaxed conditions was used to estimate the active muscle stiffness [67]. Thus, the regression coefficient (slope) in the present study only indicated the average muscle stiffness that was the sum of passive and active muscle stiffness recruited in calf raises. However, this factor did not affect the main results of this study. Moreover, there may be fascicle curvature and the heterogeneity of changes in FL within the muscle. The fascicles were identified from the mid-belly of the GM muscles in the present study. Since fascicles are almost straight at rest and become slightly curved with the increase in contraction level and decrease in muscle length, resulting in only ~6% underestimation in FL during maximum voluntary contraction (MVC) [68], which is thus a minor factor on the measurement of FL in the calf raises exercise. The FL was almost uniform throughout the muscle at both rest and submaximal isometric contractions [69]. Narici et al. [10] also reported that the measurements along the mid-sagittal axis were representative for the measurements of fascicles at both relaxed and maximal isometric contracted conditions. Therefore, we believe that the measured fascicles in this study could represent the changes of all fascicles in the GM muscle.

There are still several limitations in this study. Firstly, the influence of physical activity was not well taken into consideration in the present study. All subjects recruited in this study are only required not to exercise regularly or receive any specific physical training. Different training modes have been proven to induce the various adaptation of fascicle geometry [19] and might be affecting behaviors of fascicles and the strength of the ankle plantar flexor during calf raises. The effect of physical activity should be further investigated in future studies by using physical activity score and a cut-off score to clearly establish both groups as equally physically active in the experiment. Another limitation of this pilot study was that our measurements were restricted to the GM muscle, which is just one of the calf muscles responsible for plantar flexor. Also, this study has a relatively small number of participants. Future studies, therefore, should be conducted with a larger sample in each group of sex, other calf muscles, and other movements involving plantar flexion, such as walking and hopping, allowing the better understanding of gender-specific characteristics in plantar flexor muscles.

In conclusion, sonomyography can examine the dynamic geometric properties of muscle and tendon, providing valuable information in the understanding of the gender-specific characteristics during motion. The results of this pilot study indicate that the architectural changes of GM muscle for males allowed their muscles to generate a higher mechanical power output during calf-raise exercises. Moreover, the muscle stiffness of the males recruited in the calf raises exercises was larger than that of the females. These findings suggest that the muscle of men might operate to provide higher output to support their heavier body weight economically. The body mass might be one of the factors in the behavior difference of muscle and tendon between gender. Future research is necessary to determine the influence of body weight on muscle activity during normal gait and their clinical/physiological implications for joint stability and muscle and tendon injury risk.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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Research Article

A Study on the Improvement of Walking Characteristics of the Elderly with Vibration Stimuli Applied to the Tibialis Anterior Tendon

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The purpose of this study was to identify the gait pattern of the elderly with aging and to analyze the elderly's gait changes by the focal tendon vibratory stimulation. A total of 10 elderly males and 15 young adult males participated in this study. Using 3D motion analysis, we analyzed that difference between the elderly gait and young adults gait and the changes of the elderly gait by applying focal vibratory stimuli. As a result, specifically in the early stance, the elderly's gait was more flexed and the lower extremity extensors of the elderly worked harder. When the focal vibratory stimuli were applied, joint angle of the elderly was induced to that of the young adults. There was a reduction in demands for supporting bodies and progressing gait in the stance phase. This means that focal vibratory stimuli affect the gait of the elderly. Also, the changes of the gait of the elderly varied according to the characteristics of the focal vibratory stimuli. This implies that the activity of the motor may be dependent on vibratory stimuli characteristics.

1. Introduction

Walking is one of the most important activities in daily life. Walking is a learned activity in which the moving body is supported successively by one leg and the other [1]. Walking is conducted almost unconsciously, but biomechanical subtasks, such as body support, forward propulsion, and maintaining postural stability, must be successfully performed [2]. Successful biomechanical subtasks require complex and well-coordinated activity of lower extremities muscles. However, for elderly experiencing neurological and physiological changes due to aging, the activity of these lower extremities muscles will be diminished. Therefore, maintaining walking abilities is very important for the elderly.

For this reason, a lot of studies have been conducted on the gait of the elderly to date. The gait of the elderly has the following characteristics: a decreased walking velocity [3], a shorter stride length [4], a reduced force at push-off [5], a flatter foot landing pattern at heel-strike [4], and a decreased range of the motion of the lower limbs [6]. Using the results of the studies that characterize the gait of the elderly, applied research on assistance, improvement, and rehabilitation of the elderly gait is needed.

There is a focal muscle tendon vibratory stimulation that can affect neurological and physiological changes in the elderly. There are a number of studies that have shown that focal muscle tendon vibratory stimulation stimulates somatosensory receptors, resulting in responses to the muscular system [7–9] and the central nervous system [10, 11].

As such, there have been a number of studies using vibration giving helpful results. However, they have some limitations about vibration characteristics, and it is much harder to find studies that are closely related to the elderly. In specific, they do not consider the characteristics of vibration (frequency, intensity) and the individual differences against the vibration. Another limitation is that the biomechanical analyses were not applied to the elderly gait.

The purpose of this study was to identify the gait pattern of the elderly with aging and to analyze the elderly's gait changes by the focal muscle tendon vibratory stimulation.

2. Methods

2.1. Subjects. 15 young adult males (age: 26.4 ± 1.5 year, height: 171.6 ± 2.7 cm, weight: 66.1 ± 5.7 kg) and 10 elderly (age: 70.8 ± 2.8 year, height: 164.1 ± 6.7 cm, weight: 66.1 ± 8.0 kg) participated in this experiment. All subjects had no diseases in their nervous and musculoskeletal system and were capable of gait independently without any assisting devices. This study was approved by Chonbuk National University Institutional Review Board (IRB File No. JBNU 2015-06-012).

2.2. Equipment. A small scale linear actuator (0934, Samsung Electro-Mechanics, Korea) was used to apply vibration to the tibialis anterior tendon. In addition, a function generator was used to adjust the frequency and intensity of vibration. To capture the gait, a total of 15 active infrared emitting diode markers were attached to each major joint according to Halen-Hays marker set. To collect the infrared light, a total of 3 position sensors (Optotrak Certus, Northern Digital Inc, Canada) were used. To measure the ground reaction force, a total of 4 force platforms (Bertec Co., Ltd, USA) were used.

2.3. Vibratory Stimuli Application. To investigate the changes of the elderly gait in the lower extremity according to the characteristics of the applied vibratory stimuli, the frequency and intensity of the vibration were adjusted and vibration perception threshold was measured on the vibration frequency in the tibialis anterior tendon. Based on measurement result, vibration is applied to the tibialis anterior tendon during gait.

By combining the stimulus site, vibration frequency, and perception threshold, vibratory stimulus condition is set. No vibration is applied, and nonstimulation appeared. Vibration at perception threshold intensity (threshold vibration) and 180 Hz of frequency are applied to tibialis anterior tendon, and TAT_180 Hz_Theshold or T180 Hz_Treshold appears. Vibration at 80% of threshold (subthreshold) and 180 Hz of frequency are applied to tibialis anterior tendon, and TAT_180 Hz_Sub Threshold or T180 Hz_Sub Threshold appears.

2.4. Protocol. The subjects walked on flat ground at least 10 m at preferred speed. The focal vibratory stimuli were randomly applied. All the subjects walked 3 times per each stimulus condition.

2.5. Analysis. To investigate the profiles of the gait in the lower extremity, a 3D human musculoskeletal system modeling and analysis software (SIMM, MusculoGraphics Inc., USA) was used. The stance phase was set as the period for analysis. The joint angle, joint moment, joint power, and support moment of a lower extremity during a stance phase were chosen as the analysis parameters.

The time history profiles of the angle, moment, power, and support moment are illustrated as the result. Then, our analysis concluded that the profiles of the elderly gait differ from young adults and we analyzed the change in the elderly gait with applied focal vibratory stimuli characteristics.

To analyze improvement effect about joint angle by focal vibratory stimuli, we analyzed the following: (1) mean of the difference between the elderly with nonstimulation and young adults, (2) mean of the difference between the elderly with 180 Hz vibration and young adults, (3) mean of the difference between the elderly with 190 Hz vibration and young adults, and (4) mean of the difference between the elderly with 200 Hz vibration and young adults. As for support moments and joint power, we analyzed the means of time averages of support moments and power during double limb stance phase and single limb stance phase [12]. We also performed paired T-test ($p < 0.05$) to examine statistical significance using SPSS 20 (IBM Corp, USA).

3. Result

3.1. Level Gait in the Elderly and Young Adults

3.1.1. Ankle Joint Profiles. Figure 1 shows the ankle joint profiles during the level gait of the two groups. In the flexion angle, the young adults showed plantar flexion and dorsiflexion, while the elderly only showed the dorsiflexion, of which the angle was much greater than that of the young adults. At that moment, both groups showed the same phase. But, the elderly showed the dorsiflexor moment and plantar flexor moment, which were smaller than those of the young adults. In the power, at the loading response phase (LR), phase change timing and magnitude were slightly different from those of the young adults. Also, after 60% of the stance phase, the elderly showed that the phase change was clearly different from that of the young adults.

3.1.2. Knee Joint Profiles. Figure 2 shows the knee joint profiles of the two groups. In the flexion angle, both groups performed level gait with flexion. But, the elderly showed greater flexions compared to the younger group. At that moment, the moment phase change patterns were the same in the two groups. But, the timing of change was different. The elderly showed a higher extensor moment at 10~60% of stance phase and a lower flexor moment at 60~80% of stance phase compared to the young adults. In the power, likewise, the phase changes of the power of the two groups were the same. But, the timing of the change was different. And at 10~60% of stance phase, the elderly showed negative powers and positive powers which were higher than those of the young adults. Then, there were lower positive powers and higher negative powers.

3.1.3. Hip Joint Profiles. Figure 3 shows the hip joint profiles of the two groups. In the flexion angle, the elderly showed a much higher flexion and very little extension. Moreover, the timing of changing from flexion to extension differed from that of the young adults. This means that the elder group performed level walking with their hip joint flexing; the gait period is different from that of the young adults. At that moment, the elderly showed a greater extensor moment compared to the young adults. Also, the timing that the extensor moment changed to a flexor moment was different from that of the young adults. In the power, the elder group

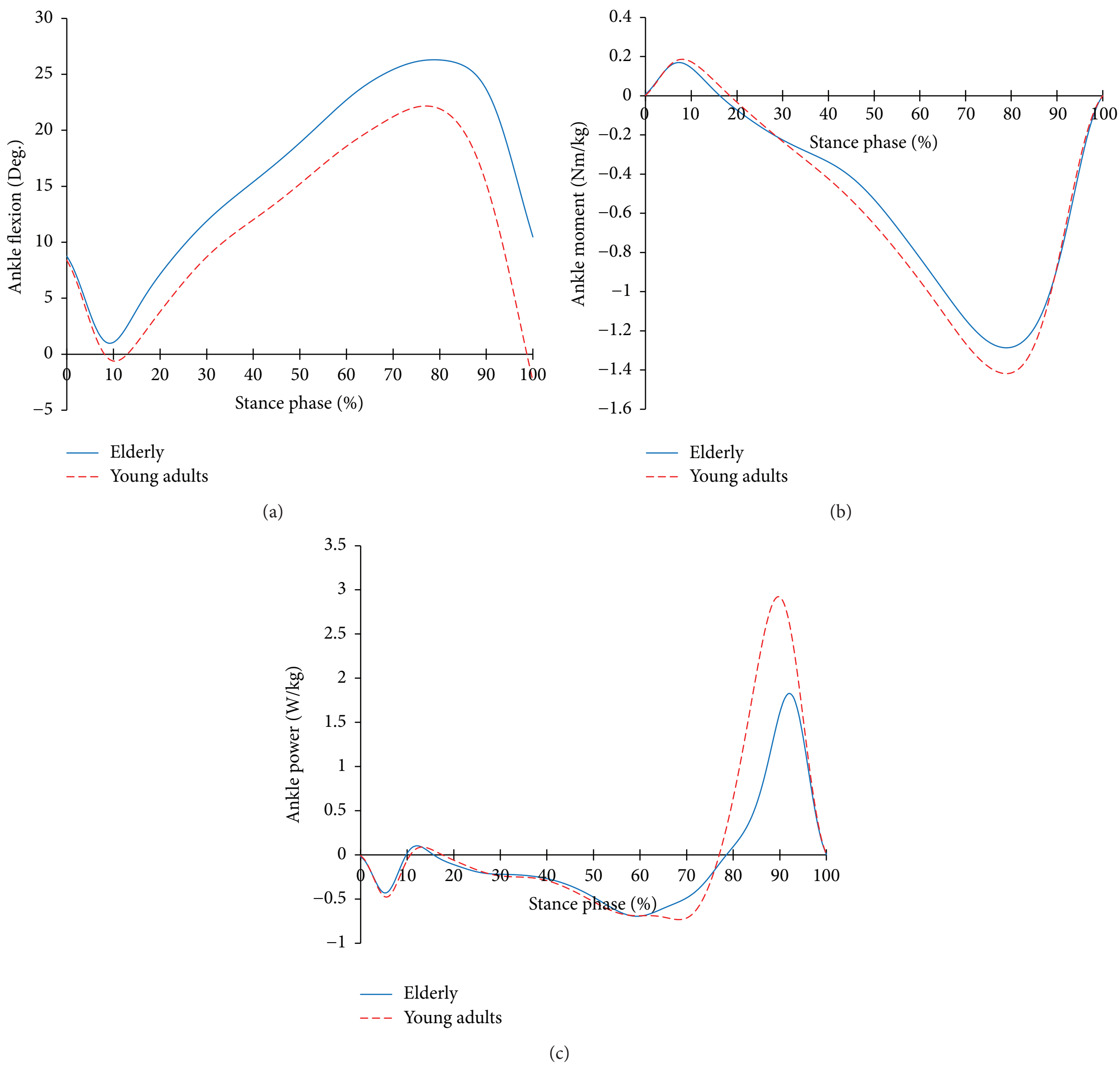


Figure 1: Ankle joint profiles in the elderly and young adults. (a) Ankle joint angle; (b) ankle joint moment; (c) ankle joint power.

showed energy absorption (negative power) at 0~10%. Then, they showed larger energy generation (positive power) and energy absorption compared to the young adults. As with the angles and the moments, the timing of changing phases was different from those of young adults.

3.1.4. Support Moment Profiles. Figure 4 shows the support moment profiles of the two groups, while Figure 5 shows the support moments of both groups normalized to the peak of their support moments, respectively. In Figure 4, the support moment is higher until reaching 80% of the stance phase and then lower after exceeding 80% of the stance phase than young adults. In Figure 5, the features are even more apparent. After 65% of the stance phase, the normalized support moment of the elderly is clearly lower than that of the young adults.

3.2. Level Gait in the Elderly during Tibialis Anterior Tendon Vibratory Stimuli

3.2.1. Ankle Joint Profiles during Tibialis Anterior Tendon Vibratory Stimuli. The profiles of the ankle joints differing due to the changes in the tibialis anterior tendon vibratory stimuli frequency and intensity are shown in Figures 6–8. As for the angles, both the reduction of dorsiflexion at 0~15% of the stance phase and the increase in dorsiflexion after 65% of the stance phase happened under focal vibratory stimuli. At that moment, the slight reduction in the dorsiflexor moment at 0~15%, the reduction in the plantar flexor moment at 20~65%, and the increase in the plantar flexor moment after 65% of the stance phase all happened under focal vibratory stimuli. In the power, the reduction in the negative power and positive power at 0~15% and the increase in the negative power at

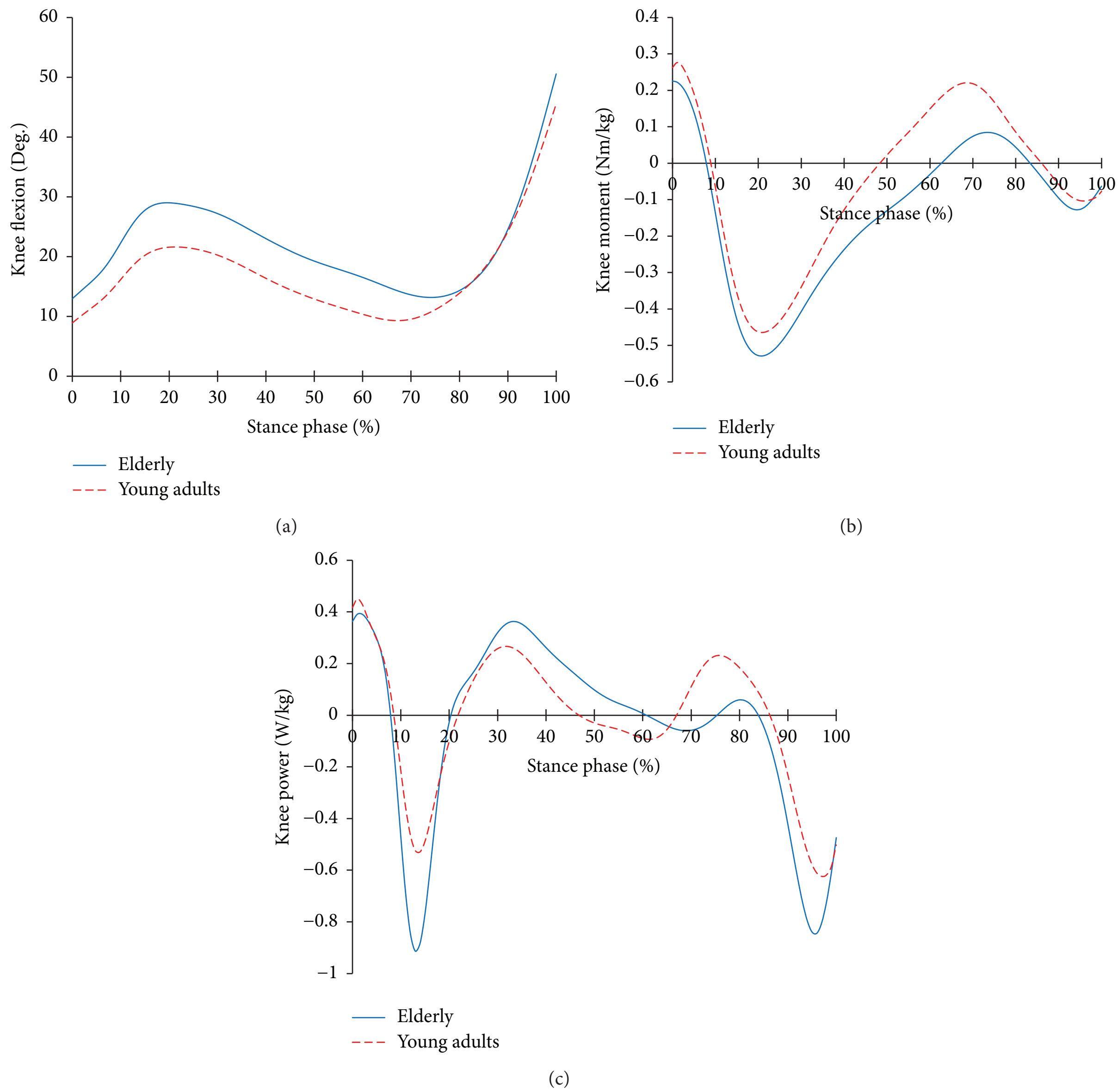


Figure 2: Knee joint profiles in the elderly and young adults. (a) Knee joint angle; (b) knee joint moment; (c) knee joint power.

60~80% both happened under focal vibratory stimuli conditions. Except for the 180 Hz, an increase in the positive peak power after 80% of the stance phase was observed.

3.2.2. Knee Joint Profiles during Tibialis Anterior Tendon Vibratory Stimuli. Figures 9–11 show the profiles of the knee joints with the frequency and intensity of tibialis anterior tendon vibratory stimuli. All focal vibratory stimuli resulted in less flexion at 15~40% and increase of flexion at 60~85%. At these moments, the flexor moment increased as the frequency became higher. And, at 35–65%, all focal vibratory stimuli resulted in an increase of the extensor moment. In the power, the positive power and the negative power reduction in the loading response phase, fast phase change timing into positive power, and the reduction of the negative power in the preswing phase happened in all focal vibratory stimuli conditions.

3.2.3. Hip Joint Profiles during Tibialis Anterior Tendon Vibratory Stimuli. The profiles of the hip joints differing due to the changes in the tibialis anterior tendon vibratory stimuli frequency and strength are shown in Figures 12–14. Except for 180 Hz, the flexions of the hip joints at 15~65% (from mid-stance phase to terminal stance phase) at 190 Hz and 200 Hz both decreased. And, the extension of the hip joint at the end of the preswing phase slightly increased. In that moment, all vibratory stimuli resulted in a reduction of the extensor moment at 15–50% and a reduction of the flexor moment after 65%. In the power, positive power was observed at the loading response phase, unlike the case of nonstimulation condition.

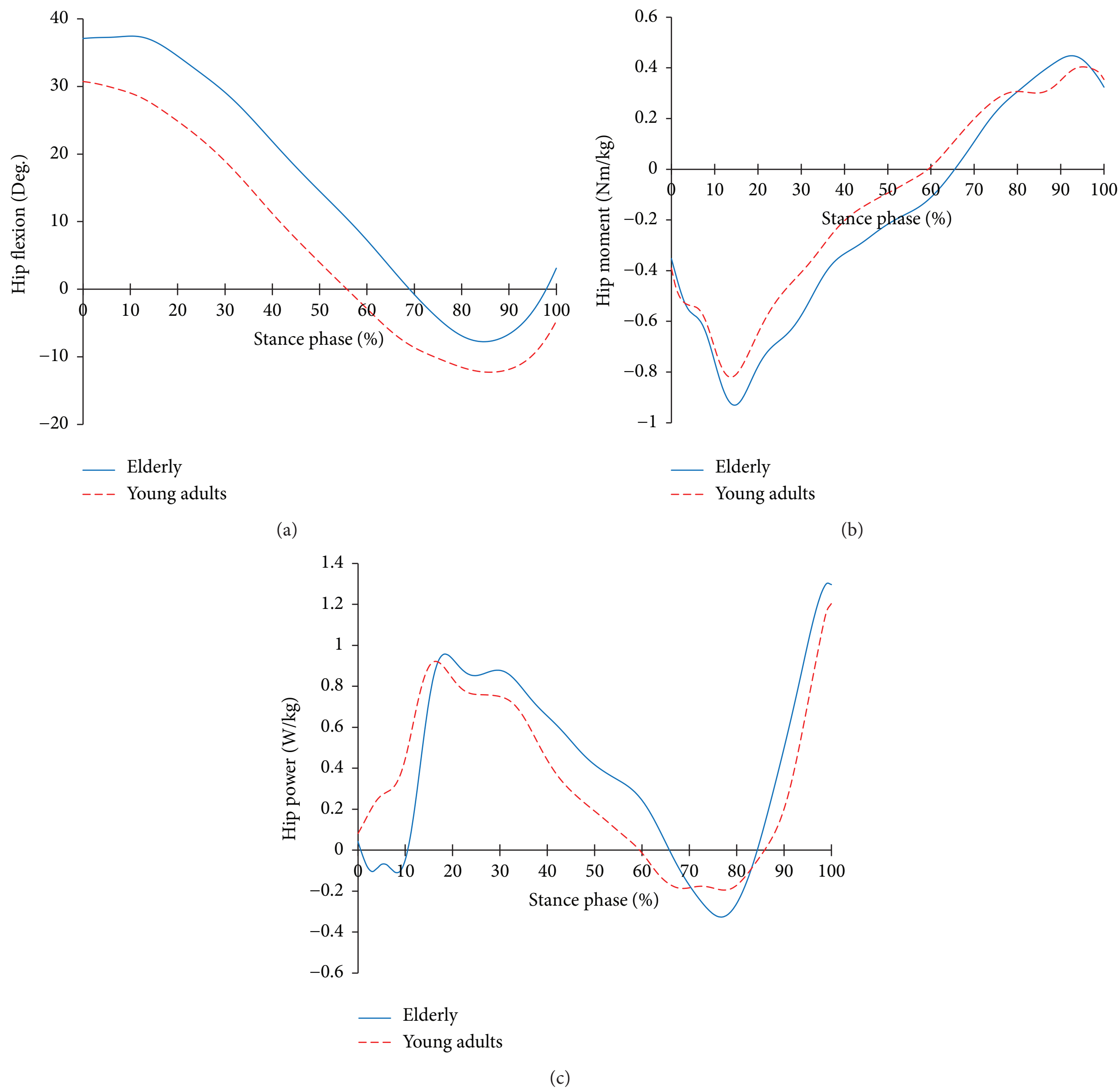


FIGURE 3: Hip joint profiles in the elderly and young adults. (a) Hip joint angle; (b) hip joint moment; (c) hip joint power.

After this, all focal vibratory stimuli conditions resulted in a reduction of the positive power and the negative power from the mid-stance (MSt) to terminal stance (TSt) and a reduction in the positive power at the preswing phase (PSw).

3.2.4. Support Moment Profiles during Tibialis Anterior Tendon Vibratory Stimuli. The variations in the support moments of the elderly according to focal vibratory stimuli are shown in Figure 15. At the early stance, support moments in all focal vibratory stimuli conditions showed that they were lower than those in nonstimulation conditions. And at the late stance, the support moment is slightly higher than that of the nonstimulation condition.

3.3. The Vibratory Perception Threshold of the Elderly in the Tibialis Anterior Tendon. The vibratory perception thresholds were measured according to frequency in the range from 100 Hz to 300 Hz and the results are shown in Figure 16. The most sensitive vibration frequency is 190 Hz, and the vibration threshold rapidly increased at 200 Hz.

The statistical differences of the thresholds measured in the range from 180 Hz to 220 Hz are shown in Table 1. The 180 Hz has a statistical difference of 200 Hz or more frequency except for 190 Hz. And 190 Hz is the same. The 200 Hz is statistically different from all frequencies except for 220 Hz.

3.4. Variation of Kinematic and Kinetic Parameters When the Focal Vibratory Stimuli Applied. The differences in the joint angle profiles of the elderly and young adults according to the vibration frequency were shown in Tables 2 and 3. Table 2 shows the mean difference in threshold intensity. The decrease in the mean difference means that the profiles of the

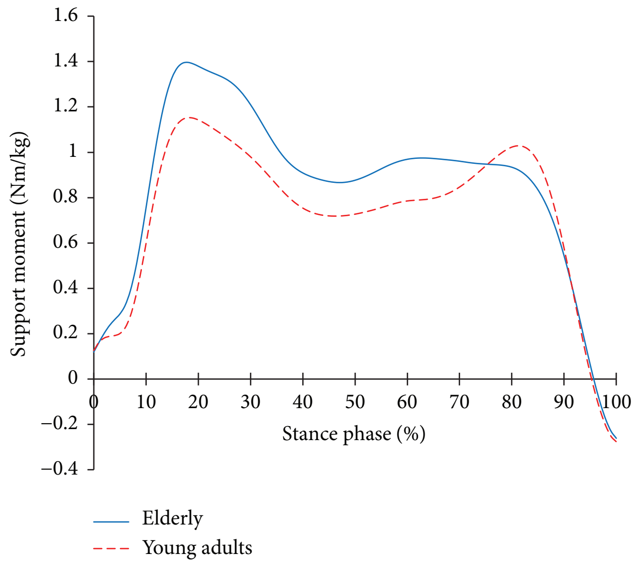


Figure 4: Support moment in the elderly and young adults.

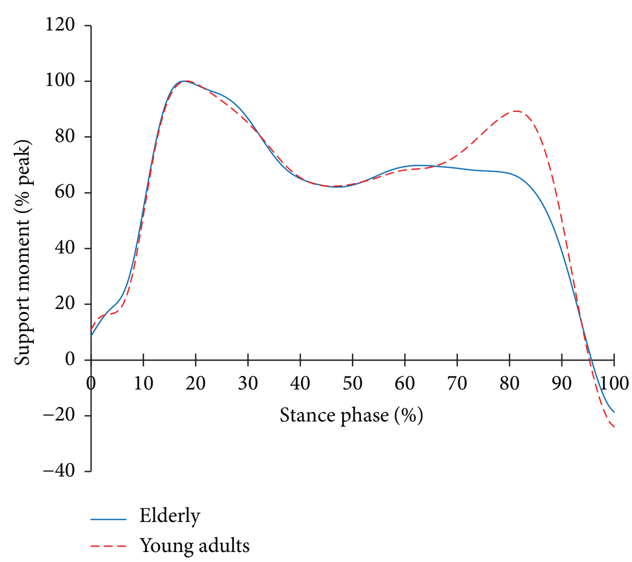


Figure 5: Peak normalized support moments in both groups.

elderly are similar to the young adults', and the results are shown in the stance and substance phases. At stance phase, the mean difference of the ankle angle was 4.31 degrees and the mean differences in the all vibration conditions were higher than that ($p < 0.05$). The same was true for the knee joints, but it was reduced for the hip joints.

For more details, in the loading response (LR), the mean differences in the ankles were reduced, whilst in the knees, they were increased. In the mid-stance (MSt), the mean differences were reduced in all joints. In the terminal-stance (TSt), the mean differences in the ankle joints and the knee joints increased, whilst in the hip joints, they were reduced. These results are almost the same even under subthreshold conditions as shown in Table 3.

Table 1: p-value of the perception threshold with focal vibratory stimuli.

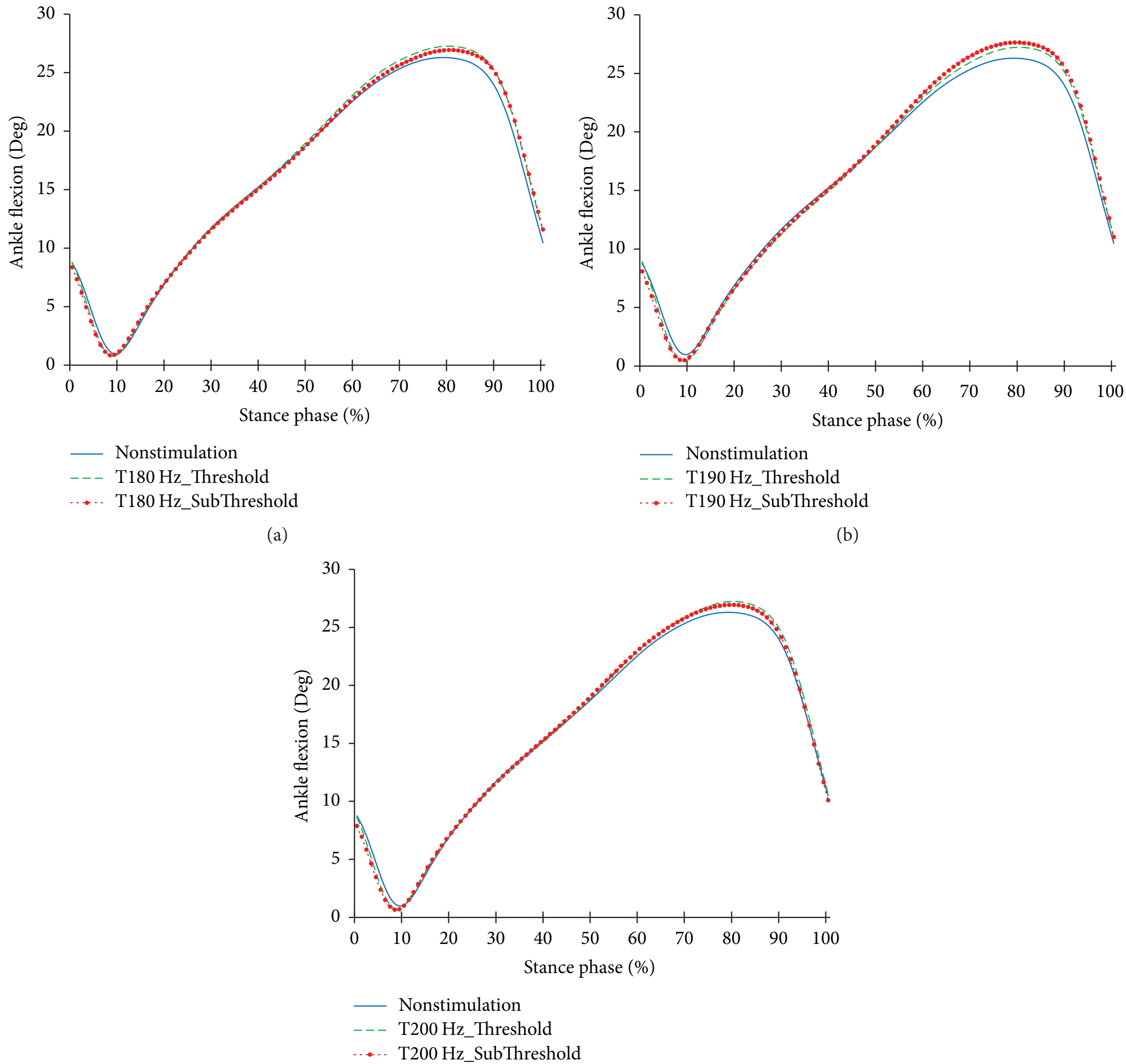
p-value	180 Hz	190 Hz	200 Hz	210 Hz	220 Hz
180 Hz	—	0.075	0.001	0.001	0.008
190 Hz	0.075	—	0.002	0.004	0.002
200 Hz	0.001	0.002	—	0.009	0.079
210 Hz	0.001	0.004	0.009	—	0.362
220 Hz	0.008	0.002	0.079	0.362	—

The means of the support moment and joint power, according to the frequency, were shown in Tables 4 and 5. The support moment and joint power are kinetic parameters for causing movement. Therefore, to consider the functional task of the gait, the mean during single limb support (SS) and double limb support (DS) was analyzed. In particular, power is calculated by taking the absolute value [13].

In Table 4, the elderly's support moment with NS during DS was lower than that of the young adults, whilst that during SS was higher. When the focal vibratory stimuli of the threshold intensity was applied (Table 4), the support moments across all vibratory stimuli conditions increased more than those of the NS conditions of the elderly. On the other hand, the support moments during SS decreased. In the power of the ankle joints, the power of the NS condition of the elderly during DS and SS was smaller than that of the young adults. When the focal vibratory stimuli of the threshold intensity was applied (Table 4), the power during DS except 200 Hz decreased than that of the NS of the elderly, whilst during SS it increased except 180 Hz. In the power of the knee joints, the power of the elderly with NS during DS and SS was greater compared to the young adults. When the focal vibratory stimuli of the threshold intensity was applied (Table 4), the powers across all focal vibratory stimuli conditions decreased more than those of the elderly with NS. In the power of the hip joints, the power of the elderly with NS during DS and SS was greater compared to young adults. When the focal vibratory stimuli of the threshold intensity was applied (Table 4), the powers across all focal vibratory stimuli conditions decreased more than those of the elderly with NS. These results are almost the same even under subthreshold conditions as shown in Table 5.

4. Discussion

4.1. Level Gait in the Elderly. During the loading response, the dorsiflexion of the ankle joints is reduced in both groups, resulting in the foot landing on the ground. Here, the ankle joints of the elderly showed more dorsiflexion (Figure 1(a)). This is a factor weighting forward rotation of the shank, further accelerating the passive flexion of the knee joints. After the loading response, both groups showed a development of dorsiflexion, accompanied by the development of the plantar flexor moment to control the dorsiflexion and support the body. From 30%, the plantar flexor moment of the elderly continued to develop while being smaller than that of the young adults (Figure 1(b)). However, the power was similar to that of the young adults (Figure 1(c)). It



(a) (b) (c)

Figure 6: Ankle joint angle profiles in the focal vibratory stimuli conditions. (a) Ankle joint angle in the 180 Hz; (b) ankle joint angle in the 190 Hz; (c) ankle joint angle in the 200 Hz.

seems to be a gait strategy of the elderly, which is to secure stability as, during the single limb support phase, the center of mass (COM) is lowered by increasing dorsiflexion. After this, the young adults saw a decrease in the negative power at 70% and it developed to a positive power, starting the plantar flexion of the ankle joint. However, in the elderly, the phase change of the power started at 60% (Figure 1(c)), even though the dorsiflexion was still in progress at the ankle (Figure 1(a)). This may indicate a strategy to control the accelerated dorsiflexion through a faster plantar flexion. However, this may not control sufficiently shank rotating forward caused by dorsiflexion. Then, at 80–100% of stance phase, the positive power of the elderly was lower than that of the young adults and this is consistent with previously studies [4, 14, 15]. This positive power is generated by the plantar flexor to push the body forward. The smaller positive power of the elderly is a gait strategy [4] to reduce instability in posture that could be caused by the heels elevated by plantar flexors. But, this could lead to potential impairment by decreasing muscle capacity with aging in terms of the mobile function and trunk stability [16].

Both groups showed a development of the flexion in the knee joint during the loading response (Figure 2(a)). This is the result of the action of the flexors' activities to absorb the impact force at the initial contact and the shank rotating forward over the foot. In order to control this, both groups showed an increase in the eccentric contraction of the extensors, where its magnitude was more in the elderly (Figure 2(c)). The reason for this appears to be that while the young adults would break the proceeding of the shank

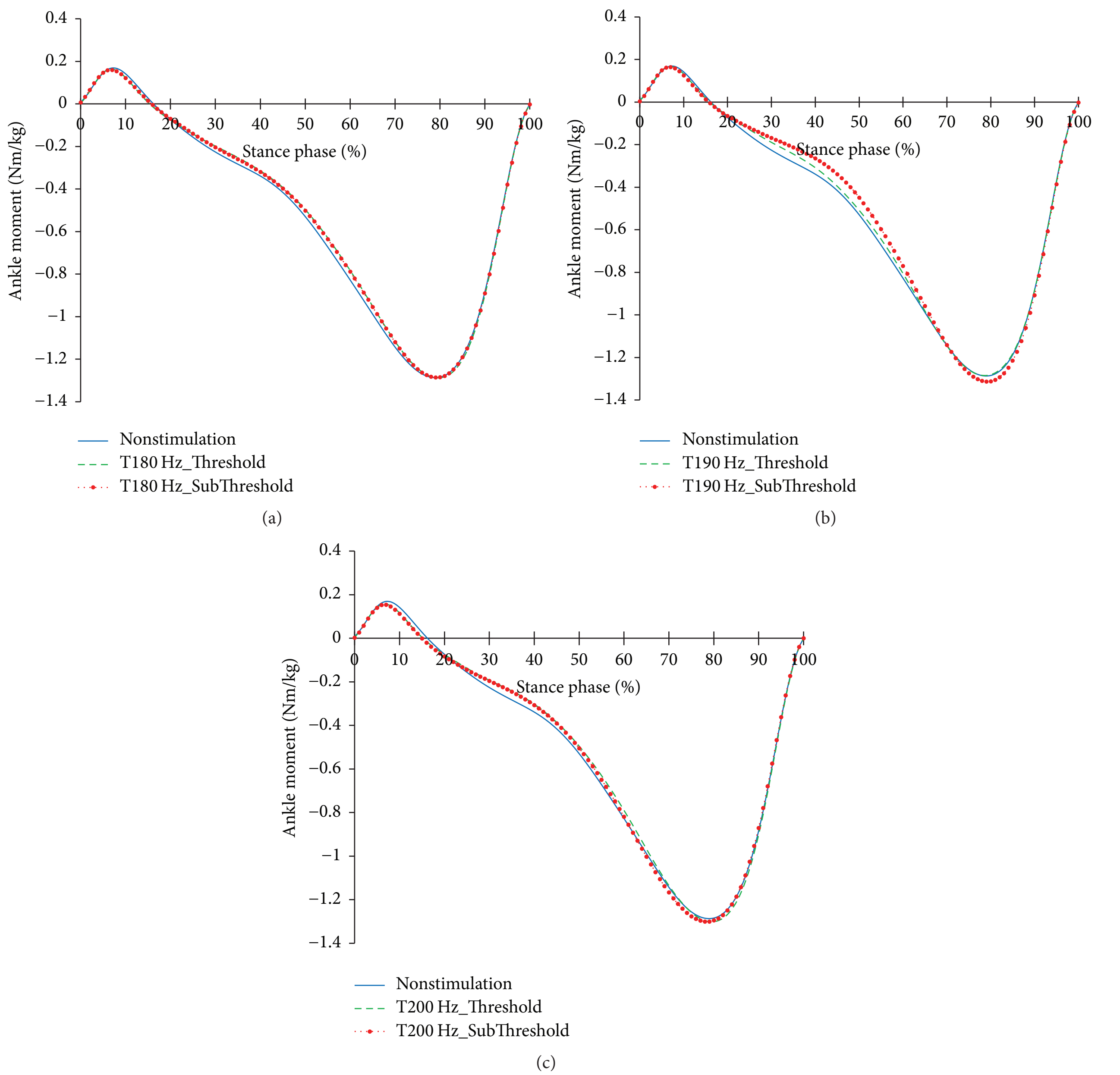


Figure 7: Ankle joint moment profiles in the focal vibratory stimuli conditions. (a) Ankle joint moment in the 180 Hz; (b) ankle joint moment in the 190 Hz; (c) ankle joint moment in the 200 Hz.

by a plantar flexion during the loading response, the brake of the shank is weaker with the elderly, due to the larger dorsiflexion. This seems to be a gait strategy to secure stability. However, due to the physiological weakening with aging, it can be a great burden on lengthening extensor. And there is a potential risk of a large damage when extensor suddenly extended or when failure to control length occurs. After the loading response, the extensor is still needed to achieve upright alignment and accelerate the thigh forward (Figure 2(b)). While the flexion decreased prior to the preswing phase in the elderly, the flexion was larger than that of the young adults. To support this, a larger and longer extensor moment and power compared to the young adults are required for the elderly during the single limb support phase and then smaller flexor moment occurred (Figure 2(b)). With this, it is possible to ensure stability during the single limb support phases. However, due to the reduced flexor activities, the lifting of the heel is limited, which may affect the reduced function of forward propulsion. Then, with the elevation of the heel due to the continued development of dorsiflexion and plantar flexion, the flexion of the knee joint is accelerated. To control this, the eccentric contraction of the extensor is increased (Figure 2(c)). Due to dorsiflexion increasing the knee flexion in the already large

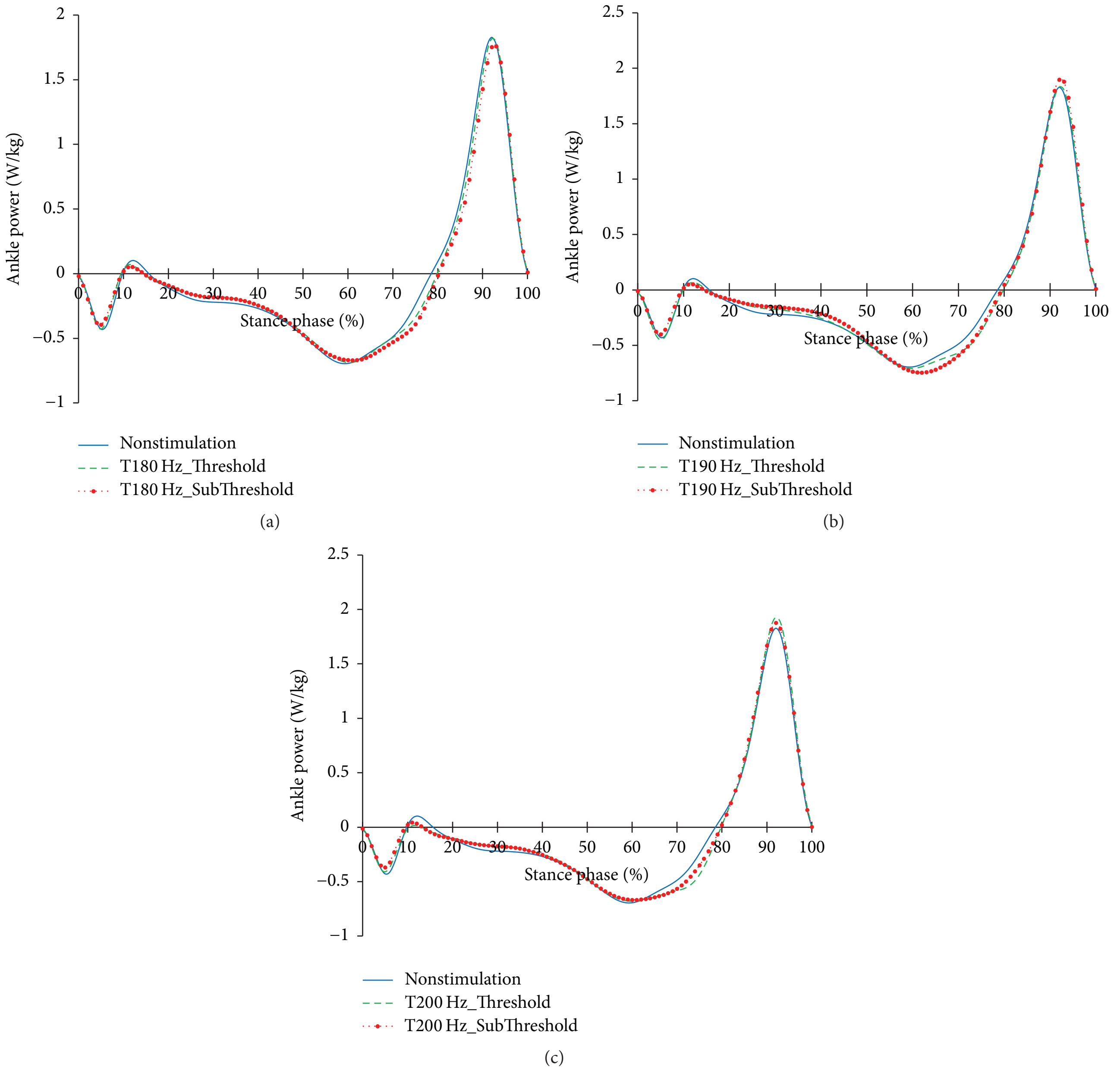


Figure 8: Ankle joint power profiles in the focal vibratory stimuli conditions. (a) Ankle joint power in the 180 Hz; (b) ankle joint power in the 190 Hz; (c) ankle joint power in the 200 Hz.

flexion state of the knee joint, the elderly had a higher negative power than that of the young adults. This can be a reason to increase the strain on the extensor.

At the hip joints, the young adult group sees a decrease in flexion, enters into an extension, and then performs a flexion again. On the other hand, the elder group maintains the flexion at the early stance. Then, while the flexion is reduced, the flexion of the elderly is larger and lasts longer compared to the younger group. Then, it is reversed to a flexion after an extension that is smaller than that of the younger group (Figure 3(a)). Hip joint power is clearly different compared to the younger group during the loading response phase (Figure 3(c)). It controls the flexion of the hip joints caused by large dorsiflexion at the ankle joint and the subsequent knee joint flexion; it helps the control of the flexion at the knee joint, as well (Figure 3(c)). However, the eccentric contraction at the knee and hip joints would increase the strain on the weakened muscles with aging. After the loading response phase, the extensor of the hip joints concentrically contracts to extend thigh. And the demands of joint moment and the power to extend the thigh are higher compared to the young adults (Figures 3(b) and 3(c)). At the late stance, the extension of the elderly is smaller compared to the young adults. This would be the result of the characteristics of the elderly, which are the increased forward inclination of the pelvis [15], contracture of the flexors [16], and, as a result,

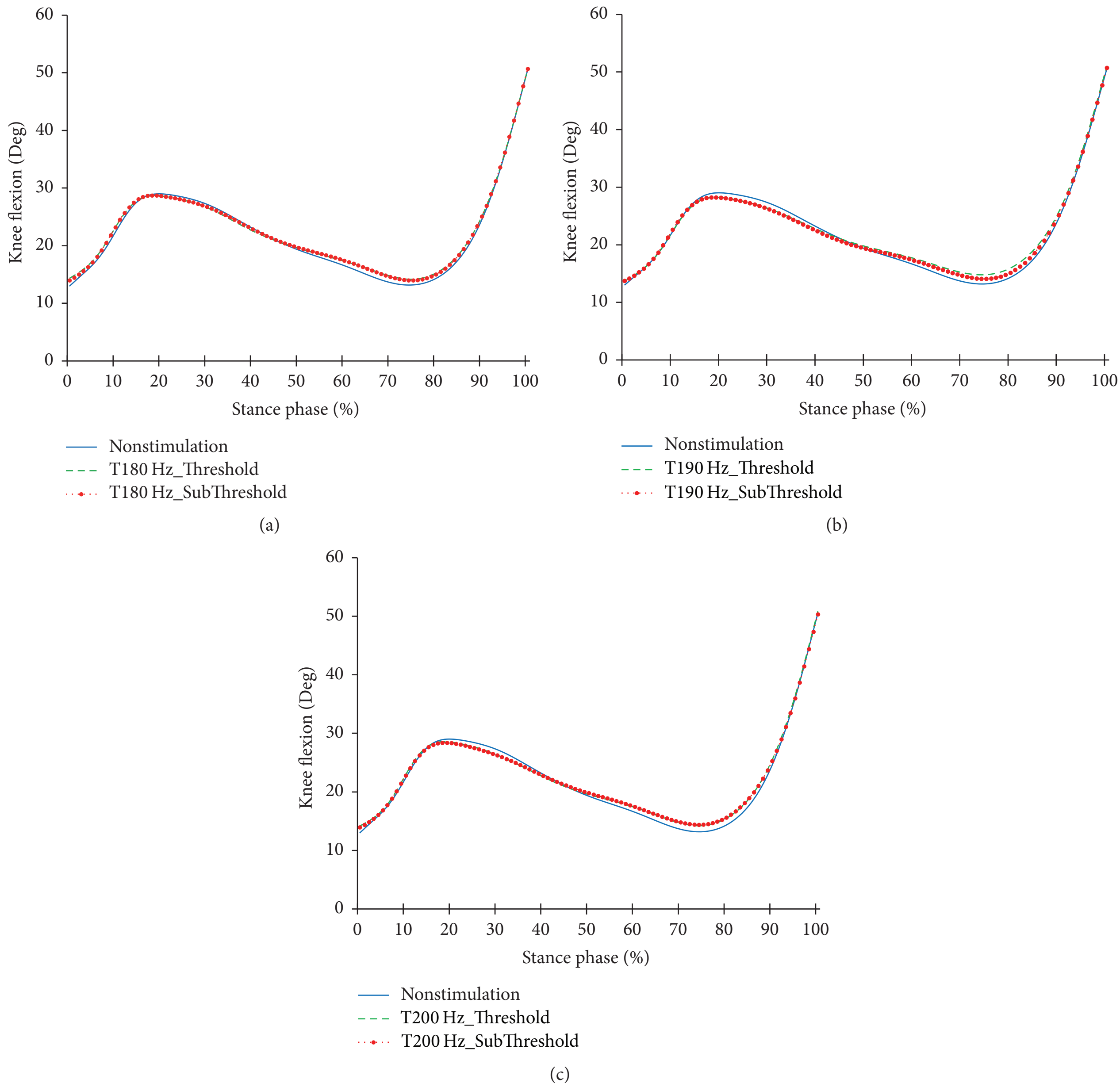


Figure 9: Knee joint angle profiles in the focal vibratory stimuli conditions. (a) Knee joint angle in the 180 Hz; (b) knee joint angle in the 190 Hz; (c) knee joint angle in the 200 Hz.

more eccentric contraction of the flexors. That is, it is a mechanism to stabilize through the flexion during the single limb support phase. As a result, while the young adult is in an extension at the toe-off (at 100% of the stance phase), the elderly are in flexion.

Compared to young adults, the gait characteristics of the elderly are that they walk as the segments are in flexion. For this, the extensors of each segment work harder. This is the gait strategy of the elderly to support their bodies bodies to prevent the collapse due to the flexion of the segments and to secure stability. Figure 4 shows the result of the support moment [17] which can depict the function of support in a comprehensive manner for the extensors of each segment.

In Figure 4, the support moment is higher than that of the young adults in the early stance. This is maintained until 85% of the stance phase, after which it reduces. That is, the elderly put more emphasis on stability through the support over the entire stance phase. However, due to aging, the elderly's physiological and neurological weakening occurs and it reduces muscle capacity, so higher support moment can be a serious strain. After 85%, the plantar flexor starts its work to create a forward propulsion. For the elderly, the activities are reduced to secure more stability [4]. As a result, the support moment after 85% may have decreased. The characteristics are more obvious; they are, respectively, normalized to the peak of the support moment of each group

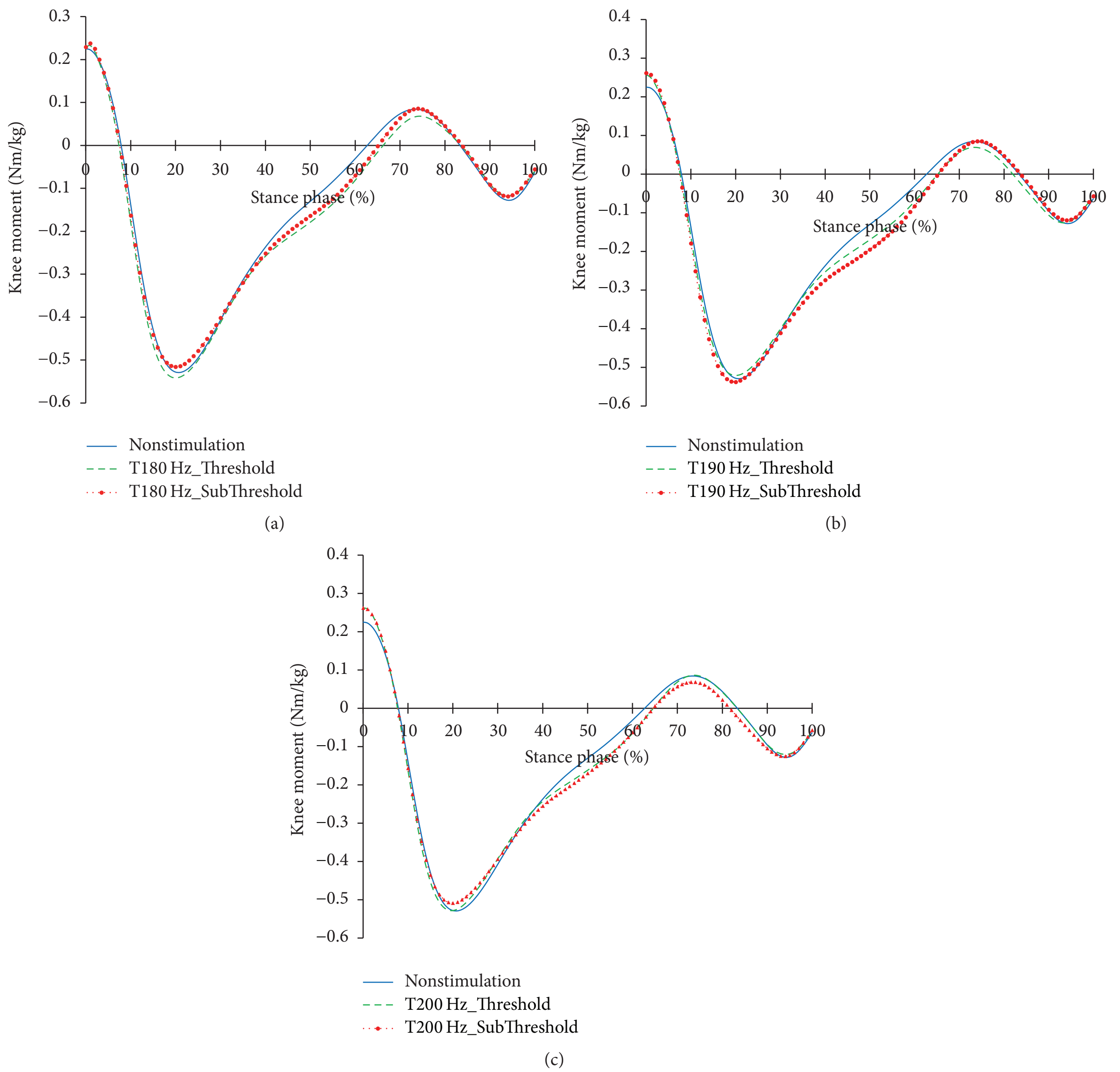


FIGURE 10: Knee joint moment profiles in the focal vibratory stimuli conditions. (a) Knee joint moment in the 180 Hz; (b) knee joint moment in the 190 Hz; (c) knee joint moment in the 200 Hz.

(Figure 5). From 65%, a rapidly peak uphill like a young adult does not appear to the elderly. This means that, at the terminal stance phase, the action of the plantar flexor becomes the priority to give support, rather than push forward. While this will limit the advancement of the lower limbs and the forward propulsion, it would be more advantageous in stabilization.

4.2. Changes in the Elderly Gait during Tibialis Anterior Tendon Vibratory Stimuli. When the vibratory stimuli were applied, the dorsiflexion decreased in all frequencies during the loading response (Figure 6). The reduction of dorsiflexion was a result of the decrease in the dorsiflexor moment and power (Figures 7 and 8). As the foot will be more inclined to plantar flexion compared to the nonstimulation condition, it would control the forward rotation of the shank. The dorsiflexion, which is reduced by the vibratory stimuli, would affect the flexion of the knees and hip joints caused by the excessive dorsiflexion and the eccentric contraction of the extensors to control them. After the reduction of the dorsiflexion of the ankle joint, the flexion in the knee joints decreased, and the positive and the negative powers both decreased (Figures 9 and 11). The flexion at the hip joints decreased (Figure 12). The positive power especially was generated as the negative power decreased (Figure 14). As a result, the flexion in lower limbs was reduced in general, so that the body weight would be supported in an

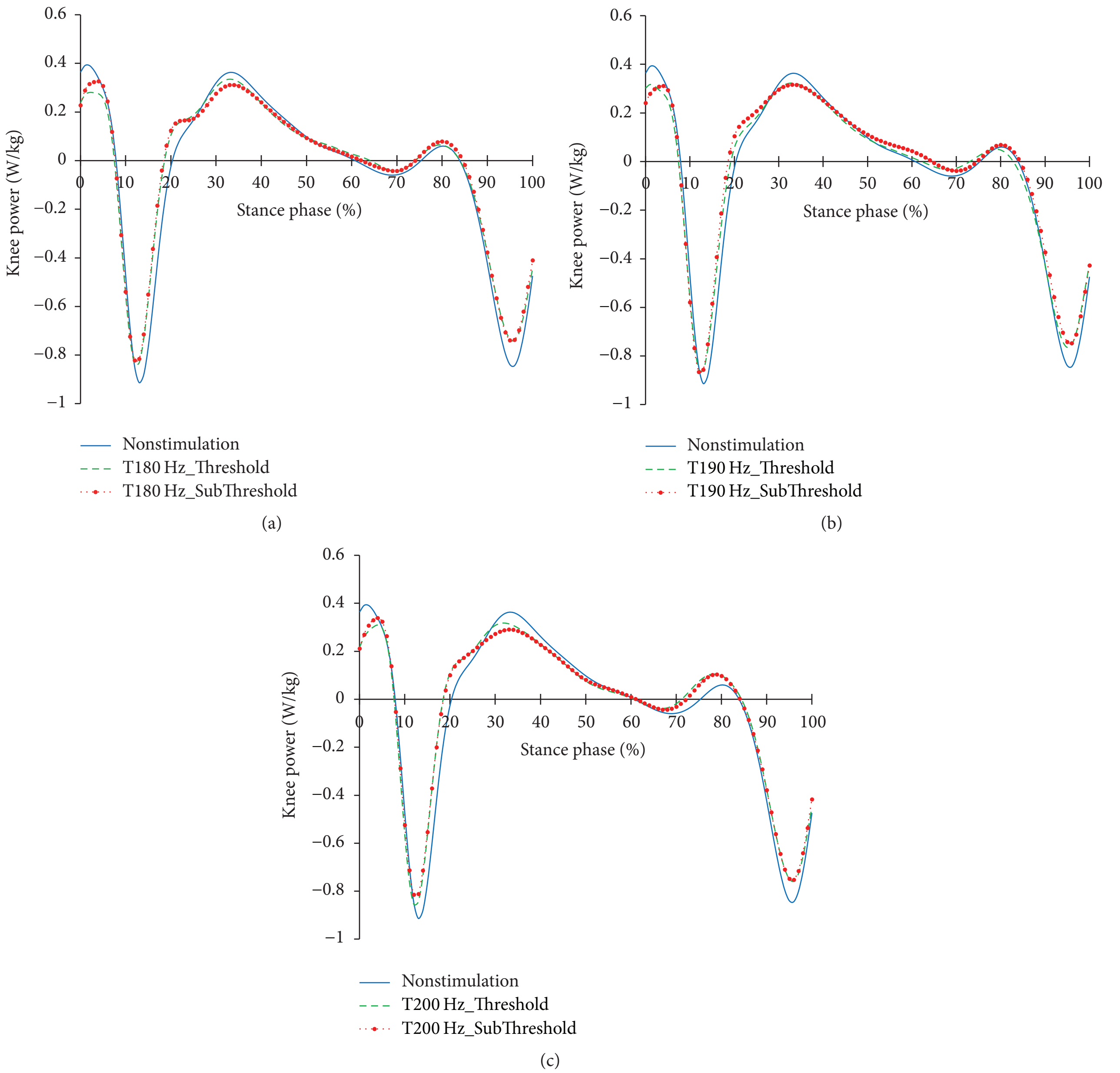


FIGURE 11: Knee joint power profiles in the focal vibratory stimuli conditions. (a) Knee joint power in the 180 Hz; (b) knee joint power in the 190 Hz; (c) knee joint power in the 200 Hz.

extension state. The concentric contraction of the hip joint extensors especially relieved the burden of the eccentric, and in combination with the reduced dorsiflexion, the shock absorbing burden of the knee extensor was reduced. That is, at the early stance, the vibratory stimuli induced the elderly gait pattern in a direction to relieve the shock absorption and the body support that had been highly burdened with a large flexion of the lower extremity segment. Such a change in the elderly gait pattern was more profound at 190 Hz and 200 Hz.

After the loading response, which was followed by dorsiflexion, the hip joints' flexion kept decreasing to the direction of extension. Here, the timing of power generation for extension came earlier and smaller (Figure 14). At the knee joints, too, the flexion to the extension direction was reduced, while the power to create extension was generated sooner and smaller (Figure 11). This may be because, as the dorsiflexion was reduced, the overall flexion in the lower extremity segments was reduced, too.

Because the flexion was reduced, the beginning of the extension would be accelerated. It would also require less muscle work requirements to counteract the smaller flexion. In the end, vibratory stimuli would contribute to achieve upright alignment sooner during the single limb support phase, along with the state of extension facilitated during the loading response phase.

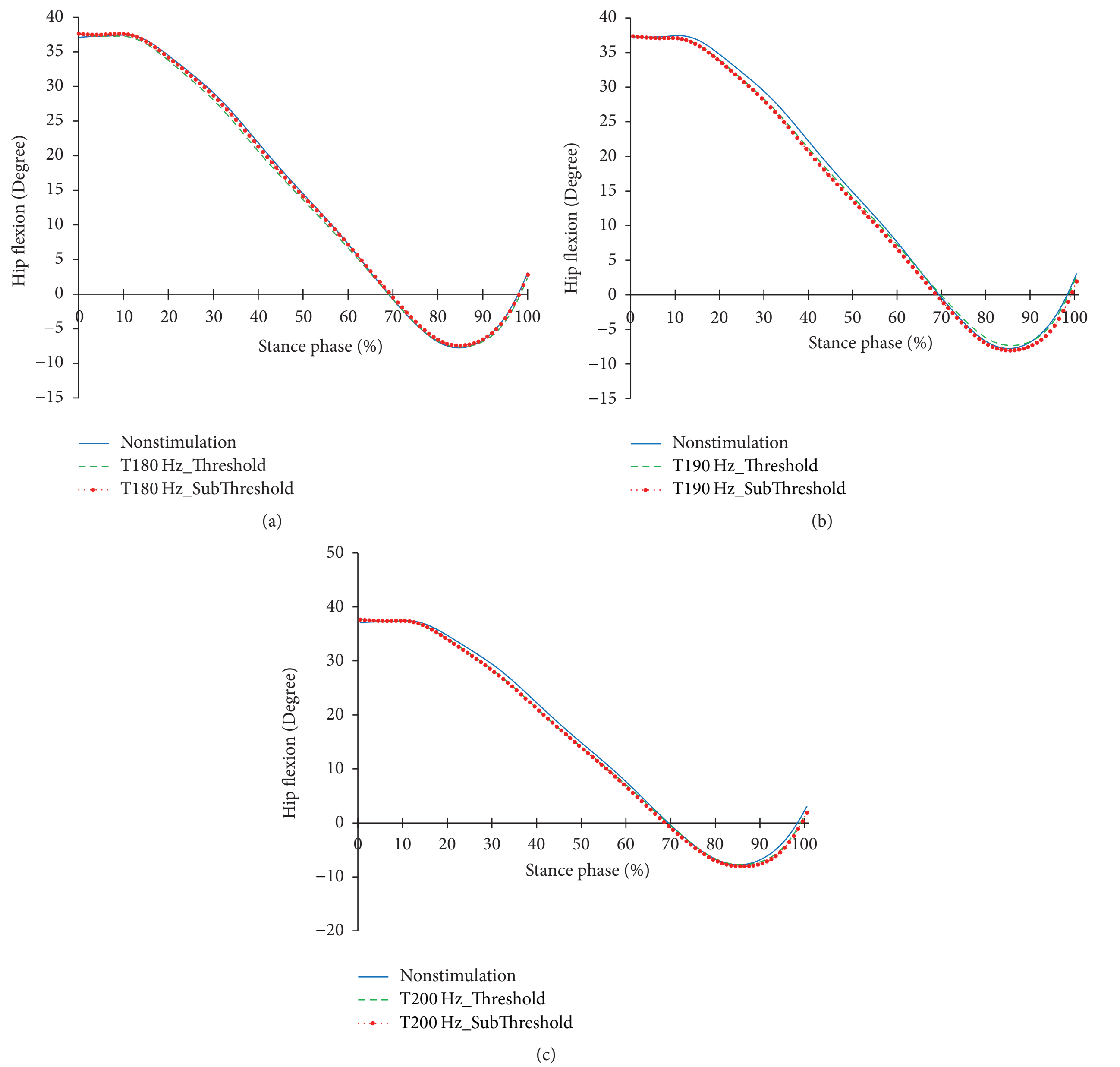


Figure 12: Hip joint angle profiles in the focal vibratory stimuli conditions. (a) Hip joint angle in the 180 Hz; (b) hip joint angle in the 190 Hz; (c) hip joint angle in the 200 Hz.

As the gait with vibratory stimulus progressed, the dorsiflexion increased more than that of nonstimulation since the 55% of the stance phase (Figure 6). To control this dorsiflexion, negative power of the plantar flexor lasted longer than nonstimulation condition (Figure 8). As the dorsiflexion increased, the flexion of the knee increased, resulting in an increase in extensor moment and positive power less than nonstimulation was equal to nonstimulation (Figure 11). Soon, the negative power to control the hip extension decreased (Figure 14). An increase in the dorsiflexion of the ankle joint and flexion of the knee joint will lower the center of mass, thereby ensuring stability and achieving careful forward walking. It will also improve insufficient body support during single limb support phase by rapid negative power reduction in nonstimulation condition.

After 85%, the dorsiflexion decreased, which increased knee flexion. And hip flexion reversed to extension. In focal vibratory stimuli conditions, the dorsiflexion declined to nonstimulation levels, and this tendency became more pronounced as the frequency increased. The plantar flexor moment is similar to nonstimulation, while positive power increased. This tendency became more pronounced as the frequency increased, too (Figure 8). The hip flexor moment was slightly lower than that of the nonstimulation condition (Figure 13), and positive power also decreased (Figure 14). This contributed to a reduction in the demands of the

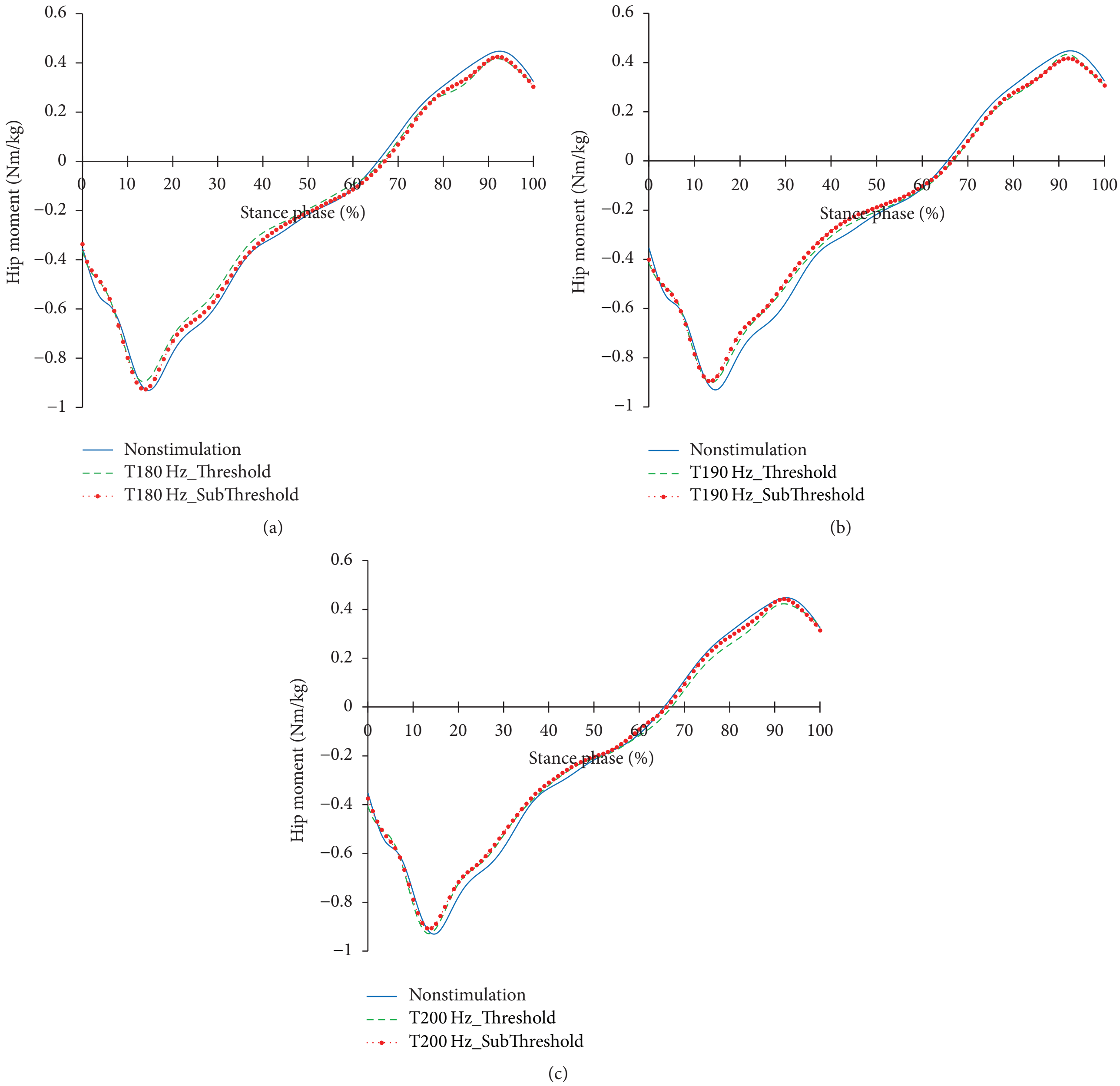


FIGURE 13: Hip joint moment profiles in the focal vibratory stimuli conditions. (a) Hip joint moment in the 180 Hz; (b) hip joint moment in the 190 Hz; (c) hip joint moment in the 200 Hz.

knee extensor to prevent knee collapse before toe-off. The increased activity of plantar flexor pushed the tibia further backward, and the reduced activity of the hip flexor pulls the thigh less forward. This activity caused the knee to extend. In addition, the flexion of the knee, due to the focal vibratory stimuli in the terminal stance phase, was less extensible rather than in the nonstimulation condition. In this state, the reduction of the dorsiflexion causes the flexion of the knee to reach a level of nonstimulation's flexion. This means that the reversal from extension to flexion was less than in nonstimulation, and the result will also contribute to a reduction in the negative power of the knee extensor.

When the focal vibratory stimuli were applied, the gait characteristics of the elderly were as follows: reduction of the body support at the early stance as a result of the decrease in flexion of the knee and hip by reduced dorsiflexion. At the late stance, there was an increase of the moment for single support because of increased dorsiflexion and the flexion of the knee joint. There was also a reduction in eccentric contractions of the knee extensors because of activities of the plantar flexor and the flexor of the hip. That is, the focal vibratory stimuli will change the gait of the elderly and affect the overall function of the lower extremity muscles during gait.

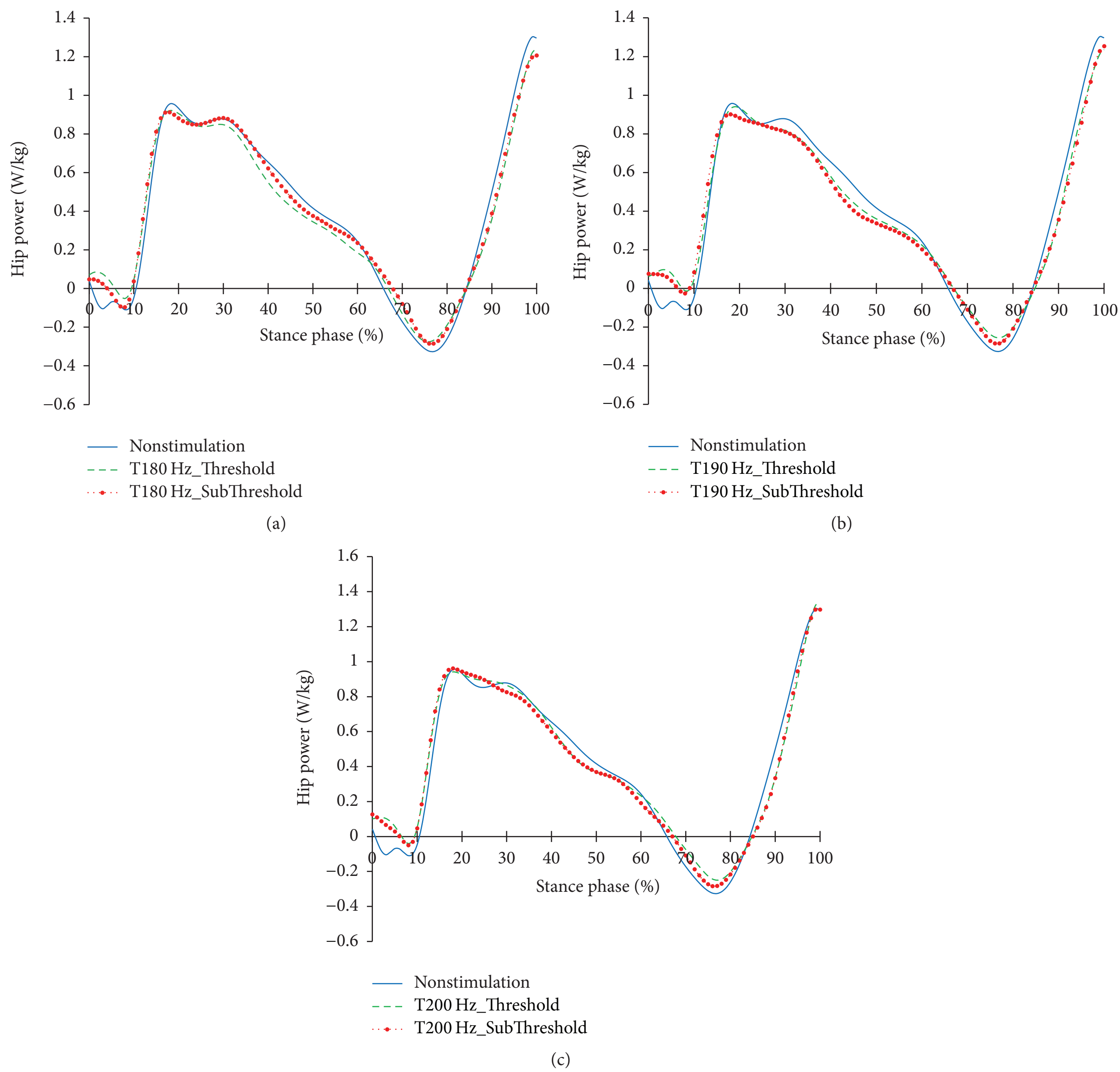


Figure 14: Hip joint power profiles in the focal vibratory stimuli conditions. (a) Hip joint power in the 180 Hz; (b) hip joint power in the 190 Hz; (c) hip joint power in the 200 Hz.

The changes in the function of the extensor muscles of each segment due to the focal vibratory stimuli are shown in Figure 15. Support moments decreased in the early stance and increased in the late stance in all focal vibratory stimuli conditions. In the elderly whose physiological function is weakened by aging, the reduction of support moment at the early stance means that the burden of the body support of the extensor muscles is relaxed. And the increase of the support moment at the late stance means the increase of stability during the single support phase.

4.3. Improvement Effects of the Focal Vibratory Stimuli. To examine improvement effects of the focal vibratory stimuli, the variations of the support moment and joint power and the similarity to angle profiles of the young adults were analyzed.

During the entire stance phase, only the hip joint angles were found to be similar to that of young adults'. However, since the movement of each segment of the lower extremity progresses sequentially and organically in the time domain, it is important to investigate it by dividing it into subperiods of the gait.

When the focal vibratory stimuli of the threshold intensity were applied in the LR, the difference in the ankle angle profiles of the young adults was decreased than that of the elderly with NS being as shown in Table 2 ($p < 0.05$). This means that the dorsiflexion in the LR is similar to the

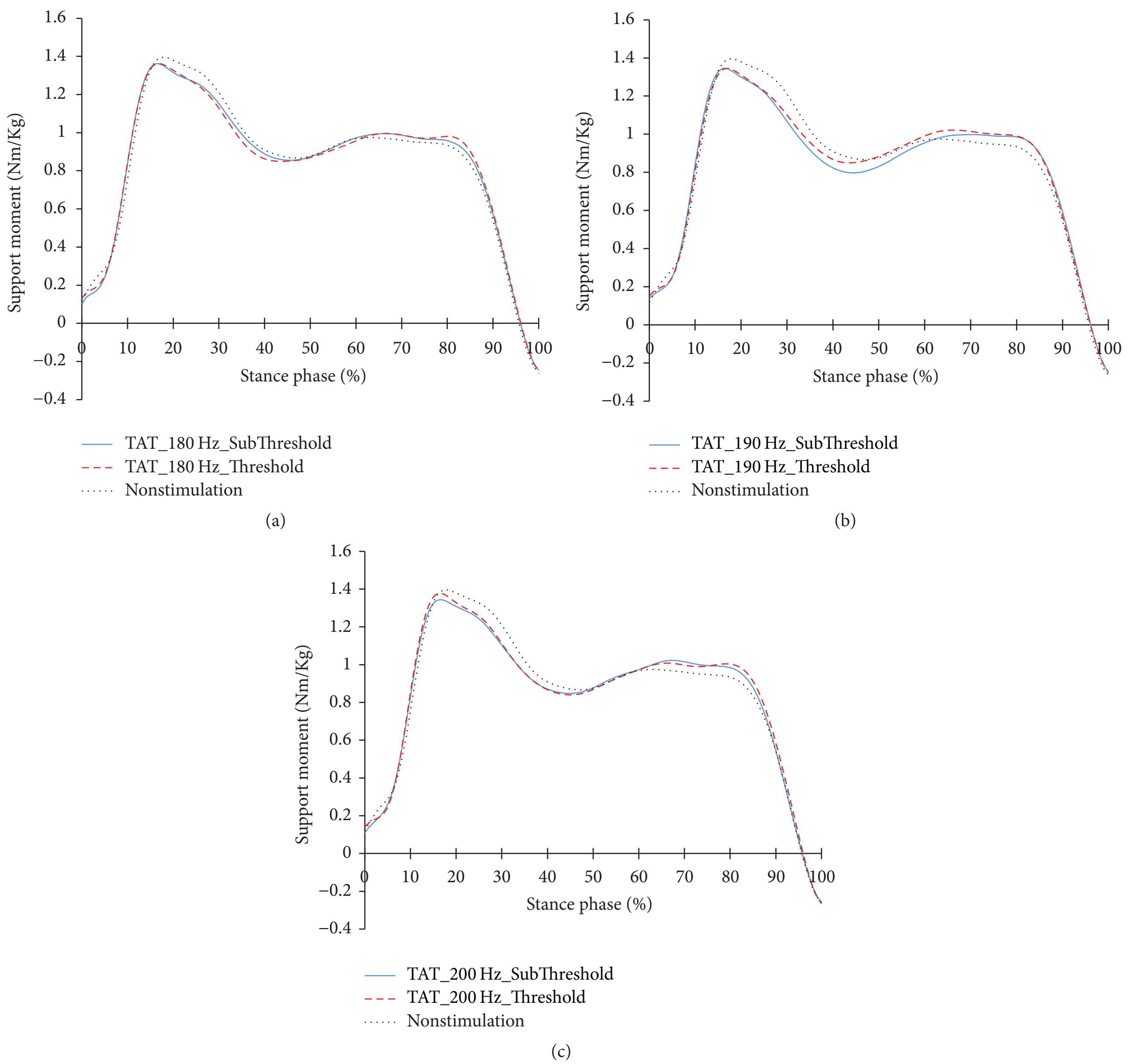


Figure 15: Support moments of the elderly with focal vibratory stimuli conditions. (a) Support moments of the elderly with 180 Hz focal vibratory stimuli; (b) support moment of the elderly with 190 Hz focal vibratory stimuli; (c) support moment of the elderly with 200 Hz focal vibratory stimuli.

young adults, and it results from more plantar flexion by the focal vibratory stimuli. After LR, the profile difference increased ($p < 0.05$), which is the same as the result of Figure 6. This is an effect of the focal vibratory stimuli and it will contribute to the reduction of COM height as described in Section 4.2. In the knee joint, the difference in the angle profiles during LR was slightly increased. This means increased knee flexion and it is associated with shock absorption. The knee flexion and flexor moment in the LR are intended to absorb the impact force [13]. Therefore, this result reveals that the focal vibratory stimuli positively contributed to the shock absorption function of the knee joint muscles.

In the MSt, the profile differences of the knee angle were reduced, which is due to the reduction of the dorsiflexion in the LR as described in Section 4.2. The difference in the profiles after MSt increased. This is the result of the dorsiflexion, which is increased by the vibratory stimuli and the increase of the stability assurance strategy. In the hip joints, the difference in profiles was reduced in all subperiods of the gait as shown in Table 2 ($p < 0.05$). This means that the focal vibratory stimuli leads the profile of the elder's hip joint angle toward that of the young adults. This means that, like young adults, the hips joints walk in a more extended state, which will certainly contribute to a reduction in power to support the body.

Table 2: Angle profiles' differences between the young adults and the elderly with NS and between the young adults and the elderly with all vibratory stimuli conditions of the threshold intensity (mean ± SD).

	Stance phase	LR	MSt	TSt	PSw
Ankle joint					
Elderly with NS	4.31 ± 1.32	0.84 ± 0.21	3.20 ± 0.16	4.05 ± 0.12	8.60 ± 1.38
with 180 Hz	*4.73 ± 1.54**	**0.46 ± 0.27***	*3.28 ± 0.16**	*4.63 ± 0.23**	*9.79 ± 1.40**
with 190 Hz	*4.48 ± 1.54**	**0.37 ± 0.19***	**2.86 ± 0.18***	*4.48 ± 0.26**	*9.59 ± 1.34**
with 200 Hz	*4.56 ± 1.48**	**0.44 ± 0.26***	**3.14 ± 0.15***	*4.49 ± 0.23**	*9.43 ± 1.29**
Knee joint					
Elderly with NS	4.89 ± 1.22	4.83 ± 0.35	7.00 ± 0.18	4.79 ± 0.99	1.41 ± 0.82
with 180 Hz	*5.24 ± 1.09**	*5.71 ± 0.32**	**6.70 ± 0.28***	*5.57 ± 0.90**	*1.84 ± 0.71**
with 190 Hz	*5.31 ± 0.95**	*5.03 ± 0.29**	**6.41 ± 0.19***	*5.95 ± 0.82**	*2.41 ± 0.67**
with 200 Hz	*5.22 ± 1.02**	*5.39 ± 0.33**	**6.56 ± 0.28***	*5.59 ± 0.88**	*2.13 ± 0.69**
Hip joint					
Elderly with NS	8.41 ± 1.05	7.27 ± 0.34	10.00 ± 0.28	8.77 ± 1.02	5.63 ± 0.57
with 180 Hz	**7.91 ± 0.87***	*7.32 ± 0.25*	**9.07 ± 0.15***	**8.38 ± 0.84***	**5.35 ± 0.41***
with 190 Hz	**8.04 ± 0.84***	**7.12 ± 0.23**	**9.07 ± 0.22***	**8.68 ± 0.80**	*5.64 ± 0.40*
with 200 Hz	**7.93 ± 0.92***	*7.46 ± 0.24**	**9.21 ± 0.16***	**8.39 ± 0.87***	**5.15 ± 0.38***

SD: standard deviation; NS: nonstimulated; LR: loading response; MSt: midstance; TSt: terminal-stance; PSw: preswing; the italic text indicates the increase in the profiles' differences; the bold text indicates the decrease in the profiles' differences. *Statistical differences ($p < 0.05$).

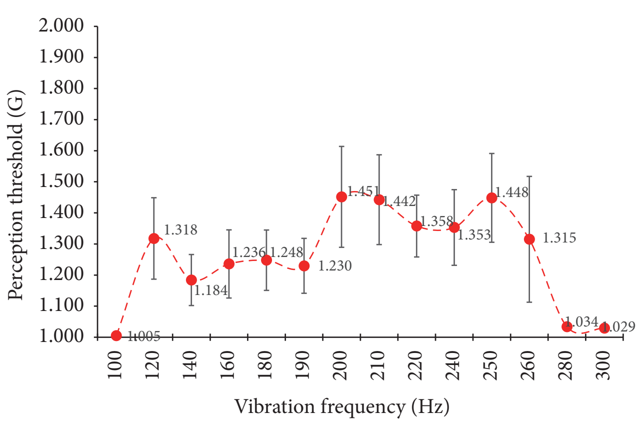


Figure 16: Perception threshold of the elderly with tibialis anterior tendon vibratory stimuli.

From these results, it can be seen that the joint angles, which are kinematic variables of the gait, are induced to the profiles of the young adults by the focal vibratory stimuli in the subperiods as the gait progresses. These results are also found in the subthreshold intensity as shown in Table 3.

In the support moments of Table 4, the support moments of the elderly with NS during DS are smaller than those of the young adults ($p < 0.05$). This will be due to the low support moments at the PSw (Figure 15). This is a strategy to secure a more stable gait, but it is a negative factor for forward propulsion. When the focal vibratory stimuli were applied, all the support moments increased ($p < 0.05$). This will contribute more to stability than forward propulsion. In order to facilitate forward propulsion, COM should be accelerated through extension of the lower extremity. However, the ankle and knee flexions increased in the late stance (Figures 6 and 9). Therefore, the focal vibratory stimuli will further promote the stability of the gait.

The support moments of the elderly with NS during SS were higher than the young adults' ($p < 0.05$). This means that the activity of the extensors of the lower extremity is greater than that of the young adults during single limb stance, as shown in Figure 5. This means that, in order to perform functional tasks during the SS, the recruitment of the extensors of the lower extremity is much higher than the young adults', and the energy demands, therefore, will also be high. This is evident in the power of the knees and hips even during DS ($p < 0.05$). Considering the neurophysiological weakening caused by aging of the elderly, this will be a great burden. However, when the focal vibratory stimuli were applied, both the support moments and the power of the knee and hip joints decreased during SS ($p < 0.05$), and the same results were obtained during DS. This means that the activity of the extensor for the gait and the corresponding energy demand decreased. As a result, the burden of proceeding the gait is alleviated. In addition, considering that the joint angles gradually became similar to the young adults' during the subperiods of the gait (Table 2), it can be inferred that the efficiency of gait progression in the neurophysiologic aspect is increased.

4.4. The Elderly Gait Depending on Vibration Intensity and Frequency. Vibratory stimulation can generate evoked cortical potentials in sensory and motor cortical areas [10]. When direct high frequency vibration is applied, cortical areas receive and process proprioception, which generates evoked cortical potentials [11, 18]. Forner-Cordero et al. [10] examined changes in corticomotor excitability. They are applied to dominant distal wrist flexor tendon and then the amplitude of Motor evoked potential (MEP) is measured.

TABLE 3: Angle profiles' differences between the young adults and the elderly with NS and between the young adults and the elderly with all vibratory stimuli conditions of the subthreshold intensity (mean ± SD).

	Stance phase	LR	MSt	TSt	PSw
Ankle joint					
Elderly with NS	4.31 ± 1.32	0.84 ± 0.21	3.20 ± 0.16	4.05 ± 0.12	8.60 ± 1.38
with 180 Hz	*4.59 ± 1.55**	**0.55 ± 0.28***	**3.21 ± 0.12**	**4.03 ± 0.20***	*9.74 ± 1.50**
with 190 Hz	*4.77 ± 1.56**	**0.57 ± 0.18***	**3.04 ± 0.17***	*4.87 ± 0.31**	*9.92 ± 1.30**
with 200 Hz	*4.55 ± 1.35**	**0.68 ± 0.20***	*3.29 ± 1.22**	*4.50 ± 0.16**	*8.95 ± 1.22**
Knee joint					
Elderly with NS	4.89 ± 1.22	4.83 ± 0.35	7.00 ± 0.18	4.79 ± 0.99	1.41 ± 0.82
with 180 Hz	*5.26 ± 1.13**	*5.53 ± 0.39**	**6.85 ± 0.25***	*5.55 ± 0.97**	*1.82 ± 0.76**
with 190 Hz	*5.02 ± 1.03*	*5.08 ± 0.35**	**6.34 ± 0.25***	*5.46 ± 0.90**	*1.90 ± 0.73**
with 200 Hz	*5.23 ± 1.03**	*5.28 ± 0.34**	**6.54 ± 0.24***	*5.75 ± 0.88**	*1.97 ± 0.60**
Hip joint					
Elderly with NS	8.41 ± 1.05	7.27 ± 0.34	10.00 ± 0.28	8.77 ± 1.02	5.63 ± 0.57
with 180 Hz	**8.34 ± 0.93***	*7.58 ± 0.30**	**9.65 ± 0.20***	*8.79 ± 0.90*	**5.70 ± 0.45**
with 190 Hz	**7.59 ± 0.89***	**7.18 ± 0.25**	**8.81 ± 0.13***	**8.01 ± 0.86***	**4.92 ± 0.39***
with 200 Hz	**7.75 ± 0.96***	*7.52 ± 0.26**	**9.14 ± 0.17***	**8.10 ± 0.90***	**4.84 ± 0.38***

SD: standard deviation; NS: nonstimulated; LR: loading response; MSt: midstance; TSt: Terminal-stance; PSw: preswing; the italic text indicates the increase in the profiles' differences; the bold text indicates the decrease in the profiles' differences. *Statistical differences ($p < 0.05$).

TABLE 4: Mean differences between the young adults and the elderly with NS and between the elderly with NS and the elderly with all vibratory stimuli conditions of the threshold intensity (Mean ± SD).

	Young adults		Elderly with NS	With 180 Hz	With 190 Hz	With 200 Hz
Support moment						
DS	0.450 ± 0.167	>	0.445 ± 0.144	*0.469*$^+$ *± 0.160*	*0.463*$^+$ *± 0.158*	*0.474*$^+$ *± 0.162*
SS	0.884 ± 0.070	<	1.045* ± 0.088	***1.028$^+$ ± 0.080**	***1.032 ± 0.073**	***1.035 ± 0.080**
Ankle power						
DS	1.208 ± 0.524	>	0.662* ± 0.301	***0.639$^+$ ± 0.300**	***0.657 ± 0.303**	**0.690*$^+$ *± 0.321*
SS	0.378 ± 0.121	>	0.329* ± 0.105	***0.322 ± 0.106**	**0.338 ± 0.115*	**0.338 ± 0.113*
Knee power						
DS	0.302 ± 0.100	<	0.375* ± 0.134	**0.333$^+$ ± 0.119**	**0.351$^+$ ± 0.121**	**0.341$^+$ ± 0.120**
SS	0.156 ± 0.064	<	0.193* ± 0.109	**0.175$^+$ ± 0.096**	**0.176$^+$ ± 0.101**	**0.176$^+$ ± 0.096**
Hip power						
DS	0.368 ± 0.174	<	0.423* ± 0.226	**0.354$^+$ ± 0.208**	**0.360$^+$ ± 0.209**	**0.371$^+$ ± 0.222**
SS	0.413 ± 0.149	<	0.505* ± 0.145	***0.467$^+$ ± 0.145**	***0.467$^+$ ± 0.145**	***0.490$^+$ ± 0.153**

SD: standard deviation; NS: nonstimulated; the italic text indicates the increase in the mean; the bold text indicates the decrease in the mean; *Statistical differences with the young adults ($p < 0.05$). $^+$Statistical differences with the elderly with NS ($p < 0.05$).

They reported that MEP amplitude for dominant flexor carpi radialis increased significantly. Therefore, the change in the elderly gait pattern due to the focal vibratory stimuli may be the result of the focal vibration stimulation affecting the central nervous system.

In this study, the elderly gait was changed according to the frequency and stimulus intensity of the applied vibration. In stimulation intensity condition, when the vibration of a 180 Hz threshold intensity was applied, the kinematic and kinetic variables of the elderly gait changed. Even at subthreshold intensity conditions of 180 Hz, the variables changed, and the change pattern was almost similar to the change pattern at the threshold intensity condition. A similar pattern of changes in threshold and subthreshold intensities at 180 Hz frequency also occurred at the 190 Hz and 200 Hz vibration stimuli. In our previous study [19], we investigated the changes in somatosensory evoked potentials (SEPs) according to the stimulus intensity at each vibration frequency. As a result, when the stimulus intensity was 80% of the threshold intensity (increasing 5%), the SEPs of the vibratory stimuli were significantly different from the SEPs of the nonstimulation. There was no significant difference between the stimulus intensity of 80% or more. Therefore, the reason why the change in the subthreshold pattern and the change in the threshold pattern are similar is due to the potential in the somatosensory area.

Table 5: Mean differences between the young adults and the elderly with NS and between the elderly with NS and the elderly with all vibratory stimuli conditions of the subthreshold intensity (Mean ± SD).

	Young adults		Elderly with NS	With 180 Hz (Sub-thres.)	With 190 Hz (Sub-thres.)	With 200 Hz (Sub-thres.)
Support moment						
DS	0.450 ± 0.167	>	0.445 ± 0.144	*0.455 ± 0.157*	*0.470^{+} ± 0.160*	*0.455 ± 0.157*
SS	0.884 ± 0.070	<	1.045* ± 0.088	***1.035^{+} ± 0.078**	***1.008^{+} ± 0.081**	***1.032 ± 0.075**
Ankle power						
DS	1.208 ± 0.524	>	0.662* ± 0.301	***0.606^{+} ± 0.291**	**0.669 ± 0.317*	**0.671 ± 0.317*
SS	0.378 ± 0.121	>	0.329* ± 0.105	***0.328 ± 0.106**	***0.327 ± 0.115**	**0.330 ± 0.113*
Knee power						
DS	0.302 ± 0.100	<	0.375* ± 0.134	**0.338^{+} ± 0.116**	**0.339^{+} ± 0.118**	**0.341^{+} ± 0.117**
SS	0.156 ± 0.064	<	0.193* ± 0.109	**0.171^{+} ± 0.093**	**0.183 ± 0.097**	**0.170^{+} ± 0.091**
Hip power						
DS	0.368 ± 0.174	<	0.423* ± 0.226	**0.362^{+} ± 0.209**	**0.353^{+} ± 0.209**	**0.372^{+} ± 0.224**
SS	0.413 ± 0.149	<	0.505* ± 0.145	***0.491^{+} ± 0.147**	***0.464^{+} ± 0.142**	***0.488^{+} ± 0.151**

SD: standard deviation; NS: nonstimulated; the italic text indicates the increase in the mean; the bold text indicates the decrease in the mean. *Statistical differences with the young adults ($p < 0.05$). $^{+}$Statistical differences with the elderly with NS ($p < 0.05$).

In stimulation frequency condition, the change of the support moment differs depending on the vibration frequency. This implies that the function of the extensor muscles of the supporting legs changes according to the vibration frequency. This may be because the excitability of the central nervous system is dependent on the frequency of vibration. Steyvers et al. [20] investigated corticospinal excitability according to the frequency of muscle tendon vibration. They measured the MEP according to the frequency of vibration using transcranial magnetic stimulation (TMS) and reported that muscle tendon vibration exerts a frequency-dependent effect on corticospinal excitability.

We investigated the sensory threshold of vibration according to the vibration frequency of the elderly (a total of 11 elderly), illustrated in Figure 16. The vibration threshold values from 100 Hz to 300 Hz were measured. As a result, only one can feel the vibrations of 100 Hz, 280 Hz, and 300 Hz, and there are more than 7 people who cannot feel the vibration of 120 Hz~160 Hz and 240 Hz~260 Hz. So, as can be seen in Figure 16, the most sensitive vibration frequency is 190 Hz, and the vibration threshold is rapidly increased at 200 Hz.

Table 1 shows the statistical differences of the vibration threshold values from 180 Hz to 220 Hz. 180 Hz has a statistical difference of 200 Hz or more except for 190 Hz, and 190 Hz is the same. On the other hand, 200 Hz is statistically different from all frequencies except for 220 Hz. Sensory perception thresholds are related to the peripheral sensory receptors and thus the sensory area of the cerebral cortex. In other words, the fact that the vibration threshold varies according to the frequency of the applied vibration suggests that the response of the central nervous system will be different depending on the frequency of the vibration, and accordingly, the activity of the motor may be frequency-dependent.

4.5. Benefits and Risks of the Focal Vibratory Stimuli. In this study, we applied the focal vibratory stimuli to the tibialis anterior tendon of the elderly during gait and confirmed that the focal vibratory stimuli affect the kinematic and kinetic gait of the elderly and induce variations in the gait profiles. As a result, it was found that the focal vibratory stimuli positively contribute to the relaxation of neurophysiological demands for gait performance and the efficiency of gait progression.

The focal vibration applied in this study is at least 6 seconds, which is a very short time. Therefore, the results of this study show that the focal vibratory stimuli have acute effects. As shown in this study, many studies have revealed acute effects of vibration stimulation and are well described in the study of Luo et al. [9]. There are various vibration applying times that are not only from seconds to minutes but also over 1 hour [21]. Also, some studies have applied up to 12 weeks (3 month). These studies have shown that vibratory stimulation contributes positively to EMG, muscle force, and neuromuscular performance. Lapole and Pérot [22, 23] reported that the tendon-vibration program for two weeks increased triceps surae force production and also reduced stiffness and reflexes and said that the vibration stimulation could be beneficial to immobilized persons as hypo-activity.

There are more recent studies that summarize the effects of the focal vibratory stimuli only [24], and the vibration applying time is from 6 seconds to 12 weeks. Constatino et al. [25] applied local vibration for 4 weeks to chronic poststroke patients and found statistically significant improvement in grip muscle strength, pain, and quality of life and a decrease in spasticity and said that local muscle vibration treatment might be an additional and safe tool in the management of chronic poststroke patients, granting its high therapeutic efficiency, limited cost, and short and repeatable protocol of use. Camerota et al. [26] applied repeated focal muscle vibration (r-fMV) to patients with severe gait impairment due to multiple sclerosis for 30 minutes; this was repeated for 3 consecutive days. They measured the effect of the repeated focal muscle vibration on gait by a gait analysis that was performed before r-fMV (T0) and 1 week (T1) and 1 month (T2) after the last session of r-fMV. They reported that, after the r-fMV, the most of spatiotemporal parameters improved multiple sclerosis patients' quality of life. Also, they concluded that r-fMV improves gait function in multiple sclerosis patients.

Currently, studies using vibratory stimulation for more than one year are rare. Although the long-term effect of more than one year is difficult to clarify in this study, it is expected that positive effects will be possible through long-term application of vibration through previous studies applying vibration from a week to a month. The effect of long-term application of vibration can be estimated through functional electrical stimulation (FES). Because the external stimuli are different from each other, the stimuli delivered in the human body are the same as the electrical impulses through the nerves.

Kern et al. [27] performed home-based daily training by functional electrical stimulation (H-FES) on 25 patients suffering complete lower motor neuron paraplegia, and they investigated results before H-FES and 1 year and 2 years after it. They reported that after 1 year of H-FES, there were increases in muscle excitability and contractility and in 26% of muscle bulk and that myofiber size increased after 2 years of H-FES. Therefore, more than one year of vibratory stimulation may have similar effects to those studies' results. Furthermore, it is expected that the range of clinical applications of vibratory stimulation will be broadened through studies [28–30] that have proven to be effective in brain rehabilitation through vibration stimulation.

The various effects of the vibratory stimuli have been revealed, and potential risks must be considered in order to use them for clinical rehabilitation and therapeutic purposes. By applying vibration for a long time, the vibration perception threshold can be increased [31]. This is due to "sensory adaptation" by sustained or repetitive stimulation [31]. As the threshold increases, the vibratory stimulation initially presented can no longer activate the sensory system, so it is difficult for the effects suggested by related studies to occur. Another risk is skin keratinization at sites where vibration is repeated continuously or repeatedly. Continuous friction, pressure, and irritation accelerate skin's keratinization and, if prolonged, cause callus [32]. Because of the callus, the threshold of sensation will increase; eventually, it will be required to stop the application of vibrations or change the site stimulated. Finally, there is a potential risk to the perception threshold intensity. Sensory stimulation that is suddenly felt on the distal side during gait may cause confusion in the progress of the gait or cause sudden changes (i.e., unwanted movements). In addition, suprathreshold above the threshold may result in discomfort or loss of balance [33, 34]. In this study, subthreshold stimuli showed similar effects to threshold stimuli (Tables 2–5). Therefore, it is appropriate to apply subthreshold intensity vibration to movements like gait.

5. Conclusion

The purpose of this study was to identify the gait profiles of the elderly with aging, examine variations of gait parameters of the elderly by the focal tendon vibratory stimulation, and determine the effects of the focal tendon vibratory stimulation on the elderly gait. And the results were as follows:

The elderly walk as the segments are in flexion. Because of this, the extensors of the lower limbs work harder specifically in the early stance.

When the focal vibratory stimuli were applied, the kinematic and kinetic parameters were affected, resulting in relieving the neurophysiological demands to conduct gait.

The response of the central nervous system to vibration is dependent on the frequency. Accordingly, the activity of the motor may be dependent on vibration stimulation characteristics.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Research Article

Virtual Reality Telerehabilitation for Postural Instability in Parkinson's Disease: A Multicenter, Single-Blind, Randomized, Controlled Trial

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Introduction. Telerehabilitation enables patients to access remote rehabilitation services for patient-physiotherapist videoconferencing in their own homes. Home-based virtual reality (VR) balance training has been shown to reduce postural instability in patients with Parkinson's disease (PD). The primary aim was to compare improvements in postural stability after remotely supervised in-home VR balance training and in-clinic sensory integration balance training (SIBT). *Methods*. In this multicenter study, 76 PD patients (modified Hoehn and Yahr stages 2.5–3) were randomly assigned to receive either in-home VR telerehabilitation ($n = 38$) or in-clinic SIBT ($n = 38$) in 21 sessions of 50 minutes each, 3 days/week for 7 consecutive weeks. VR telerehabilitation consisted of graded exergames using the Nintendo Wii Fit system; SIBT included exercises to improve postural stability. Patients were evaluated before treatment, after treatment, and at 1-month follow-up. *Results*. Analysis revealed significant between-group differences in improvement on the Berg Balance Scale for the VR telerehabilitation group ($p = 0.04$) and significant Time × Group interactions in the Dynamic Gait Index ($p = 0.04$) for the in-clinic group. Both groups showed differences in all outcome measures over time, except for fall frequency. Cost comparison yielded between-group differences in treatment and equipment costs. *Conclusions*. VR is a feasible alternative to in-clinic SIBT for reducing postural instability in PD patients having a caregiver.

1. Introduction

Up to 75% of people with Parkinson's disease (PD) have impaired postural control, which can often lead to postural instability and an increased risk of falls as a consequence [1]. While postural instability in PD may involve dysfunctions in several subsystems [2, 3], it is the impaired multimodal integration of sensory feedback from the visual, proprioceptive, and vestibular systems that can predominantly contribute to deficits in gait and balance [4, 5] as seen in other neurological conditions [6, 7]. Moreover, since dopaminergic medications have limited effects on postural instability in PD, rehabilitation is perhaps the most effective nonpharmacological approach to reducing the risk of falls [8]. National and international guidelines stress the importance of starting rehabilitation at an early stage of the disease to prevent mobility-related disability and comorbidities (e.g., pain) [9]. However, growing disability, travel distances, and uneven distribution of rehabilitation services can make access to care problematic for PD patients [10].

An innovative approach to fitness training and rehabilitation is exergaming with active video games that combine body movement with gaming skill, in which players use body movements to control and play games in engaging virtual reality (VR) scenarios. An additional advantage of exergaming is that it can be performed independently at home with minimal equipment and at accessible cost. For example, the highly popular Nintendo Wii Fit and balance board is a VR fitness application that holds potential for use as an adjunct to sensory integration balance training (SIBT), one of the most effective ways to improve postural stability in PD [11].

VR-based telerehabilitation balance programs have been proven feasible and effective in several neurological conditions [12, 13]. While telerehabilitation and VR applications have been used separately to evaluate or treat balance dysfunctions in PD [14–18], whether they are feasible, safe, and effective when combined with a telerehabilitation setting warrants investigation. The primary aim of this study was to compare improvements in postural stability after in-home VR-based balance training with the Nintendo Wii Fit system (TeleWii) and after in-clinic SIBT in PD patients. The secondary aim was to compare pre- and posttreatment differences in perceived balance confidence, mobility-related function, quality of life, fall frequency, and the difference in the costs of the two rehabilitation programs. We hypothesized that TeleWii might be as effective as SIBT in improving postural control by acting on sensorimotor integration processes and that the total costs for the in-home TeleWii program would be lower than in-clinic SIBT.

2. Methods

Four neurorehabilitation units [Neuromotor and Cognitive Rehabilitation Research Center (CRRNC) AOUI Verona, Azienda ULSS N. 1 Belluno, Azienda ULSS N. 9 Treviso, and Azienda ULSS N. 15 Alta Padovana, Cittadella] participated in this multisite, single-blind randomized controlled trial (RCT). The participating centers, all located in Veneto, deliver rehabilitation services in predominantly rural areas.

2.1. Participants. From December 2013 to December 2015, consecutive outpatients with medical diagnosis of PD confirmed according to the United Kingdom Parkinson's Disease Society Brain Bank criteria [19] were assessed for eligibility. Inclusion criteria were age > 18 years, modified Hoehn and Yahr (H&Y) stages 2.5 to 3 [20], stable medication usage in the previous month, ability to perform postural transfer and maintain upright standing posture for at least 10 minutes, and the presence of a caregiver. Exclusion criteria were cardiovascular, orthopedic, and otovestibular disorders (dizziness); visual or other neurological conditions that could interfere with balance; severe dyskinesias or on-off fluctuations; Mini-Mental State Examination (MMSE) score < 24/30; and severe depression as measured on the Geriatric Depression Scale (GDS). All patients were informed about the experimental nature of the study and gave their written informed consent before enrolment. The study was carried out following the tenets of the Declaration of Helsinki and approved by the local ethics committee (n. 75/CE, AULSS9, RSF 319/2010).

2.2. Interventions. The trial steering committee designed two treatment protocols. To ensure uniform delivery of treatment, one physiotherapist from each center received instruction in the TeleWii protocol, and one physiotherapist received instruction in the SIBT protocol [11]. Both groups underwent 21 individualized treatment sessions of 50 minutes each, 3 days/week (Monday, Wednesday, and Friday) for 7 consecutive weeks. During the study period, patients were not allowed to receive any other type of rehabilitation. No other restrictions on physical activity were set.

2.2.1. TeleWii Set-Up. A TeleWii-Lab comprising the Nintendo Wii console for motion controlled inputs, the Wii Fit gaming system, and balance board (Nintendo Co., Ltd., Kyoto, Japan) was set up at each rehabilitation unit [21]. For this study, a laptop computer connected to a high-resolution web-camera was used to establish real-time remote visual communication via Skype® software (Skype/Microsoft) between the rehabilitation unit and the patient's home. A research team member installed an identical TeleWii set-up at the patient's home.

2.2.2. TeleWii Training. Patients were instructed to exercise with TeleWii only when in the ON state. The physiotherapist gave a full explanation of the training protocol and conducted a trial TeleWii session at the hospital lab. A logbook was provided for reporting any issues with the Skype connection or difficulties with the training program. In-home TeleWii training consisted of 21 sessions of balance exercises of 50 minutes each. During each session, the physiotherapist supervised two patients simultaneously. A brief warm-up consisted of stretching exercises of the upper and lower extremities with self-applied gentle joint mobilization while lying supine on a mat. TeleWii training included the following 10 exergames selected by the physiotherapist according to the patient's clinical condition and progressive improvement over time [15]. The Skype video calls lasted the entire duration of each training session. A caregiver was always present to monitor the patient during training and warrants its safety (Table 1).

Table 1: TeleWii balance training program.

Name of exercise	Exercise description	Expected impact on mobility
Table tilt	Shift the body weight in all directions with feet placed in a fixed position. Make a plan of movements to tilt the virtual platform, bring the balls in the holes and go to the next level of difficulty	Improve the correct use of ankle and hip strategy during static condition. Improve the quick change of strategy from ankle to hip and vice versa
Penguin slide	Shift the body weight toward the right and left direction to bend the virtual ice platform, with feet placed in a fixed position. Make a plan of movements to catch as much fishes as possible	Improve the correct use of ankle and especially hip strategy during static condition
Balance bubble	Shift the body weight forward to move the avatar forward; lean left and right to steer	Improve the correct use of ankle and hip strategy during static condition. Improve the quick change of strategy from ankle to hip and vice versa
Ski slalom	Lean the body left and right to ski down a slalom course and pass between flags with your avatar	Improve the correct use of ankle and hip strategy during static condition. Improve the quick change of strategy from ankle to hip and vice versa. Improve the ability to orientate the trunk in the space
Skateboarding	Push off the ground with right/left foot to skate forward with your avatar, and lean left or right to turn; if the speed slows down, lean toward one side to pick up speed; jump off the virtual ramps by raising heels to perform a trick in midair	Improve the correct use of ankle, hip, and stepping strategy during quasi-static condition. Improve the quick change of strategy from ankle to hip or stepping and vice versa. Improve the ability to orientate the trunk in the space
Perfect 10	Shake hips back, front left, or right to add up to the given number with your avatar. The aim is to make a sum of 10	Improve the correct use of ankle and hip strategy during static condition. Improve the quick change of strategy from ankle to hip and vice versa. Improve the dual task performance (motor & cognitive task)
Tilt city	Tilt the Wii remote to move the virtual board at the top of the screen. Shift your body weight left and right to tilt the virtual boards at the bottom. Make a plan of movements to drop the balls into the matching colored pipe	Improve the correct use of hip strategy during static condition. Improve the coordination between upper and lower limbs (dual motor task)
Snowball fight	Shift your body weight right or left to move out your avatar from behind a protective barrier; use the Wii remote at the screen to throw snowballs; when throwing, watch out for incoming snowballs and avoid them by shifting your body weight	Improve the correct use of ankle and hip strategy during static condition. Improve the quick change of strategy from ankle to hip and vice versa. Improve the coordination between upper and lower limbs (dual motor task). Improve the attentional strategies to multiple stimuli
Rhythm parade	Stepping in place to move your avatar and wave the controller when scrolling icons coming from the top of the screen hit the circles place at the bottom	Improve the correct use of all strategies during static condition. Improve the quick change of strategy from hip to stepping and vice versa. Improve the coordination between upper and lower limbs (dual motor task)
Bird's-eye bulls-eye	Stand on the board with feet placed in a fixed position. Flap the arms to land your avatar on the targets; lean in and flap to fly your avatar forward; stay centered on the board and flap to go higher with your avatar; shift the body weight right or left to turn; stop flapping to land your avatar on a target and to get a bonus; rack up bonus time and head for the finish; small flaps help hover; big flaps help to soar	Improve the correct use of ankle and hip strategy during static condition. Improve the quick change of strategy from ankle to hip and vice versa. Improve the coordination between upper and lower limbs, and between upper limbs (dual motor task)

CoM, center of mass; CoP, center of pressure. The exercises are listed in order of task difficulty starting from single-task through dual-task performance.

2.2.3. Sensory Integration Balance Training. In-clinic SIBT consisted of 21 sessions of balance and gait exercises lasting 50 minutes each. A brief warm-up session of stretching exercises was followed by static and dynamic balance exercises under different sensory conditions (free vision, blindfolded, wearing a visual-conflict dome, firm/compliant surfaces, and neck extensions) (Table 2) [7, 11, 22].

During each session, the patients performed 10 exercises, at random: 4 self-destabilization, 4 external destabilization, and 2 combined self-destabilization and external destabilization exercises. Each exercise was repeated from 5 to 10 times for 5 minutes depending on the patient's capabilities. Exercises were progressed by increasing the number of repetitions, the task difficulty (greater forward/sideward stepping

Table 2: Sensory integration balance training program.

Type of exercise	Task explanation	Expected impact
	Self-destabilization exercises (mainly feedforward)	
Static weight bearing	In stance with feet placed shoulder-width apart, transfer the body weight back and forth on the tips of the toes and the heels.[*°@^]	Improve correct use of ankle strategy during static condition.
	In stance with feet placed shoulder-width apart, transfer the body weight mediolaterally from the right to the left foot.[*°@^]	Improve correct use of ankle and hip strategy during static condition; improve quick change of strategy from ankle to hip and vice versa.
	In stance with feet placed shoulder-width apart, transfer the body weight in all directions (i.e., drawing a cone with head).[*°@^]	Improve correct use of ankle and hip strategy during static condition; improve quick change of strategy from ankle to hip and vice versa.
Trunk twist	Sitting in a chair without armrests, with feet placed shoulder-width apart on the floor, twist the torso as much as possible toward the right and the left.[*°@]	Improve trunk mobility in sitting conditions.
	In stance with feet placed shoulder-width apart, twist the torso as much as possible toward the right and the left.[*°@^]	Improve trunk mobility in standing conditions.
Postural transfers	Sitting in a chair without armrests, with feet placed shoulder-width apart on the floor, sit-to-stand.[*°@^]	Improve correct use of ankle and hip strategy during postural transfers.
	Sitting in a chair without armrests, with feet placed shoulder-width apart on the floor, sit-to-stand while grasping a glass of water.[*°^]	Improve correct use of ankle and hip strategy during postural transfers; improve coordination between upper and lower limbs (dual motor tasking).
Dynamic weight bearing	In stance with feet placed shoulder-width apart, step up and down in place, varying the height with each step while catching and throwing a ball.[*]	Improve correct use of ankle, hip, and stepping strategy during static condition; improve quick change of strategy from ankle to hip (or stepping) and vice versa; improve coordination between upper and lower limbs (dual motor tasking).
	Front and side lunges.[*°]	Improve correct use of all strategies during dynamic condition; improve quick change of strategy from hip to stepping and vice versa.
	External destabilization exercises (mainly feedback)	
External perturbed	In stance with feet placed shoulder-width apart on the floor, recover balance after external perturbations by the PT to the patients' chest/upper back/shoulders in anteroposterior and mediolateral directions.[*°@^]	Improve correct use of all strategies during quasi-static condition; improve quick change of strategy; improve proper reaction to unexpected postural destabilization in all directions.
Unstable surfaces	In stance work on progressively thicker compliant surfaces (1.5, 3.5, and 8 cm) according to patient's abilities.[*°@+]	Improve correct use of ankle, hip, and stepping strategy during static condition; improve quick change of strategy; improve ability to orientate the trunk in space.
	In an upright position, recover balance on a rigid, square-shaped wooden platform with a roller surface.[*°]	Improve correct use of ankle, hip, and stepping strategy during dynamic conditions; improve quick change of strategy, improve weight bearing ability and capacity to properly orientate the trunk in space.
	Walking over progressively thicker compliant surfaces (1.5, 3.5, and 8 cm) according to patient's abilities.[*°]	Improve correct use of ankle, hip, and stepping strategy during dynamic conditions; improve quick change of strategy; improve weight bearing ability and capacity to properly orientate the trunk in space.
Swiss ball	Maintain balance while sitting on a Swiss ball, with feet placed shoulder-width apart; in the second part of the exercise, the patient alternatively raises the right and the left leg from the floor.[*°]	Improve trunk control, orientation, and stability.

Table 2: Continued.

Type of exercise	Task explanation	Expected impact
	Self-destabilization and external destabilization exercises (feedback and feedforward)	
Dual-task	Keep walking while catching and throwing a ball with the PT.*	Improve correct use of all strategies during dynamic condition; improve quick change of strategy; improve proper reaction to unexpected postural destabilization in all directions.
	Keep walking while quickly changing direction (forward, backward, sideways).*	Improve correct use of all strategies during dynamic condition; improve quick change of strategy.
	Keep walking while bouncing a ball and switching from right to left hand.*	Improve correct use of all strategies during dynamic condition; improve quick change of strategy; improve proper reaction to unexpected postural destabilization in all directions.
	Keep walking while increasing the amplitude of leg movements (increasing stride length) and swing movement of the arms.*	Improve correct use of ankle, hip, and stepping strategy during dynamic conditions; improve quick change of strategy; improve coordination between upper and lower limbs (dual motor tasking).
	Keep walking while paddling with a stick.*	Improve correct use of ankle, hip, and stepping strategy during dynamic conditions; improve quick change of strategy; improve coordination between upper and lower limbs (dual motor tasking).

CoM, center of mass; CoP, center of pressure; PT, physiotherapist; manipulation of sensory conditions: *free vision, °blindfolded, @wearing a visual-conflict dome, ^firm/compliant surfaces (1.5, 3.5, and 8 cm thick), and +neck extension.

distance, thicker compliant surface), and the duration of holding a given position. The PT gave verbal and manual instructions and, when necessary, provided support at the patient's pelvis or chest [11].

3. Outcomes

At each study center, outcomes were assessed by a single examiner blinded to treatment assignment. Gait and balance measures were evaluated before treatment (T0), after treatment (T1), and at 1-month follow-up (T2). The test order was the same across all evaluation sessions as reported below. Measurements and interventions were conducted with the patients in the ON state.

3.1. Primary Outcome. The Berg Balance Scale (BBS) is a 14-item validated scale that evaluates static and dynamic balance dysfunctions (score range 0–56, with higher scores indicating better performance). The minimal detectable change (MDC) is 5 points for PD patients [23].

3.2. Secondary Outcomes. The Activities-Specific Balance Confidence (ABC) scale evaluates a patient's perceived level of balance confidence in activities of daily living (score range 0–100, with higher scores indicating better performance) [24]. A score below 75.6 suggests increased risk of falls. The 10-Meter Walking Test (10-MWT) measures gait speed. The minimal clinically important difference (MCID) scores in the geriatric population are 0.05 m/sec (small meaningful change) and 0.13 m/sec (substantial meaningful change) [25]. The minimal detectable change in PD patients is 0.25 m/sec (fastest gait speed) [23]. The Dynamic Gait Index (DGI) evaluates an individual's ability to modify gait in response to task demands (score range 0–24, with higher scores indicating better performance). The MCID for older adults with a DGI score < 21/24 is 1.80 [26]. Parkinson's Disease Quality of Life questionnaire (PDQ-8) measures quality of life [27]. The number of falls in the previous month was recorded in a self-report log. At the follow-up evaluation, the patients completed a satisfaction questionnaire investigating domains considered relevant for the patient; responses for each domain were marked on a 5-point Likert-type scale (1: strongly agree; 5: strongly disagree) (Table 3).

Patients were provided with logbook to record their feelings and any difficulties or adverse events they had experienced at each training session.

3.2.1. Costs of Rehabilitation. The direct cost categories included the cost of personnel for screening, assessments (before, after, and follow-up), treatments (one-session training and treatments), and resource utilization. Personnel costs (in euro) were calculated based on the amount of work an average worker performs in 1 hour (staff-hour approach) according to national standard rates. Costs for resource utilization (per type) were calculated taking into account a depreciation rate of 20% per year of the average market value. Indirect costs (utilities, facilities, etc.) were calculated as 25% of the direct costs according to the Italian manual for costing healthcare in public hospitals.

3.3. Sample Size. For sample size calculation, we estimated that 70 patients (35 per group) would provide 90% power

Table 3: Satisfaction questionnaire items.

(1) My privacy was respected during my rehabilitation care.
(2) The instructions my physiotherapist gave me were helpful.
(3) All staff members were courteous.
(4) The rehabilitation sessions were carried out on time without delays.
(5) I was satisfied with the number and duration of treatment sessions.
(6) The location of the facility was easily accessible.
(7) My physiotherapist seemed to have a genuine interest in me as a person.
(8) All staff members understood my problem or condition.
(9) I was satisfied with the treatment provided by my physiotherapist.
(10) I was satisfied with the outcomes of rehabilitative treatment.
(11) I was satisfied with the modalities of rehabilitative treatment.
(12) I believe that this type of treatment is adequate to improve my balance disturbances.
(13) I was satisfied with the overall quality of my rehabilitation care.
(14) I would repeat this treatment if I need rehabilitation care in the future.

Responses were scored on a 5-point Likert-type scale from 1 "strongly agree" to 5 "strongly disagree."

(5% probability of type 1 error) to detect a difference pre- and posttreatment of 4.5 points (variance 33.64) on the BBS score (primary outcome) [28]. Assuming a 9% dropout rate, a total of 76 patients were necessary to perform this study.

3.4. Randomization. The principal investigator (NS) was responsible for randomization procedures. After screening, a list was generated using computer-generated random number tables (allocation ratio 1 : 1). Eligible patients were consecutively entered into the list and allocated to the TeleWii or the SIBT group.

3.5. Statistical Analysis. The single imputation (simple mean) method was used to handle missing data. Descriptive statistics included means and standard deviation. The X^2 test was utilized for categorical variables. Since the data were normally distributed (Shapiro-Wilk Test), parametric tests were used for inferential statistics. A two-way mixed ANOVA was applied using "Time" as the within-group factor and "Group" as the between-group factor. Two-tailed Student's t-test for unpaired data was used for between-group comparisons. The clinical relevance of changes in primary and secondary outcome scores after treatment and at follow-up was evaluated according to published MCID values [25, 26]. The level of significance was set at $p < 0.05$. Bonferroni's correction was applied for multiple comparisons ($p < 0.025$). Statistical analysis was performed with SPSS 20.0 (IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY, USA).

4. Results

One hundred and thirty-five patients were consecutively assessed to the neurorehabilitation centers. Twenty-six patients were excluded because they did not meet the inclusion criteria, 13 declined to participate in this study, and 20 had technological issue including the lack of Internet connection and motivation of using technology.

A total of 76 patients with idiopathic PD were randomized to the TeleWii ($n = 38$) or the SIBT ($n = 38$) group; 36 in the TeleWii and 34 in the SIBT group completed the study. Two patients in the TeleWii group and 4 in the SIBT group withdrew for medical reasons or because of difficulty arranging transportation to the study site (Figure 1). No adverse events were reported during the study period.

There were no significant between-group differences in demographic and clinical data (Table 4) or in primary and secondary outcome measures at baseline (T0).

4.1. Primary Outcome. Significant between-group differences were found for BBS scores ($p = 0.04$) (Table 5). Post hoc between-group comparisons showed that these differences were significant at 7 weeks (completion of training programs [T1]) ($p = 0.02$). Both groups showed an overall significant improvement in performance at T1 and at follow-up evaluation (T2). At T1, the SIBT group improved by 4.21 ($p < 0.001$), and the TeleWii improved by 3.74 ($p < 0.001$). At T2, the SIBT group and the TeleWii improved by 4.05 and 3.21, respectively (Table 5).

4.2. Secondary Outcomes. There were no significant between-group differences in secondary outcomes. A significant "Time ∗ Group" interaction was found in the DGI. The difference in the DGI for the SIBT group reached the MCID at T1 but fell below it at T2 (1.71 instead of 1.80). The difference for the TeleWii group was 0.85 at T1 and 0.93 at T2. Both groups showed an overall significant improvement as measured on the ABC, 10-MWT, DGI, and PDQ-8 (Table 5). The difference in the 10-MWT for the SIBT group indicated a substantial change in performance at T1 (0.14) and a small change at T2 (0.05). The difference in the 10-MWT for the TeleWii group was 0.03 at T1 and 0.02 at T2.

There was no statistical significant difference in satisfaction rates between the TeleWii (mean score 4.57 ± 0.32) and the SIBT groups (mean score 4.66 ± 0.32).

The total cost of rehabilitation was €23.299,00 for the TeleWii group and €28.899,80 for the SIBT group. In both groups, the breakdown in total cost per patient was €24 for physiatrist screening and €28.20 for physiotherapy evaluation (posttreatment and follow-up). The initial physiotherapy evaluation cost is €56.40 because an additional session was required (the first part of the two-step procedure). The total treatment cost was €246.75 for the TeleWii group and €493.50 for the SIBT group. The equipment cost was €106.90 for the TeleWii group and €6.30 for the SIBT group. The indirect costs were €122.63 for the TeleWii group and €152.11 for the SIBT group. The total cost for rehabilitation for patient was € 383.55 for the TeleWii group and € 602. 1 for the SIBT group.

5. Discussion

Two main findings emerged from this study. First, static and dynamic postural control was improved in the PD

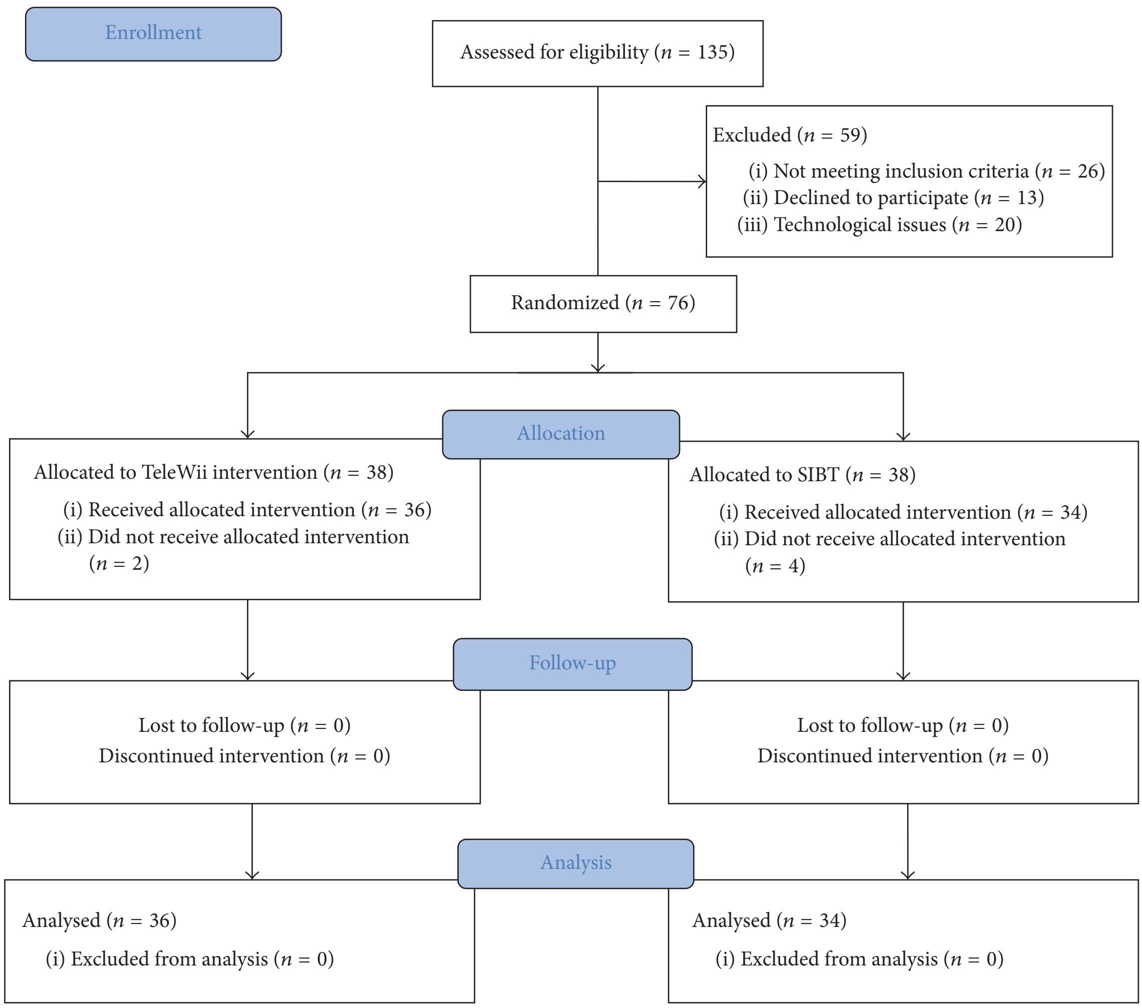

Figure 1: Flow diagram.

patients who had received in-home VR-based balance training (TeleWii), while improvements in mobility and dynamic balance were greater, on average, in those who had received in-clinic SIBT. However, the practical relevance of these differences was minimal. Second, comparable effects on perceived confidence in performing ambulatory activities, gait speed, fall frequency, and quality of life were achieved with both treatment modalities. In addition, the total cost of rehabilitation using TeleWii was lower than that of SIBT.

The Nintendo Wii Fit system has been proposed as a feasible and useful tool for balance training in people with PD [14, 16–18, 28, 29]. Its rationale relies on providing augmented visual and auditory feedback to progressively challenge postural control during a given task. This strategy might bypass the deficient internal motor generation system present in PD patients and improve motor response [30]. Two studies have examined the effects of balance training on postural instability in PD using a home-based setting [16, 28]. In a study published by Esculier et al. [16] involving 10 patients with moderate PD and 8 healthy controls, patients received 6-week home-based balance training using Nintendo Wii and balance board (40 min/session, 3 sessions/week). At the end of the treatment, the PD group reported significant improvements in static and dynamic balance, mobility, and functional ability when compared with healthy controls. Although no significant within-group changes were reported on the ABC scale, at the end of the program the PD patients reported increased balance and stability in activities of daily living (ADL). Zalecki and colleagues [28] reported similar findings in a larger sample of PD patients (n = 24) with moderate PD in which scores on the BBS scale were improved by 4.5 points and by 6.5 points on the ABC scale after treatment. The lack of a control group of patients and follow-up evaluation precludes drawing any conclusions, however. Nevertheless, these positive findings warrant future study.

Exergaming with Nintendo Wii has been shown to improve static and dynamic postural control in people with PD as evaluated on the BBS [16, 28]. In our study, a statistically significant difference was found for the TeleWii group. Though neither training modality achieved a MCID (5 points) in the BBS [23], the improvement was greater after SIBT than TeleWii (4.21 versus 3.74 points).

In both groups, the training effects may be ascribed to the improved use of different resources for postural stability and

Table 4: Baseline demographic and clinical characteristics.

Characteristic	TeleWii Group (n = 38)	SIBT group (n = 38)	Baseline comparison p value
Age (years) (mean ± SD)	67.45 (7.18)	69.84 (9.41)	0.14
Gender (number of males/females)	23/15	28/10	0.22
Disease duration (years) (mean ± SD)	6.16 (3.81)	7.47 (3.90)	0.14
Dominant PD phenotype (NT/T/YO)	21/12/5	14/15/9	0.24
More affected side (B/R/L)	7/21/10	8/20/10	0.95
Modified H&Y stage median (Q1–Q3)	2.50 (2.5–2.5)	2.50 (2.5–3.0)	0.76
UPDRS score (mean ± SD)	44.13 (24.05)	50.76 (24.12)	0.15
Falls (number) (mean ± SD)	0.58 (1.44)	1.84 (5.29)	0.24
MMSE score	26.77 (1.48)	28.64 (6.96)	0.16
GDS score	8.26 (5.17)	9.79 (5.34)	0.21

SD, standard deviation; PD, Parkinson's disease; NT, nontremor dominant; T, tremor dominant; YO, younger onset; B, bilateral; R, right; L, left; Q1: lower quartiles in degrees; Q3: upper quartiles in degrees; H&Y, Hoehn and Yahr; UPDRS, Unified Parkinson's Disease Rating Scale; Falls, number of falls in previous month; MMSE, Mini-Mental State Examination; GDS, Geriatric Depression Scale; $p < 0.05$.

orientation [2]. First, the improvement in postural reactions and movement strategies (i.e., reactive, anticipatory, and voluntary) may have been related to the different training modalities. The SIBT protocol involves more dynamic training, whereas the TeleWii requires the use of feedback, feedforward, and voluntary strategies while performing the exergames, which are quasi-static and focused mainly on self-destabilization tasks. The balance training offered by TeleWii consisted of exercises such as weight shifting, symmetric foot stepping, and controlled movements near the limits of stability repeated in a high number of repetitions and a complex and motivating environment. All these tasks required an active control of body alignment and tone concerning gravity, support surface, visual environment, and internal references. Based on the interpretation of convergent sensory information from somatosensory, vestibular, and visual systems, the patient was requested to implement anticipatory postural adjustments to stabilize the body's center of mass and select an appropriate motor sequence to accomplish the task. In contrast, the lack of exercises focused on compensatory postural adjustments induced by external destabilization should be acknowledged as the main drawback of this approach. The execution of external destabilization exercises could be included in such rehabilitation protocols only with a greater involvement of the caregiver. The effects of TeleWii training may have been reinforced by visual and auditory cueing, which in our study was conceptualized as a motor-learning tool, and by feedback on balance performance that motivated patients to make appropriate postural adjustments [29].

Second, it is conceivable that Wii training led to improvements in sensory strategies (i.e., sensorimotor integration and reweighting). With progressive training, patients were able to rapidly reweight and select the more reliable sensory information to maintain their postural stability. Although postural instability may have multifactorial causes, it primarily results from impaired central integration [3, 31]. In our previous studies, we showed that SIBT might improve sensory integration processes not only in PD [11] but also in other neurological diseases [6, 7]. Similarly, TeleWii might improve the ability to integrate and reweight the incoming sensory inputs and shape the system of coordinates on which the body's postural control is based [2]. In addition, it offers an enriched VR environment of visual and auditory cueing that may improve motor learning [15, 30].

Finally, VR-based exercise programs have been shown to elicit the integration of motor and cognitive abilities (i.e., attention, executive functions) and stimulate the brain's reward circuitry [16, 28, 30, 32]. VR engages participants in cognitive and motor activities (i.e., dual tasking) simultaneously that require planning, attention, sensory integration, and processing of stimuli from the virtual environment [30]. TeleWii enhances this experience more than SIBT by its ability to deliver a combined motor-cognitive experience in an ecologically valid therapeutic environment [29, 30].

SIBT was found to be more effective than TeleWii on the DGI, reaching a higher MCID score than TeleWii after training. This is particularly relevant, given that postural instability and falls [33] in PD become a clinical concern in the middle stages of the illness, though walking difficulties and unsteadiness while turning may often arise also in the early stage of PD. The SIBT training effects may also be ascribed to gain in strength and lean body mass. Although we did not include any measure of muscle strength and body mass among outcome measures, it is conceivable that the exercises requiring postural transfers and walking (for detail see Table 2) may lead to gains in strength and lean body mass. Future studies should consider the training effects of both pieces of training regarding biomechanical constraints that may affect balance such as muscle strength and lean body mass [2].

TeleWii opens new opportunities for treating postural instability, giving individuals access of care from their home [10] especially for those residing in rural areas. This model saves time and travel costs and allows the delivery of rehabilitation services at scale (i.e., one physiotherapist monitoring two or more patients). In our study, this approach was the main factor that reduced the treatment cost, whereby one physiotherapist supervised two patients in real-time. Second, competent staff can supervise training to address specific deficits and adjust task complexity accordingly [10].

Table 5: Descriptive and inferential statistics for clinical outcome measures.

Outcomes	Before T0 Mean (SD)		After T1 Mean (SD)		Follow-up T2 Mean (SD)		Intervention phase Between-group difference (95% CI) mean (LB, UB)		Repeated-measures ANOVA			Post hoc analysis					
									Group	Time	Time × group	Between-group differences		Within-group differences			
														TeleWii		SIBT	
	TeleWii	SIBT	TeleWii	SIBT	TeleWii	SIBT	After	FU	p	p	p	After p	FU p	After p	FU p	After p	FU p
Primary outcome																	
BBS (0–56)	48.63 (6.31)	45.61 (7.97)	52.37 (3.29)	49.82 (5.70)	51.84 (4.53)	49.66 (6.59)	2.54 (0.41, 4.67)	2.18 (−0.40, 4.77)	0.04*	<0.001*	n.s.	0.02*	n.s	<0.001*	0.002*	<0.001*	<0.001*
Secondary outcomes																	
ABC (0–100)	70.31 (18.17)	64.12 (21.37)	79.62 (14.16)	72.52 (21.20)	76.34 (15.98)	71.73 (19.92)	7.10 (−1.16, 15.36)	4.61 (−3.65, 12.87)	n.s.	<0.001*	n.s.	n.s.	n.s.	<0.001*	<0.001*	<0.001*	<0.001*
10-MW (m/s)	1.59 (0.49)	1.46 (0.42)	1.62 (0.43)	1.60 (0.44)	1.57 (0.42)	1.52 (0.37)	0.35 (-0.16, 0.23)	0.04 (−0.14, 0.22)	n.s.	0.02*	n.s.	n.s.	n.s.	n.s	n.s.	0.035	n.s
DGI	20.39 (2.56)	19.34 (2.49)	21.24 (2.56)	21.18 (2.15)	21.32 (2.81)	21.05 (2.54)	0.53 (−1.03, 1.13)	0.26 (−0.96, 1.49)	n.s.	<0.001*	0.04*	n.s.	n.s.	0.005*	0.008*	<0.001*	<0.001*
Falls (number)	0.58 (1.44)	1.84 (5.30)	0.38 (1.33)	0.61 (1.81)	0.29 (0.94)	0.81 (3.31)	−0.23 (−0.95, 0.49)	−0.52 (−1.65, 0.60)	n.s.	n.s	n.s	n.s.	n.s.	n.s.	0.034*	n.s.	n.s.
PDQ-8	30.72 (15.54)	30.53 (16.04)	24.16 (14.78)	24.21 (15.85)	25,82 (14.89)	23.91 (13.20)	−0.05 (−7.06, 6.95)	1.90 (−4.52, 8.34)	n.s.	<0.001*	n.s.	n.s.	n.s.	<0.001*	0.01*	0.016*	0.006*

Before: pretreatment; after: posttreatment; FU: one-month follow-up; SD: standard deviation; TeleWii: telerehabilitation using virtual reality-based training; SIBT sensory integration balance training; p: p value; BBS: Berg Balance Scale (higher score indicates better performance); falls, number of falls in the previous month; ABC: Activities Balance Confidence scale (higher score indicates better performance); 10-MWT, 10-Meter Walking Test; DGI, Dynamic Gait Index; PDQ-8, Parkinson's Disease Quality of Life questionnaire; CI: confidence interval; LB: lower bound; UB: upper bound; ANOVA: analysis of variance; *statistically significant. For repeated-measures ANOVA, p value is significant if <0.05. For post hoc analysis, p is significant if <0.025.

The strengths of the present study are the large patient sample and the comprehensive evaluation of balance disorders about different functions and domains. Its limitations are the lack of instrumental evaluation to assess balance performance, postural reactions, and changing muscle strength and lean body mass. Moreover, these findings cannot be generalized to PD patients with significant cognitive decline, because the use of TeleWii may be unsafe.

To conclude, as a part of the multifaceted management of motor symptoms in PD, TeleWii is a feasible and valid alternative to SIBT for reducing postural instability in PD patients at modified Hoehn and Yahr stages 2.5–3 and having caregiver assistance. TeleWii holds promise and potential to enrich rehabilitation care at home in people with PD but policy issues, especially reimbursement, need still to be addressed.

Disclosure

No commercial party has a direct financial interest in the results of the research supporting this manuscript. No organization has or will confer a benefit on the authors with which the authors are associated.

Conflicts of Interest

The authors declare no potential conflicts of interest regarding the research, authorship, and publication of this article.

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Research Article

The Exercise-Induced Irisin Is Associated with Improved Levels of Glucose Homeostasis Markers in Pregnant Women Participating in 8-Week Prenatal Group Fitness Program: A Pilot Study

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Background. Both exercise and pregnancy influence serum irisin concentration. *Aim.* To determine how the interaction of pregnancy and exercise affects irisin level and whether various patterns of exercise adherence had different effect on irisin concentration. *Methods.* It was a one-group pretest-posttest study among 9 Caucasian nulliparous healthy women in normal pregnancy (age 23 ± 3 years, 21 ± 2 weeks of gestation; mean ± SD) who participated in 8-week group fitness program. Before and after exercise intervention, we determined serum concentrations of irisin and selected parameters of lipid profile and glucose homeostasis markers. *Results.* In active women, irisin slightly decreased with the development of pregnancy. After 8 weeks of exercising, irisin correlated negatively with fasting glucose ($R = -0.922$; $p = 0.001$), glycated hemoglobin ($R = -0.784$; $p = 0.012$), and insulin concentrations ($R = -0.845$; $p = 0.004$). In women exercising below recommended level, we observed a significant drop in irisin concentration, whereas in women exercising at least three times a week this myokine slightly increased (31% difference; 90% confidence limits ±28; a large, clear effect). *Conclusions.* Irisin stimulated by prenatal exercise may improve glucose homeostasis markers in healthy women and compensate for metabolic changes induced by pregnancy. Moreover, the frequency of exercise may regulate the changes in exercise-induced irisin concentration.

1. Introduction

Although pregnant women should perform at least 150 min of moderate-intensity aerobic activity per week [1], only 15% of them adhere to these guidelines [2]. In pregnancy, physical inactivity and excessive weight gain have been recognized as independent risk factors for maternal obesity and related pregnancy complications, including gestational diabetes mellitus (GDM) [1, 3]. Healthy pregnancy can be associated with resistance to the action of insulin on glucose uptake and utilization. This leads to more use of fats than carbohydrates for energy by mother and saves carbohydrates for the growing fetus [4]. In 1–14% of pregnant women, this condition develops into GDM [5], which increases the risk of macrosomia, birth complications, and maternal diabetes after pregnancy. It may also increase the risk of obesity and type 2 diabetes in offspring later in life [6]. Thus, any strategy to prevent GDM should be considered.

Garces and coworkers [7] suggest that irisin concentration is significantly related to the changing insulin sensitivity in healthy pregnant women, regardless of the trimester of gestation and other variables. Irisin is an exercise-inducible myokine that regulates the differentiation of adipose tissue, increasing the energy expenditure and reducing weight and insulin resistance [8]. In addition, irisin activates oxygen consumption in white fat cells and thermogenesis [9]. Irisin protein expression in placenta is low and, therefore, probably not a major contributor to serum concentrations and potential effects of the myokine in pregnancy [10]. Higher irisin concentration was noted in middle and late pregnancy compared to early pregnancy in healthy women, with an increase of approximately 16% and 21%, respectively [7]. Kuzmicki et al. also observed that serum irisin increases markedly in pregnant women, but this increase seems to be significantly lower in patients with GDM [11]. The study by Ural et al. [12] supports these data. Thereby irisin may be a useful biomarker in early pregnancy to predict the development of GDM [13].

Rodrigues et al. [14] have presented a systematic review on how the intensity, duration, and type of exercise can affect the serum irisin concentration in healthy adults, both in men and in nonpregnant women. However, data concerning the influence of physical activity on irisin levels during pregnancy has not been published so far. Thus in this study, we aimed to determine how the interaction of uncomplicated pregnancy and structured exercise program affects serum irisin. The second objective of the study was to answer whether various patterns of exercise adherence had different effect on this myokine concentrations.

2. Methods

The design was a one-group pretest-posttest study among 9 Caucasian nulliparous healthy women in normal pregnancy (age 23 ± 3 years, 21 ± 2 weeks of gestation; mean ± SD). All women volunteered for the study by completing an electronic form available on the web site of the experiment. The eligibility criteria were a positive assessment of woman's health and normal pregnancy confirmed by an obstetric care provider, single pregnancy, and meeting recommended level of physical activity between the conception and the beginning of the experiment. Women's health condition and the course of pregnancy were assessed on the routine medical consultation, according to the national law. The level of physical activity before the experiment was assessed using the Pregnancy Physical Activity Questionnaire [15]. Exclusion criterion was history of miscarriages over 12 weeks of gestation and/or more than two successive miscarriages in the first trimester. The flow of participants through the study is presented in Figure 1.

We conducted the study in Laboratory of Physical Effort and Genetics in Sport, at Gdansk University of Physical Education and Sport (AWFiS) in Poland between January and March 2016. It was performed according to the principles of the Helsinki Declaration and the project's approval of the Bioethics Commission in Gdansk (KB 8/13 and KB 22/15). The participants signed the informed consent before testing.

2.1. Assessment of the Exercise Capacity. At the beginning of exercise program, all women underwent an exercise test on a cycloergometer with electronically regulated load (Viasprint 150P). In order to establish the maximum oxygen uptake we have used stationary respiratory gas analyzer (Oxycon Pro, Erich JAEGER GmbH, Germany). It was calibrated prior to each test according to the manufacturer's instructions. Breath-by-breath data were averaged to provide a data point for each 15-second period.

The test started with a 5-minute adaptation phase when women sat on a chair. There followed a 4-minute warm-up with relative load of $0.4\ \mathrm{W \cdot kg^{-1}}$ of body mass. After the warm-up, the load increased by $0.2\ \mathrm{W \cdot kg^{-1}}$ every minute, up to refusal. Before the experiment we instructed women to use the 0–10 Borg's Perceived Exertion Scale [16]. They were allowed to stop the test at any time. As women's maximal effort, we treated the test results when they achieved the perceived exertion level of 9 or 10 and the value of Respiratory Exchange Ratio (RER) was above 1. Women were cycling during the test for an average of 16 ± 2 min. After the test, the participants rested for 3 minutes sitting on a chair. The highest oxygen uptake achieved during the maximum effort and maintained for 15 seconds was taken as maximal oxygen capacity ($VO_{2\,max}$).

Based on the RER value we had set heart rate zones for exercise sessions. The lower heart rate limit corresponded to the RER value of 0.85. Above this intensity carbohydrates usually start to be predominant source in energy yielding in response to exercise [17]. The upper heart rate limit was set at the RER value equal to 1, which corresponds to the maximal lactate steady state (MLSS) [18]. MLSS represents the exercise intensity above which a continuous increase in blood lactate is unavoidable and refers to the term "anaerobic threshold" [19]. Keeping heart rate between these thresholds ensured that participants performed aerobic exercises and optimize cardiopulmonary fitness [17]. Aerobic physical activity, apart from numerous benefits typical for general populations, compensates for the physiological changes in woman's body induced by pregnancy [20]. It is also considered that it safely helps to control glycemic homeostasis during gestation [21].

2.2. Blood Collection and Analysis. Before the first exercise session, blood samples were taken from the antecubital vein into the vacutainer tubes with $EDTAK_2$ by a professional nurse. For the purpose of assessing glucose level blood was taken into the vacutainer tubes with sodium fluoride. In order to control glucose alternation, glycated hemoglobin was also determined. After the blood collection, all women ate the same light breakfast and after 50–60 minutes of rest they started to exercise. The same schedule of blood collection was applied before the last exercise session at the end of 8-week exercise program. At both time points, the blood samples were taken in a fasting condition. We asked participants to follow recommendations for proper nutrition during pregnancy as well as not to introduce any changes in diet or additional supplements during the experiment.

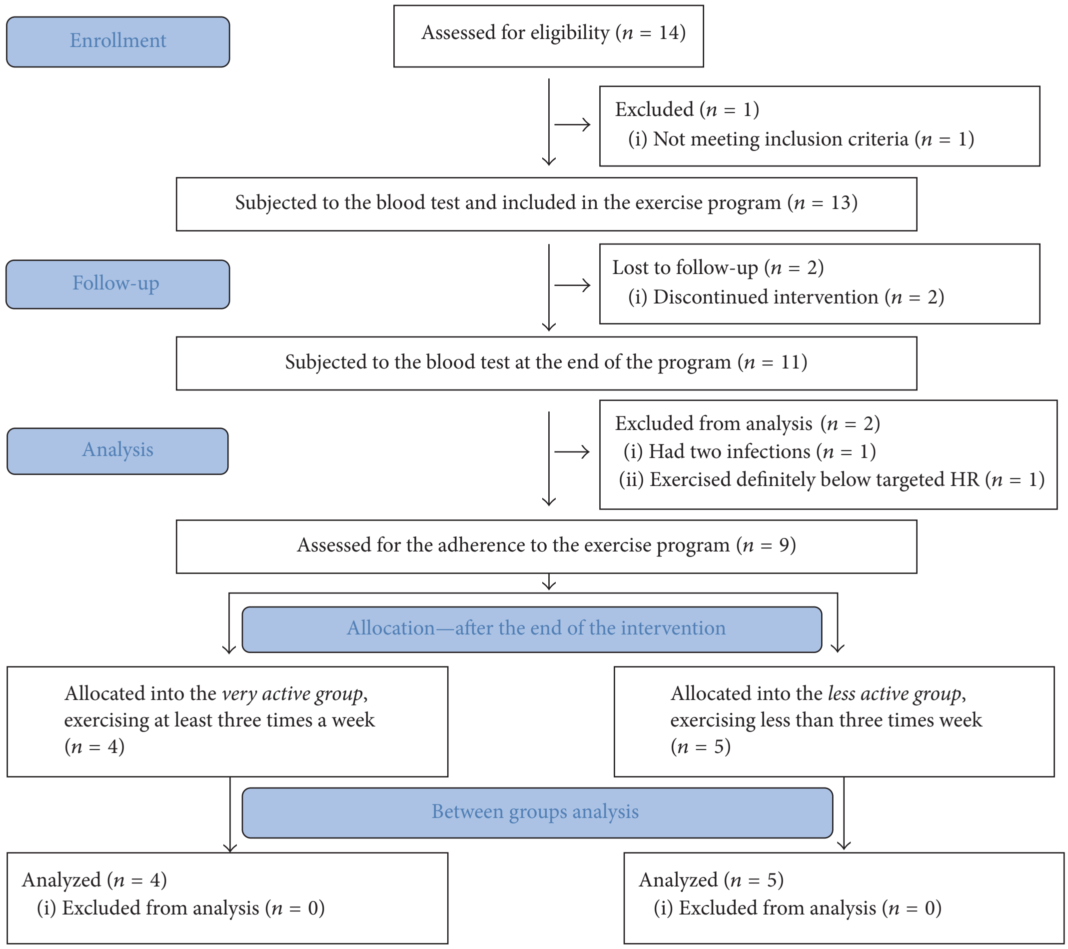

Figure 1: The flow of participants through the study.

Immediately following the blood collection, one portion of the sample was transferred to centrifuge tubes containing aprotinin (catalog number RK-APRO) from Phoenix Pharmaceuticals Inc. The final concentration of aprotinin was 0.6 Trypsin Inhibitor Unit/1 ml of blood. The samples were centrifuged at 2000 g for 10 min at 4°C. The separated plasma samples were frozen and kept at −70°C until later analysis. Quantification of plasma irisin was based on a competitive enzyme immunoassay and the assay kits were purchased from Phoenix Pharmaceuticals Inc. (catalog number EK 067-16). Details of the ELISA assay have been described elsewhere [22]. The dilution of sample was 1 : 5. The intra-assay coefficients of variability (CVs) and interassay CVs reported by the manufacturer were 4%–6% and 8%–10%, respectively. Due to many doubts in assessing irisin we used the one of a recommended commercial kit [23].

Insulin was determined also by enzyme immunoassay methods using commercial kit DiaMetra (DCM076-8). The within assay variability was ≤5%. The hematological measurements were performed using conventional methods with a Coulter® LH 750 Hematology Analyzer (Beckman-Coulter, USA). Glucose was assessed using analyzer Cobos 6000. The serum concentrations of the total cholesterol (TC), high and low density-lipoproteins (HDL, LDL), and triglycerides (TG) were determined with commercial kits using enzymatic methods (Alpha Diagnostics, Poland).

2.3. Prenatal Exercise Program as Experimental Intervention. Pregnant women participated in the 8-week structured exercise program, designed by the principal researcher of the study according to the available guidelines [1, 24]. Group exercise sessions were held three times a week on Mondays, Wednesdays, and Fridays from 9.30–10.30 a.m. at the sport facilities of Gdansk University of Physical Education and Sport. Full attendance in the program provided women with recommended level of physical activity of at least 150 minutes per week.

Each session consisted of warm-up and aerobic part in the form of high-low impact fitness choreography with music (25 min), strength-conditioning exercises (25 min), stretching and breathing exercises, and relaxation (10 min). To maintain proper intensity of exercise during aerobic part we used heart rate monitors (Polar RS400, Finland) in each session with individually adjusted heart rate zones. We trained women how to observe changes in their heart rate and to keep it within the stated ranges. Additionally,

Table 1: Characteristics of the study participants.

Variable at baseline	All pregnant women $n = 9$ (M ± SD)	Very active group[1] $n = 4$ (M ± SD)	Less active group[2] $n = 5$ (M ± SD)
Age, y	29 ± 3	29 ± 4	29 ± 3
Gestational age, wk	21 ± 3	22 ± 2	21 ± 3
BMI, $kg \cdot m^{-2}$	22.5 ± 2.5	21.8 ± 3.0	23.0 ± 2.2
$VO_{2\,max}$, $ml \cdot kg^{-1} \cdot min^{-1}$	23 ± 5.0	23.5 ± 6.6	22 ± 4.1
HR zones for exercise sessions			
HR lower limit ($b \cdot min^{-1}$)	121 ± 12	121 ± 15	121 ± 12
HR upper limit ($b \cdot min^{-1}$)	143 ± 12	141 ± 15	145 ± 11

[1]Participated in exercise sessions at least three times a week; [2]physically active below recommendations, less than 3 times a week; BMI: body mass index; $VO_{2\,max}$: maximal oxygen capacity; HR: heart rate.

they monitored the exercise intensity based on the "talk test" and the Rating of Perceived Exertion (RPE) scale [1]. In the strengthening part women performed nine exercises for each muscle group in two sets of 12–16 repetitions, with a break of 30 s between sets. We instructed the participants to perform the repetitions until they felt unpleasant soreness of the targeted muscles. No equipment was used during exercises and only resistance of own body was applied.

The sessions were conducted by a certified Pregnancy and Postnatal Exercise Specialist whose competences met the European educational standard for this profession [25]. She was informed of the aim of the study and trained in terms of monitoring and maintaining the desired intensity of exercise among participants (inter alia by using rest breaks or implementing jumps and optional repetitions). The principal researcher was checking the quality of exercise program implementation once every two weeks. We used email and phone contact to keep the adherence to the program. The exercise specialist checked and registered attendance for each session. She also recorded reasons for absence and/or additional physical activity performed by the participants individually between sessions. Women were supposed to maintain the same intensity of exercise also in the individual activities, using "talk test" and RPE scale.

2.4. Statistical Analysis. Classical statistical analysis was performed using the Statistica software package (Statistica 10.0 Statsoft Poland) and Graphpad Prism 4.03 software. Continuous variables were expressed as mean ± standard deviation (SD). Univariate correlations were assessed using standardized Spearman coefficients. The p value obtained of less than 0.05 was considered statistically significant.

For more in-depth analysis, after the experiment, we assessed women for the adherence to the exercise program and allocated them into two groups (Table 1). Among nine participants of the study four pregnant women participated in exercise sessions at least three times a week (very active group; completed sessions 31 ± 4; mean ± SD). Five pregnant women exercised below recommendations, less than 3 times a week (less active group; completed sessions 20 ± 3; mean ± SD).

Due to the small size of the groups and insufficient power of classical test, all measures were compiled in Hopkins' *pre-post parallel-groups trial spreadsheet* [26]. All data were log-converted to reduce bias arising from error nonuniformity. Probabilistic conclusions about the true (large-sample) value of effects were provided in the spreadsheet as magnitude-based inferences [27]. We expressed uncertainty in each effect as 90% confidence limits and as probabilities that the true effect was beneficial (e.g., a substantial increase in the irisin level) and harmful (e.g., a substantial decrease in the in the irisin level). Clinically clear beneficial effects were those for which benefit was at least possible (>25% chance) and risk of harm was acceptably low (<0.5%). Effects where chance of benefit outweighed risk of harm (an odds ratio of benefit to harm > 66) were also deemed clear. Other effects were either clearly nonbeneficial (chance of benefit < 25%) or unclear (chance of benefit > 25% and risk of harm > 0.5%). Clear effects were reported as the magnitude of the observed value, with the qualitative probability that the true effect was beneficial, trivial, or harmful for the change (e.g., in the irisin level). The scale for interpreting the probabilities was as follows: 25–75%, possible; 75–95%, likely; 95–99.5%, very likely; >99.5%, most likely [27]. As a threshold value for the smallest important or harmful effect we used 0.2. Because the recommended level of prenatal physical activity is a minimum of 150 min per week, as reference values (control group in Hopkins' spreadsheet) we treated the results of women who met these guidelines (very active group).

3. Results

In Table 1, we presented the characteristics of the whole study group as well as the subgroups separated by the attendance rate. Very active and less active groups in terms of age, week of gestation, BMI, physical fitness, and exercise heart rate zones presented similar values (Table 1).

In all physically active women we recorded 14.78 ± 3.47 $ng \cdot ml^{-1}$ and 14.28 ± 4.39 $ng \cdot ml^{-1}$ (M ± SD) of circulating irisin in 21st and 29th week of gestation, respectively (Table 2). Other selected blood parameters before and after eight weeks

Table 2: Selected blood parameters in pregnant women ($n = 9$) before and after exercise program.

Variable	Before exercise program 21st week of gestation Mean ± SD	After exercise program 29th week of gestation Mean ± SD	Post-pre Difference in mean %
Irisin (ng·ml^{-1})	14.78 ± 3.47	14.28 ± 4.39	−3
Glucose (mg·dl^{-1})	80.78 ± 4.27	82.38 ± 4.66	2
HbA1c (%)	4.71 ± 0.28	4.80 ± 0.27	2
Insulin (μlU·ml^{-1})	3.05 ± 1.82	4.51 ± 3.39	48
TG (mg·dl^{-1})	123 ± 36.47	187.88 ± 65.15	53
TC (mg·dl^{-1})	232.89 ± 50.22	266.56 ± 34.81	14
LDL (mg·dl^{-1})	120.56 ± 38.8	148.67 ± 31.50	23
HDL (mg·dl^{-1})	88.11 ± 18	82.00 ± 15.27	−7

HbA1c: glycated hemoglobin; TG: triglycerides; TC: total cholesterol; LDL: low density-lipoproteins; HDL: high density-lipoproteins.

Table 3: Correlations between irisin, lipids, and glucose homeostasis markers in physically active pregnant women ($n = 9$).

Irisin (ng·ml^{-1})	Before exercise program 21st week of gestation	After exercise program 29th week of gestation
Glucose (mg·dl^{-1})	$R = -0.068$; $p = 0.861$	$R = -0.922$; $p = 0.001^*$
HbA1c (%)	$R = 0.093$; $p = 0.811$	$R = -0.784$; $p = 0.012^*$
Insulin (μlU·ml^{-1})	$R = 0.166$; $p = 0.668$	$R = -0.845$; $p = 0.004^*$
TG (mg·dl^{-1})	$R = -0.161$; $p = 0.460$	$R = -0.503$; $p = 0.204$
TC (mg·dl^{-1})	$R = -0.500$; $p = 0.170$	$R = -0.385$; $p = 0.306$
LDL (mg·dl^{-1})	$R = -0.617$; $p = 0.077$	$R = -0.300$; $p = 0.432$
HDL (mg·dl^{-1})	$R = -0.083$; $p = 0.831$	$R = 0.250$; $p = 0.516$

Univariate correlations were assessed using standardized Spearman coefficients; *the p value obtained of less than 0.05 was considered statistically significant; HbA1c: glycated hemoglobin; TG: triglycerides; TC: total cholesterol; LDL: low density-lipoproteins; HDL: high density-lipoproteins.

of exercise program corresponded to the reference values for pregnancy [28].

Before exercise intervention (21st week of gestation) we found no relationships between irisin concentration and glucose homeostasis markers or lipid profile (Table 3). However after 8 weeks of exercising (29th week of gestation) irisin levels correlated negatively with fasting glucose, glycated hemoglobin, and insulin concentrations (Figure 2). We observed positive association between irisin level and number of exercise sessions performed by pregnant women during 8 weeks of exercise program (Figure 3).

The irisin concentrations before the exercise program (21st week of gestation) in very active and less active groups were 15.32 ± 5.3 and 14.3 ± 1.5 ng·ml^{-1}, respectively. After 8 weeks in three participants exercising below the recommended level we observed a significant decrease in irisin concentration (average by 32%; min 31%, max 36%). We did not record similar reductions in irisin level in women who exercised at least three times a week. In this study group, the maximum decrease in the level of irisin was 4%, and the two participants had an irisin increase of 24 and 58% (Figure 4).

Changes in lipid profile and glucose homeostasis markers in response to exercise intervention in women from very active and less active groups are presented in Table 4. Comparing the mean change in the pre- and posttraining irisin level between groups using magnitude-based inferences we observed a large, clear effect. The irisin level was substantially lower in women who exercised below recommendations relative to women exercising at least three times a week.

4. Discussion

To the best of our knowledge, this is the first study determining irisin levels in pregnant women participating in a structured exercise program.

The unexpected result of our study is that the serum concentration of irisin slightly decreased with the development of pregnancy in contrast to the findings presented in other studies [7, 11, 13]. Some authors hypothesized that elevated circulating irisin is an adaptive response to compensate for the increasing insulin resistance and limit the adverse metabolic and vascular effects of pregnancy [10, 13]. Ebert et al. [29] observed that homeostasis model assessment of insulin resistance (HOMA-IR) remains as a positive predictor of irisin serum concentrations. It should be underlined that physical activity of moderate to high intensity significantly decreases insulin resistance in pregnant women [30]. We can assume that physical activity removes the potential cause for higher secretion of irisin. This can explain very similar irisin level in 21st and 29th week of gestation in regularly exercising pregnant women.

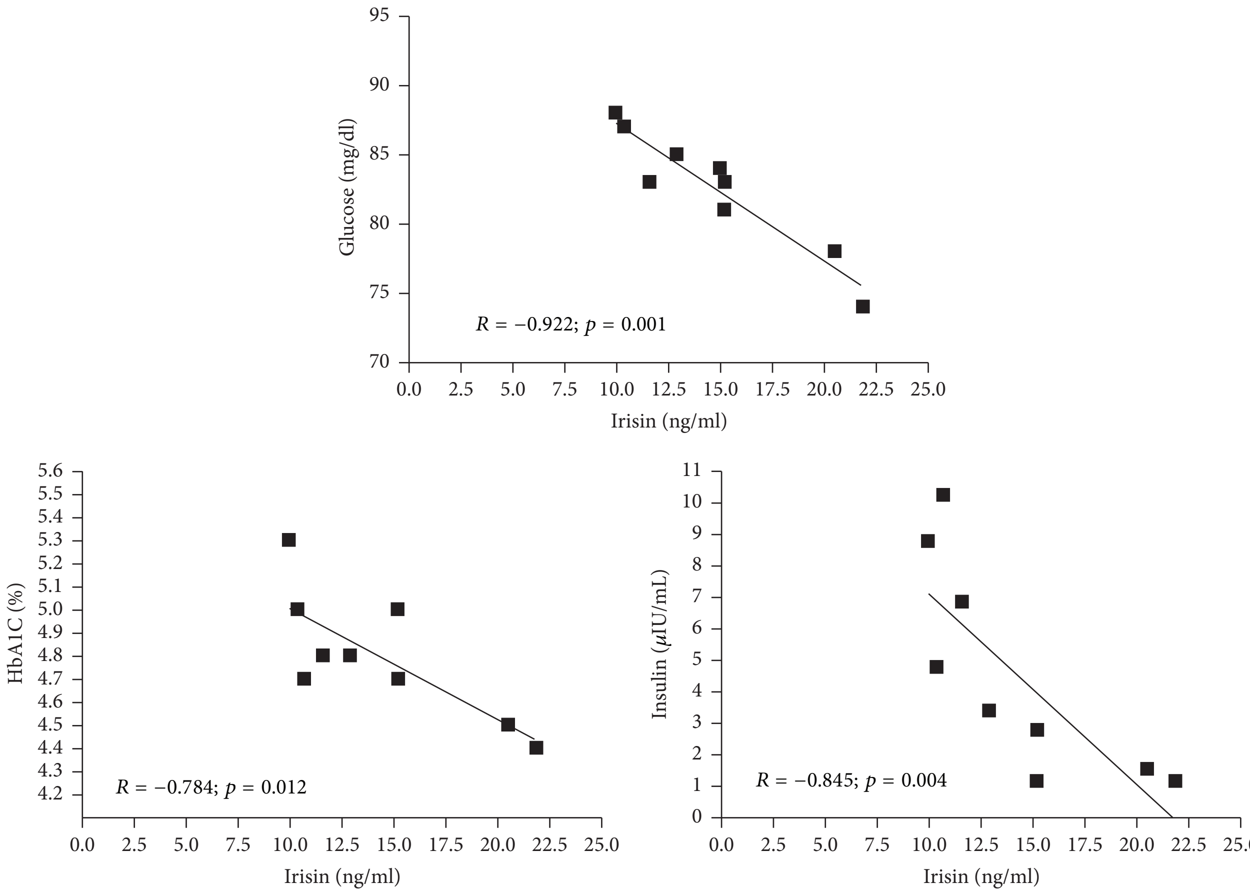

Figure 2: Correlations between irisin concentration and glucose homeostasis markers in women ($n = 9$) in 29th week of gestation after 8 weeks of exercise program.

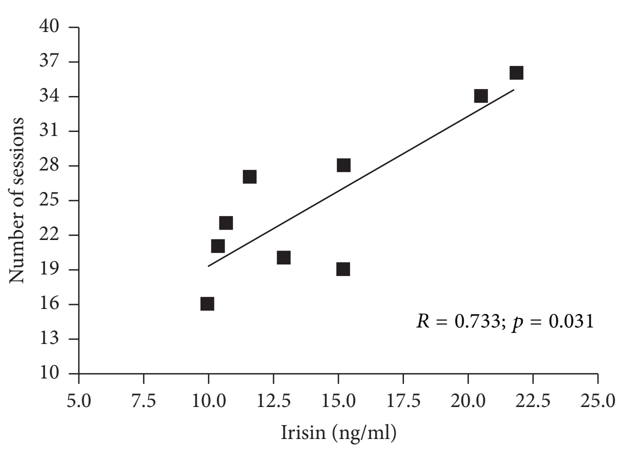

Figure 3: Correlations between irisin concentration and number of exercise sessions performed by pregnant women ($n = 9$) during 8 weeks of exercise program.

In nonpregnant healthy subjects circulating irisin levels are associated with a beneficial metabolic profile [29]. In pregnancy the interaction of circulating irisin and metabolic parameters seems to change significantly. In the study by Piya et al. [31] serum irisin in the pregnant women was positively correlated with glucose, insulin, HOMA-IR, total cholesterol, TG, LDL, and HDL. Ebert et al. [10] also found positive correlation between irisin and fasting insulin, HOMA-IR, and total cholesterol in healthy pregnant women. Among participants of our experiment, we did not record correlation between irisin, lipid profile, and glucose concentration at baseline. However, after 8 weeks of group fitness program (29th week of gestation) irisin levels inversely correlated with fasting glucose, glycated hemoglobin, and insulin concentrations. Our results might suggest that irisin stimulated by exercise leads to improvement in the levels of glucose homeostasis markers and may compensate for metabolic changes induced by pregnancy. Recently published review summarized the particular role of irisin in glucose homeostasis. Available data indicated that the elevated concentration of irisin enhanced glucose and fatty acid uptake (by 30–40%). This increase in glucose uptake results from the upregulation of glucose transporter type 4 (GLUT4) expression, without significant changes in the expression genes encoding insulin receptors [23]. Observed correlations in our group of women might confirm that information. Moreover the drop of insulin accompanied by the increase of irisin may reveal the improvement of muscle insulin sensitivity.

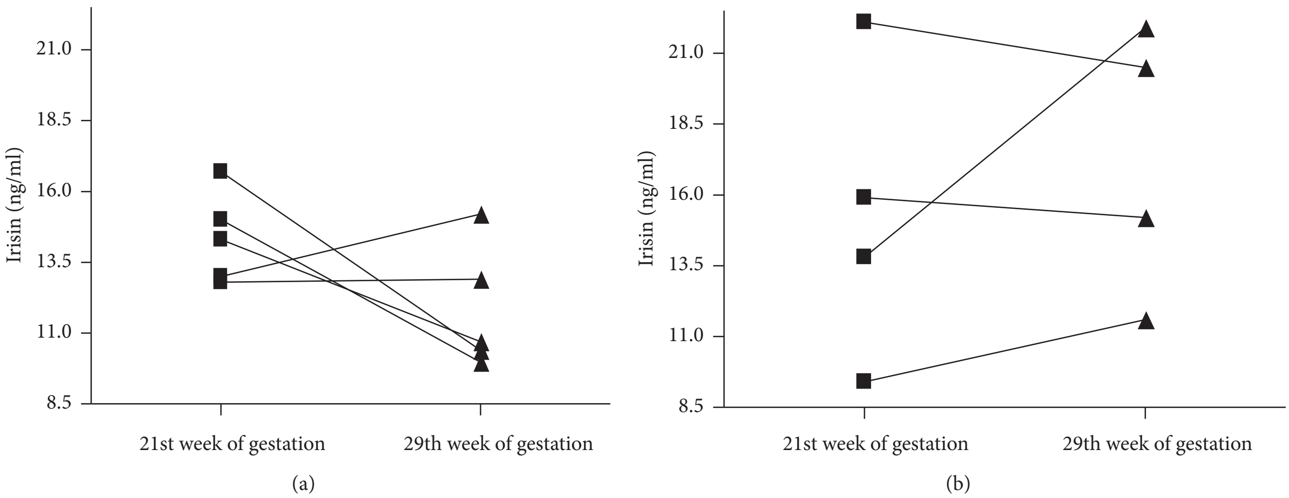

Figure 4: The irisin concentration before and after 8-week exercise program (21st and 29th week of gestation, resp.) in women who had physical activity below recommendations ((a) less active group) and in women who exercised at least three times a week ((b) very active group).

An interesting question is why we did not observe significant relationship between irisin and serum lipids in our participants. We can hypothesize that the implemented prenatal exercise program had more effect on glucose than lipid metabolism due to the assumed intensity of physical exertion. Women performed exercise with the intensity of HR corresponding to RER value between 0.85 and 1.0, which means that carbohydrates were the predominant source in energy yielding by the muscle [17]. It would be valuable to observe the irisin level and its relationship to serum lipids in pregnant women exercising with lower intensity leading to greater fat utilization in future research.

Interestingly, we observed strong positive correlation between irisin and the number of exercise sessions performed by the study participants. The influence of physical activity on irisin still is not clear. Regular exercise affects the irisin concentration in both man and women. In the study by Zhao at al. [32], after 12-week resistance exercise program, the circulating irisin was significantly elevated in the older male adults. Similarly, Kim et al. [33] observed higher serum concentrations of irisin in the trained group of nonpregnant women compared to the control group after 12 weeks of resistance training. However, due to potentially gender dimorphism of irisin [34] which probably relates to female reproductive function [7], pregnant women may respond differently to exercise regarding this myokine secretion. Until now no data are available on how prenatal physical activity affects irisin concentration. Exercise program implemented in our experiment consisted of aerobic part and strength-conditioning exercises, so two different training stimuli could have affected irisin production. In future studies it would be interesting to compare irisin levels in pregnant women undergoing various types of physical exertion.

In order to plan an effective prenatal training program, the type, intensity, frequency, and duration of exercise sessions should be appropriately adjusted to the physiological and biomechanical needs of the pregnant [24]. In this experiment, we found substantial differences in irisin, possibly determined by the frequency of exercise. In less active group (exercising less than three times a week) the exercise program induced a clear drop, whereas in very active group (exercising at least three times a week) a slight increase in irisin was noted. These different responses to exercise may be related to different total training loads during 8 weeks of the experiment resulting from different total volume of exercise during program (duration of each session multiplied by the number of sessions performed).

On the other hand, differences in irisin may depend on previous physical activity patterns. Although both groups met the same inclusion criteria and presented the similar level of various parameters at baseline, it is probable that women who could not keep the recommended exercise regime during the experiment had been less active also before its implementation. Another interpretation for our results is related to the source of irisin. Roca-Rivada and coworkers showed that both human subcutaneous and visceral fat tissue express and secret FNDC5/irisin, which indicates that irisin may be also adipokine [35]. Moreover, Dulian and coworkers also observed the rise of irisin concentration in obese men in response to low temperatures [36]. They noted correlations between body composition and irisin concentration, suggesting that subcutaneous fat tissue, rather than skeletal muscle, was the main source of irisin. To use these findings to interpret our observations in pregnant women it would be necessary to thoroughly analyze their body composition. It is also tempting to speculate that in relation to irisin there is a threshold for training load in which physical activity not only compensates for the pregnancy-induced metabolic changes, but likewise gives a posttraining supercompensation effect. Clearly, these hypotheses need to be tested in future studies.

An important finding is that among our participants the decreasing irisin was not associated with complications

Table 4: Changes in lipids and glucose homeostasis markers in women who had physical activity below recommendations (n = 5) and in women who exercised at least three times a week (n = 4).

	Group	Baseline mean ± SD	Observed change mean ± SD	Adjusted change[a] mean ± SD	Adjusted effect[b] Mean; CI	Adjusted effect[b] Inference[c]
Irisin (ng·ml^{-1})	Very active	15.32 ± 5.30	15 ± 29%	15 ± 28%	−31%	*Large*$^{\downarrow**}$
	Less active	14.34 ± 1.59	−18 ± 31%	−20 ± 13%	−54 to 3%	
Glucose (mg·dl^{-1})	Very active	77.25 ± 3.69	3 ± 3%	3 ± 4%	−2 %	Small
	Less active	83.60 ± 1.95	1 ± 3%	1 ± 3%	−10 to 6%	
HbA1c (%)	Very active	4.53 ± 0.19	2 ± 5%	−1 ± 5%	4%	Moderate
	Less active	4.86 ± 0.25	2 ± 3%	3 ± 3%	−7 to 16%	
Insulin (μIU·ml^{-1})	Very active	3.58 ± 2.28	8 ± 66%	15 ± 80%	−20%	Small
	Less active	2.38 ± 0.88	47 ± 37%	43 ± 37%	−71 to 122%	
TG (mg·dl^{-1})	Very active	131.80 ± 42.75	45 ± 24%	42 ± 28%	14%	Small
	Less active	112.00 ± 28.65	59 ± 26%	61 ± 30%	−22 to 65%	
TC (mg·dl^{-1})	Very active	218.00 ± 45.85	19 ± 5%	18 ± 5%	−0.4%	Trivial
	Less active	244.80 ± 55.39	14 ± 15%	18 ± 5%	−8 to 8%	
LDL (mg·dl^{-1})	Very active	109.75 ± 40.60	33 ± 14%	29 ± 8%	−3%	Trivial
	Less active	129.20 ± 39.56	22 ± 18%	25 ± 12%	−15 to 11%	
HDL (mg·dl^{-1})	Very active	85.50 ± 10.28	−3 ± 5%	−3 ± 6%	−6%	Small
	Less active	90.20 ± 23.59	−10 ± 30%	9 ± 29%	−29 to 24%	

Note. Less active: exercising less than three times a week, very active: exercising at least three times a week, and CI: 90% confidence interval. All data are percentages, with the exception of baseline values expressed in measurement units. Inferences shown in italic are clear at the 90% level of confidence. [a]Adjusted to overall mean of the less active and very active groups at baseline. [b]Adjusted mean change in the less active group minus adjusted mean change in the very active group. [c]Magnitude thresholds (for difference in means divided by SD of control group): <0.20, trivial; 0.20–0.59, small; 0.60–1.19, moderate; 1.20–2.19, large; 2.2–4.0, very large. $^{\uparrow}$Increase; $^{\downarrow}$decrease. Asterisks indicate effects clear at the 5% level and likelihood that the true effect is substantial: *possible, **likely, ***very likely, and ****most likely.

during pregnancy, as the results of previous studies would suggest. Other authors observed that in women with gestational diabetes mellitus the irisin concentration was lower than in healthy subjects [10–12]. In our study group of physically active pregnant women we have not reported any case of GDM or preeclampsia.

Obviously, the weakest point of our study is the small number of the participants, which definitely limits the possibility of generalizations. For ethical reasons we decided to conduct a quasi-experimental study instead of randomized control trial [37]. At least 150 minutes per week of physical activity has been recommended for uncomplicated course of pregnancy [1]. It would be unethical to randomize pregnant women to the intervention of lower physical activity level or encourage them to physical inactivity. We can assume, however, that a comparison of changes between groups of physically active and inactive pregnant females would give more varied results in serum irisin concentrations and other parameters.

Another limitation is that we could not refer our observations to the findings by other authors on irisin levels in pregnancy, as they have not presented data on the physical activity levels of their subjects.

5. Conclusions

In healthy, physically active women with uncomplicated pregnancy, the serum irisin concentration slightly decreased between the second and the third trimester. These observations contradict the results of other authors, who found that the irisin level elevates markedly with the development of pregnancy. However, pregnant women in other studies did not participate in regular physical activity. Therefore, we can conclude that the structured, prenatal exercise programs may compensate for metabolic changes induced by pregnancy, also those related to increased irisin secretion. Higher irisin concentration in serum was related to better glucose homeostasis.

The frequency of exercise substantially differentiated the level of this myokine in pregnant women.

Our results support the promotion of physical activity during pregnancy and educational activities for the obstetric care providers and exercise specialists enabling them to implement well-designed prenatal exercise programs, meeting different needs of pregnant exercisers. Because of the health benefits, pregnant women should be encouraged to fulfill the recommended level of physical activity.

Disclosure

Ewa Ziemann is a senior author.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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Research Article

Barriers to Physical Activity in Low Back Pain Patients following Rehabilitation: A Secondary Analysis of a Randomized Controlled Trial

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Background. Promoting health-enhancing physical activity following rehabilitation is a well-known challenge. This study analysed the barriers to leisure time activity among low back pain patients. *Methods.* A subset of 192 low back pain patients who participated in a randomized controlled trial promoting physical activity was analysed. Physical activity, barriers, and sociodemographic and indication-related variables were assessed by a questionnaire. Differences in barriers between active and inactive participants were tested by Pearson's chi squared test. A logistic regression model was fitted to identify influencing factors on physical activity at six months following rehabilitation. *Results.* Inactive and active participants differed significantly in nine of the 19 barriers assessed. The adjusted regression model showed associations of level of education (OR = 5.366 [1.563; 18.425]; p value = 0.008) and fear of pain (OR = 0.612 [0.421; 0.889]; p value = 0.010) with physical activity. The barriers included in the model failed to show any statistically significant association after adjustment for sociodemographic factors. *Conclusions.* Low back pain patients especially with a low level of education and fear of pain seem to need tailored support in overcoming barriers to physical activity. This study is registered at German Clinical Trials Register (DRKS00004878).

1. Introduction

Low back pain exhibits a high prevalence in medical rehabilitation and high costs for social insurers in Germany [1, 2]. Physical activity and exercise are an integral part in the management and rehabilitation of low back pain [3–8]. Across all indications the promotion of health-enhancing physical activity is of utmost importance to increase the sustainability of rehabilitation [8–10]. Nevertheless, engaging in regular exercise and implementing physical activity into a daily routine are a common problem for patients following rehabilitation [11]. However, little is known about the barriers to physical activity among low back pain patients.

In general, commonly reported barriers for undertaking physical activity can be assigned to different categories: *lack of time* (e.g., due to family, household, and occupational responsibilities) [12–16], *health and quality of life* (e.g., comorbidity) [14, 17–19], *psychological barriers* (e.g., emotional or motivational problems) [15, 16, 19], *social and sociocultural barriers* (e.g., family commitments) [12, 13, 16, 18], *access* *issues* (e.g., financial limitations, physical environment, and lack of access to exercise opportunities) [12, 15–18], *low socioeconomic status* [12], and *lack of knowledge* (e.g., dependence on professional instruction) [12, 13, 17] or *competing priorities* [13].

In order to increase physical activity behavior among low back pain patients it is important to understand what barriers prevent them from participating. Following a research project on physical activity promotion [20] the objective of the present exploratory study was to describe the perceived barriers to physical activity among a group of low back pain patients following rehabilitation. The research questions of the present secondary analysis were as follows: (1) Which barriers to physical activity do physically inactive low back pain patients describe following rehabilitation? (2) Which barriers and sociodemographic and indication-related variables are associated with physical inactivity following rehabilitation?

2. Materials and Methods

2.1. Study Design and Data Source. The cross-sectional data analysed for this work were obtained from a subset of 192 low back pain patients who completed a questionnaire on physical activity barriers after participating in a randomized controlled trial ($T0$ = start of inpatient rehabilitation (baseline), $T1$ = six-month follow-up, and $T2$ = twelve-month follow-up).

The randomized controlled trial evaluated the effectiveness of two different approaches in physical activity promotion [20]. The intervention [20] as well as details of the study sample, including details regarding the subset of patients who completed the six-month follow-up questionnaire ($T1$) compared to the baseline sample ($T0$), [21] has already been reported elsewhere.

In brief, chronic low back pain (LBP) patients were recruited in an inpatient rehabilitation center from May 2013 until the planned sample size of 264 patients was reached in April 2014. Details of the sample size calculation are described in the study protocol [20]. The inclusion criteria were (1) age 18 to 65 years; (2) starting an inpatient medical rehabilitation treatment due to low back pain. Exclusion criteria were (1) cognitive disorders; (2) insufficient understanding of the German language; (3) any kind of surgery within the last three months; (4) posttraumatic conditions (e.g., LBP following an accident); (5) a current state pension claim. Participants were randomly assigned to the intervention group (*Movement Coaching*: comprehensive multicomponent intervention with small-group intervention, phone- and web 2.0-intervention) or the low intensity control group (two oral presentations available for download afterwards). The therapist that conducted the intervention in both study groups had a Master's degree in Sport Science with the main field of study in "Rehabilitation and Health Management."

The main outcome was total physical activity. Written informed consent was obtained from each participant. The study was conducted in compliance with the Helsinki Declaration and was approved by the Ethics Committee of the German Sport University Cologne. The study is registered in the German Clinical Trials Register (DRKS00004878). Patients answered the baseline questionnaire ($T0$) at the beginning of the inpatient rehabilitation. The data on barriers and physical activity were collected at six-month follow-up ($T1$) by postal questionnaire.

2.2. Outcome Measures. Physical activity was measured with the Global Physical Activity Questionnaire [22, 23]. The GPAQ collects information on physical activity during a typical week within three areas of life (workplace, transport, and leisure time) as well as sedentary behavior. Since the differentiation of workplace and leisure time physical activity seems to be relevant in assessing health-enhancing effects in low back pain patients [24–26], we focused on leisure time physical activity solely. The GPAQ asks if physical activity during leisure time is performed during a regular week ("yes"/"no") and subsequently measures leisure time physical activity with respect to its intensity by multiplying the minutes per week for each domain by their associated MET to create MET-min scores (the metabolic equivalent (MET) is a physiological measure expressing the expended energy of physical activities; MET is defined as the ratio of the rate of energy consumption during a specific physical activity to a reference metabolic rate). Activity specific scores are summed to create total MET-min/week (MET-min/week). Thereby, each minute of vigorous physical activity is multiplied by 8 METs and each minute of moderate physical activity by 4 METs.

To identify perceived situational barriers a patient-reported questionnaire was used [27]. Asking "how strongly do the following barriers keep you from being physically active and/or doing sports in your daily routine" the questionnaire assesses 13 situational barriers. Thereby, a situational barrier is a high risk situation which impedes the realization of the behavior change. Barriers were separated into *psychosocial and external factors* (ten items): bad weather, being tired, too much work, being in a bad mood, activities with friends, not feeling like it, wanting to stay home, TV, being depressed, and stress and *physical barriers* (three items): being ill (meaning suffering from an illness or disease or feeling unwell), pain, and injury. Beyond, we extended the questionnaire with six different *access barriers* (partner against it, sport field too far away, too expensive, difficult to organize, no sport partner, and forgot to do sport). Participants were asked to rate the perceived impact of each barrier on a 4-point Likert-type scale that ranges from 1 (not a barrier at all) to 4 (very strong barrier). Higher scores indicate that the associated barrier has a greater impact on the participant's ability to participate in sports or leisure time physical activity.

Additionally, we asked about demographic and indication-related variables by nonstandardized questions at baseline (gender, age (years), height, weight, level of education, duration of low back pain at the beginning of inpatient rehabilitation and at six-month follow-up, intensity of pain during the last four weeks, pain by physical activity).

2.3. Statistical Analysis. For the sample description means and standard deviation (SD) were calculated for continuous

Table 1: Characteristics of the sample.

	Sample
Baseline (T0)	
Age (years) (n = 190) [mean (SD)]	51.3 (±7.3)
Gender: men (n = 192) [n; %]	126 (66%)
Body mass index: normal weight (n = 179) [n; %]	40 (22%)
Highest level of education "lower secondary school" (n = 188) [n; %]	100 (52%)
Duration of low back pain at baseline > 12 months (n = 187) [n; %]	182 (87%)
Active (>0 MET-min leisure time physical activity/week) (n = 192) [n; %]	111 (58%)
Intervention group (n = 192) [n; %]	92 (48%)
Six-month follow-up (T1)	
Intensity of pain during the last four weeks at six-month follow-up (min: 1; max.: 6) (n = 188) [mean (SD)]	3.6 (±1.3)
Active following rehabilitation (>0 MET-min leisure time physical activity/week) (n = 186) [n; %]	148 (77%)
By physical activity my back pain becomes more intense (0: not at all; 6: exactly) (n = 183) [mean (SD)]	2.8 (±1.9)

data and frequency tables (n; %) for categorical data. For physical activity, the number of subjects being "active" during leisure time was reported. We defined "active" reporting any physical activity during leisure time (>0 MET-min/week) and "inactive" as no physical activity during leisure time (0 MET-min/week). Low back pain at the beginning of inpatient rehabilitation ("≤12 months"/">12 months"), level of education ("lower secondary school"/"higher level of education than lower secondary school"), and body mass index ("normal weight"/"overweight or obese") were dichotomized.

For description of the barriers to physical activity (research question 1) we only included participants reporting to be physically inactive during leisure time (0 MET-min/week) at six-month follow-up ($T1$). The patient-oriented perception of barriers was described using frequencies.

To identify factors with physical inactivity following rehabilitation (research question 2) a logistic regression model was used. For this purpose, we dichotomized each barrier ("barrier"/"no barrier"). A barrier was considered if a participant responded with "4: very strong barrier" or "3: strong barrier". No barrier was considered if the participant answered "1: not a barrier at all" or "2: minimal barrier".

As we pursued an exploratory approach in our study, we first compared barriers in active and inactive participants using for each Pearson's chi squared test. Due to the explorative nature of the work we did not control for multiple testing. If there was a significant difference between the two groups, we included the specific barrier in our logistic regression model. To adjust for confounding, all sociodemographic and indication-related variables assessed were included in the model. Additionally, we controlled for the effects of the intervention from the main study by including the intervention group ("Movement Coaching"; "low intensity control group") in the analysis. Physical activity at six months following rehabilitation ("active" versus "inactive") was the dependent variable. Participants with missing values in dependent or independent variables were excluded. Analyses were performed using SPSS 24. The α-level of significance was set at p value < 0.05.

3. Results

3.1. Study Sample. Consort flow chart of the main study was already published [21]. The demographic and indication-related characteristics of the 192 participants in the present evaluation on barriers are shown in Table 1. More than half of the participants (66%) were male and the mean age was 51.3 years (±7.3). The majority of the participants reported "lower secondary school" as the highest level of education (51%) and were suffering from low back pain for more than twelve months before inpatient rehabilitation (87%). Less than a quarter of the participants reported normal weight (22%), this means a body mass index between 18.5 and 25.0 kg/m^2, and 58% of the participants were classified as physically active during leisure time at baseline. Six months after rehabilitation, the mean pain intensity was 3.6 (±1.3) on a scale from 1 to 6. The opinion of the participants in regard to fear of pain, which means the individual's assumption of a negative influence of physical activity on low back pain, could be graded as "not sure" (2.8 (±1.9) on a scale from 0 to 6) and 77% of the participants were classified active at six-month follow-up. Overall, no differences were observed in subject characteristics among randomization groups of the main study (results not shown).

3.2. Perceived Barriers of Inactive Participants. The evaluation of barriers on physical activity was restricted to the 44 participants reporting to be physically inactive during leisure time (0 MET-min/week) at six-month follow-up ($T1$).

More than half of the patients reported the internal barriers "being tired" (59%), "pain" (59%), and "stress (50%) as a strong or even very strong barrier to physical activity. Further major barriers were "being ill" (49%) and "too much work" (41%). From all barriers assessed, having a "partner not supporting" physical activity and sports (7%) and "watching" TV (14%) were reported least frequently (Figure 1).

3.3. Associations with Physical Activity following Rehabilitation. Table 2 shows frequencies for perceived barriers in inactive and active participants. Active and inactive patients

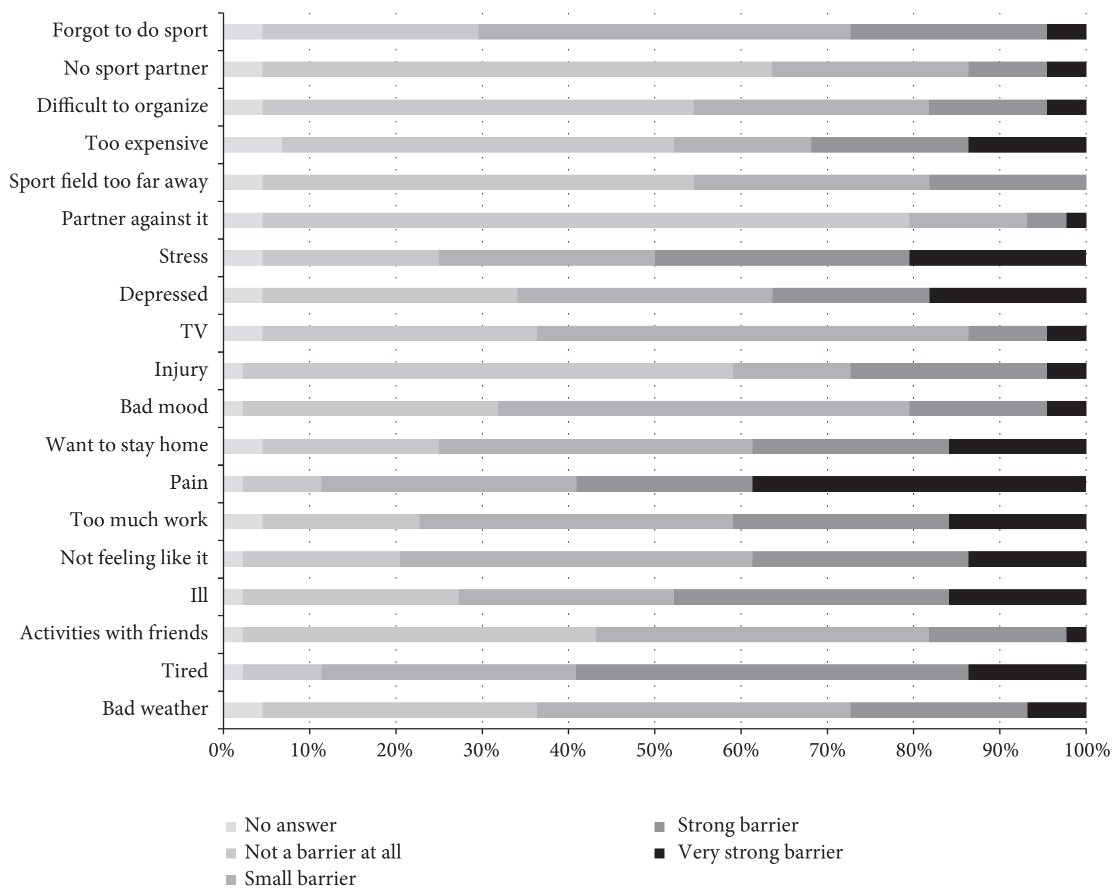

Figure 1: Perceived barriers of inactive participants at six-month follow-up (multiple answers possible).

showed statistically significant differences with regard to nine barriers, therefrom six internal barriers ("being tired" (p value < 0.001), "not feeling like it" (p value < 0.001), "want to stay home" (p value < 0.001), feeling "stressed" (p value $= 0.014$), being "depressed" (p value $= 0.006$), and "forgot to do sports" (p value < 0.001)) and three external barriers ("sport field too far away" (p value $= 0.019$), "too expensive" (p value $= 0.004$), and "bad weather" (p value $= 0.005$)), and they were reported proportionally more frequent in inactive patients. The highest proportional differences were in the barriers "want to stay home" (active: 10%; inactive: 39%) and "not feeling like it" (active: 14%; inactive: 39%).

The nine statistically significant barriers described above were included in a regression model (see Table 3). In combination with the sociodemographic and indication-related variables the model explained 51% of the variation ($R^2 = 0.51$). Two variables were statistically significantly associated with leisure time activity: the odds of patients with a level of education higher than lower secondary school to be physically active were around five times higher than of patients with highest level of education "lower secondary school" (German: Hauptschule) (OR = 5.366; 95% confidence interval [1.563; 18.425]; p value $= 0.008$). Furthermore, the persuasion that physical activity increases low back pain was associated with statistically significantly higher odds of inactivity (OR = 0.612; 95% confidence interval [0.421; 0.889]; p value $= 0.010$). None of the nine barriers included in the regression model showed an association with physical activity in the adjusted regression model.

4. Discussion

The present analysis focused on barriers to physical activity among chronic low back pain patients participating in a specific program promoting physical activity following inpatient rehabilitation. Inactive and active participants differed significantly in nine of the 19 barriers assessed. The three main barriers of inactive participants were internal barriers ("being tired," "pain," and "stress"). The adjusted regression model showed that low level of education and fear of pain were significantly associated with physical inactivity. The barriers once included in the model did not remain statistically significant.

The association of education and leisure time physical activity or sports is widely accepted [28, 29]. Our results showed that a higher level of education was associated with a higher chance of being physically active during leisure time. Thereby, our results are in line with the literature showing that a low level of education is associated with a higher chance of being physically inactive in sports or during leisure time [29–31]. Hence, literature also shows, that, in contrast to leisure time activity, low level of education tends to be associated

Table 2: Perceived barriers of inactive and active participants at six-month follow-up (dichotomized).

Perceived barrier ("very strong barrier" or "strong barrier")	Inactive (n = 44) n (%)	Active (n = 148) n (%)	p value[1]
Bad weather	12 (27%)	16 (11%)	**0.005***
Tired	26 (59%)	27 (25%)	**<0.001***
Activities with friends	8 (18%)	19 (13%)	0.376
Being ill	21 (48%)	85 (58%)	0.276
Not feeling like it	17 (39%)	20 (14%)	**<0.001***
Too much work	18 (41%)	49 (33%)	0.281
Pain	26 (59%)	64 (43%)	0.060
Want to stay home	17 (39%)	15 (10%)	**<0.001***
Bad mood	9 (21%)	21 (14%)	0.302
Injury	12 (27%)	58 (39%)	0.125
TV	6 (14%)	10 (7%)	0.132
Depressed	16 (36%)	26 (18%)	**0.006***
Stress	22 (50%)	46 (31%)	**0.014***
Partner against it	3 (7%)	4 (3%)	0.202
Sport field too far away	8 (18%)	10 (7%)	**0.019***
Too expensive	14 (32%)	21 (14%)	**0.004***
Difficult to organize	8 (18%)	14 (10%)	0.100
No sport partner	6 (14%)	10 (7%)	0.132
Forgot to do sport	12 (27%)	8 (5%)	**<0.001***

[1]Pearson chi squared; * *p value* < 0.05.

with higher workplace activity [32]. That the individual's fear that physical activity might increase low back pain was associated with a higher chance of physical inactivity during leisure time, again, is in line with other studies that were focusing on fear avoidance beliefs and chronic disability secondary to low back pain [33–35].

As the sustainable promotion of health-enhancing physical activity still is a big challenge [36, 37], the identification of target-group specific barriers to physical activity is of utmost importance. However, our adjusted regression model showed no statistically significant association of a specific barrier to physical activity. Barrier differences in active and inactive participants were confounded by education level and fear of pain. But the education level of low back pain patients cannot be changed by a physical activity promotion program and the change of fear of pain is a long lasting progress. Hence, for practical implications, taking a specific look at the barriers could give a clue about how to bypass these two major factors in future interventions. Beyond, developing physical activity promotion programs tailored to the educational level might be a promising approach on the long run.

Overall, the most common barriers mentioned in our study among low back pain patients reflect those found in other studies. In regard to external barriers, a study on barriers among persons suffering from chronic diseases across all chronic conditions also identified cost (corresponding to "too expensive" in our study) and travel time (corresponding to "sport facility too far away" in our study) as primary barriers [38]. Even though cost was identified as a barrier in several studies [39–41], in the light of the main study of the present evaluation that aimed at promoting physical activity in daily routine, it seems noticeable that cost was perceived as a barrier in our secondary analysis. With reference to internal factors lack of willpower (corresponding to "not feeling like it" in our study) [39, 40, 42–44] and existing physical ailments or chronic conditions [12, 42, 45] were identified as a barrier in several other studies. A noticeable aspect seems to be that in our study the barriers "pain" or "injury" showed a higher share in active participants. This leads to an interesting aspect: Probably the main difference between active and inactive participants might not be the specific barrier by itself but the ability to overcome it. While some internal barriers mentioned more frequently by inactive participants ("being tired"; "want to stay home"; "not feeling like it"; being "stressed" or "depressed"; "forgot to do sports") seek further specific individual support, other barriers that showed a higher share in inactive participants (e.g., "bad weather," "too expensive," and "sport field too far away") are rather external factors that are hardly to be overcome by direct support and need more complex approaches. This idea is supported by a narrative review on barriers to physical activity of patients with rheumatoid arthritis which showed that doing exercise did not influence the existence of barriers but showed that physically active patients appear to be more capable of overcoming them [46]. Veldhuijzen van Zanten et al. [46] concluded that the encouragement from health

Table 3: Associations with physical activity.

N = 139	Beta	SE (β)	Sig.	OR	95%-CI
Age (years)	0.021	0.040	0.610	1.021	[0.943; 1.105]
Gender: men versus women	0.373	0.603	0.536	1.452	[0.445; 4.736]
Body mass index: "overweight or obese" versus "normal weight"	0.984	0.647	0.128	2.675	[0.753; 9.502]
Highest level of education: "higher than lower secondary school" versus "lower secondary school"	1.680	0.629	**0.008***	5.366	[1.563; 18.425]
Duration of LBP at baseline: "≤12 months" versus ">12 months"	−1.357	1.094	0.215	0.258	[0.030; 2.196]
Intensity of pain during the last four weeks at six-month follow-up (min: 1; max.: 6)	−0.096	0.248	0.699	0.909	[0.559; 1.477]
More back pain by physical activity (0: not at all; 6: exactly)	−0.491	0.191	**0.010***	0.612	[0.421; 0.889]
Baseline leisure time physical activity: "active" versus "inactive"	0.637	0.602	0.290	1.891	[0.581; 6.151]
Study group: "control group" versus "intervention group"	−0.789	0.564	0.162	0.454	[0.150; 1.373]
Barrier: bad weather "barrier" versus "no barrier"	−0.358	0.707	0.612	0.699	[0.175; 2.792]
Barrier: being tired "barrier" versus "no barrier"	−1.207	0.633	0.056	0.299	[0.087; 1.034]
Not feeling like it "barrier" versus "no barrier"	−0.648	0.670	0.333	0.523	[0.141; 1.944]
Want to stay home "barrier" versus "no barrier"	−1.075	0.706	0.128	0.341	[0.086; 1.362]
Depressed "barrier" versus "no barrier"	0.071	0.626	0.909	1.074	[0.315; 3.663]
Stress "barrier" versus "no barrier"	−0.056	0.617	0.928	0.945	[0.282; 3.166]
Sport facility too far away "barrier" versus "no barrier"	−0.374	0.929	0.688	0.688	[0.111; 4.255]
Too expensive "barrier" versus "no barrier"	−0.592	0.670	0.377	0.553	[0.149; 2.055]
Forgot to do sport "barrier" versus "no barrier"	−0.016	0.852	0.985	0.985	[0.185; 5.229]

Dependent variable: leisure time activity following rehabilitation ("active": >0 MET-min/week versus "inactive": 0 MET-min/week); * p value < 0.05; R^2 = .051; variables not included. Barriers: activities with friends; pain; being ill; too much work; injury; TV; partner against it; difficult to organize; no sport partner. Odds ratios are adjusted for socioeconomic status variables and intervention group.

professionals and friends/family is facilitator for physical activity and exercise. Along the same lines are the results of a qualitative study on patients with chronic musculoskeletal pain suggesting that this patient group has a greater need for information and extra support to overcome existing barriers to physical activity [47].

In recent years, professional health coaching has become a promising approach to initiating behavioral changes and improving health [48, 49]. Thereby, health coaching is understood as a patient-centered education method aiming at motivating individuals to achieve health goals and improving self-management [50]. Again, this is an interesting aspect in light of the main study: in the main study, a "movement coach" was applied, supporting motivational and volitional aspects of physical activity promotion. Probably the focus on physical activity-related aspects was too narrow and psychosocial aspects as well as indication-related aspects and pain management should be more strongly integrated. As fear of pain is a modifiable factor, the relationship of pain and physical activity should be explicitly addressed during rehabilitation. In consequence, an interdisciplinary health coaching intervention conducted by a sport scientist and a psychologist might be a promising approach.

To our knowledge, this is the first study having investigated barriers to physical activity among low back pain patients who were participating in a trial promoting physical activity while in an inpatient rehabilitation clinic. Our study limitations include the recruitment from only one inpatient rehabilitation center which may limit generalizability of the results. Due to the main study, a second limitation certainly is that all participants in this secondary analysis were participating in a trial promoting physical activity voluntarily. In consequence, the results may not be generalized to patients who were less motivated to participate in the main study. Given the fact that we evaluated patients previously enrolled in a formal inpatient rehabilitation program the results may be less applicable to individuals suffering from low back pain who were not previously exposed to an intensive rehabilitation program. Furthermore, heterogeneity in the definition of physical activity and the corresponding classifications and in different questionnaires limits the comparison to other studies [51].

5. Conclusions

As the sustainable promotion of health-enhancing physical activity still is a big challenge [36, 37], the identification of target-group specific barriers to physical activity is of utmost importance. To develop application-oriented approaches in physical activity promotion, health professionals need profound information on the relationships between the barriers and sociodemographic and indication-related variables. Our results showed that there might be a need for especially supporting low back pain patients with a low level of education and fear of pain in overcoming internal and external barriers to physical activity.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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Clinical Study

An EEG Tool for Monitoring Patient Engagement during Stroke Rehabilitation: A Feasibility Study

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Objective. Patient engagement is of major significance in neural rehabilitation. We developed a real-time EEG marker for attention, the Brain Engagement Index (BEI). In this work we investigate the relation between the BEI and temporary functional change during a rehabilitation session. *Methods*. First part: 13 unimpaired controls underwent BEI monitoring during motor exercise of varying levels of difficulty. Second part: 18 subacute stroke patients underwent standard motor rehabilitation with and without use of real-time BEI feedback regarding their level of engagement. Single-session temporary functional changes were evaluated based on videos taken before and after training on a given task. Two assessors, blinded to feedback use, assessed the change following single-session treatments. *Results*. First part: a relation between difficulty of exercise and BEI was identified. Second part: temporary functional change was associated with BEI level regardless of the use of feedback. *Conclusions*. This study provides preliminary evidence that when BEI is higher, the temporary functional change induced by the treatment session is better. Further work is required to expand this preliminary study and to evaluate whether such temporary functional change can be harnessed to improve clinical outcome. *Clinical Trial Registration*. Registered with clinicaltrials.gov, unique identifier: NCT02603718 (retrospectively registered 10/14/2015).

1. Introduction

Stroke is one of the leading causes for long-term functional impairment worldwide. The mechanisms underlying effective rehabilitation following stroke have been the subject of extensive research. There is growing evidence that rehabilitation is most effective when therapists promote active patient participation in the process and full commitment to it, for example, following stroke [1, 2]. Significantly better outcome was achieved by engaged than by nonengaged patients [3, 4]. The underlying factors that seem to define the basic engagement of the patients include their emotional state and level of cognitive function [1, 5]. Factors that have a transient effect during a given rehabilitation session include the importance of the patient ascribing to the session goal, patient-therapist relations, and the exercises used [6, 7]. Other transient factors contributing to engagement are the match between the degree of exercise difficulty and the patient's current functional level [8], as well as boredom and tiredness [1]. In neuropsychological terms, increased engagement appears to correlate with increased patient attention during exercise [3]. Positive clinical outcomes, such as reduced depression and better cognitive and motor outcome, have been shown to correlate with the amount of effective recruitment of attention [1, 9, 10]. There is neurophysiologic evidence suggesting that enhanced recruitment of attention and engagement increases significantly the activation of brain regions involved in motor rehabilitation [11, 12]. Such increased activation may form compensatory connections to overcome reduced activity in these regions due to neurological disease. Increased activation driven by attention results in greater brain plasticity, which may underlie effective rehabilitation [13].

The practical role of engagement was also demonstrated in the improved clinical outcome achieved with robot-assisted rehabilitation when active patient participation is encouraged, as compared to passive protocols [14]. Nevertheless, we are not aware of any currently established marker for patient engagement or attention and therefore the generation of such marker seems to be of clinical importance.

To date, multielectrode EEG (ElectroEncephaloGraphy) systems have been shown to provide effective markers for attention [15]. But obtaining such markers necessitates a relatively long sampling time (in the range of at least several minutes) [15]. Furthermore, it is too cumbersome and therefore impractical to connect patients to a multielectrode EEG system on a regular basis for rehabilitation sessions. Effective harnessing of EEG-based measures for use in a rehabilitation setting should enable real-time feedback as opposed to feedback after many minutes [16, 17]. A tool that provides therapists with real-time feedback on attention recruitment can serve as an objective basis for real-time adjustments during treatment, which can significantly improve rehabilitation outcome in general and after stroke in particular [18].

Our previous research showed that it is possible to extract effective markers for attention from a single-channel EEG system [19, 20]. Furthermore, we simplified EEG analysis to adjust the extraction of relevant attention-related markers from ongoing EEG, without the need for external cues, on the basis of component template matching of the pattern identified by the averaged event-related potential (ERP). [21]. Template matching is the search in the sampled EEG data for a specific a priori pattern. We follow in this regard a known methodology, which scans the raw EEG data for patterns, which were identified in the averaged ERP signal [22]. Since the template we use is a marker for attention [19] we assume that the matched marker we use in this study (termed BEI, Brain Engagement Index) is also a marker for attention. It should be emphasized that, based on the above, a marker for engagement or for attention would be relevant to almost any poststroke dysfunction regardless of its precise localization. Therefore we chose in this preliminary feasibility study a variable population of patients in terms of functional level and site of injury.

The aim of the present study was to evaluate the applicability of a single-channel EEG marker, the Brain Engagement Index (BEI), during standard motor rehabilitation treatment sessions. In the first part we aimed at evaluating the relation of the BEI and functional performance in control participants, hypothesizing that BEI would peak when the participant is required to perform on a higher level, yet the demands are still not overly difficult. The level of difficulty in this part was set using a robotic training system. In the second part we evaluated the relationship between the BEI level during standard stroke rehabilitation sessions and temporary functional changes induced during these sessions. On the basis of the importance ascribed to brain engagement, as presented above [1–4], we hypothesized that higher BEI will be associated with better temporary functional change. For the sake of evaluating the temporary functional change, induced by the single physiotherapy session, we followed an established method of filming the target movements before and after sessions for evaluation of change by blinded observers [23].

2. Methods

The study consisted of two parts. The first part evaluated the effects of exercise difficulty and repetition on the BEI. The evaluation was standardized by using a robotic training system (ArmTutor) and by sampling normally functioning control patients. The second part evaluated the applicability of the BEI to patients undergoing standard, nonrobotic, motor rehabilitation sessions after stroke. Both parts of the study were approved by the Institutional Review Board of Reuth Rehabilitation Hospital, and all the participants signed informed consent forms.

3. Participants

3.1. First Part. Thirteen unimpaired controls (43–67 years old; 11 females, 2 males), without any neurological or psychiatric deficit, were included. The control participants, a convenience sample, were recruited from the personnel of Reuth Rehabilitation Hospital, Tel Aviv, Israel.

3.2. Second Part. Twenty poststroke patients were recruited to the second part of the study. We recruited patients with a full understanding, lack of self-report or documentation of major prestroke neurological and/or psychiatric disorders, and a score of 2–4/5 according to the Kendall muscle grading (https://www.niehs.nih.gov/research/resources/assets/docs/muscle_grading_and_testing_procedures_508.pdf) [24] of the relevant muscle groups. One patient was transferred to another hospital after the first session. For another patient there was disagreement between the blinded observers regarding the degree of session effect. Therefore the sample size of the second part of the study included the remaining 18 patients (39–90 years old, 4 females, 14 males), 1–3 months following stroke.

4. Tools

EEG was sampled using the MindWave dry electrode system [25], with one frontal electrode (~Fpz) and one reference electrode on the earlobe, at a sampling rate of 512 Hz. Positioning of the electrode conforms with the goal of monitoring prefrontal activity, which may correlate with attention regardless of the site of lesion [26]. The sampled data were transferred through a wireless connection to the experiment computer, where the BEI was processed.

4.1. First Part. We used the ArmTutor [27], a device developed for functional motor rehabilitation of the upper extremity, in this case elbow flexion/extension, with the track task (maintaining a ball within a moving track, with changing

Table 1: Demographic and clinical characteristics of patients.

Patient#	Age	Gender	M/P site of lesion*	Dysfunction	Target motor function
1	61	M	Lt internal capsule	Hemiparesis (2/5)	Hand to mouth
2	55	M	Lt internal capsule	Hemiparesis (2/5)	Elbow extension
3	48	M	Rt MCA	Hemiparesis (2/5)	Elbow extension
4	52	M	Lt cerebellum	Hemiparesis (4/5)	Stability on one leg
5	70	M	Rt temporooccipital region	Hemiparesis (4/5); hypoesthesia; hemianopsia; hemineglect	Weight shift to the left
6	43	M	Rt internal capsule	Hemiparesis (3/5)	Finger extension
7	61	F	Rt internal capsule	Hemiparesis (3/5)	Finger extension
8	68	M	Lt MCA	Hemiparesis (4/5)	Stability on one leg
9	77	M	Rt MCA	Hemiparesis (4/5)	Finger movement for playing a saxophone
10	69	M	Lt MC	Hemiparesis (4/5)	Sit to stand stability and endurance
11	76	F	Rt MCA	Hemiparesis (4/5)	Preparation to grasp plastic cup
12	66	M	Rt MCA	Hemiparesis (3/5)	Reach and grasp
13	90	M	Lt MCA	Hemiparesis (3/5); aphasia	Manual dexterity: place battery, screw bolt
14	39	M	Lt internal capsule	Hemiparesis (3/5); hypoesthesia	Finger extension
15	57	F	Lt basal ganglia	Hemiparesis (4/5)	Stability of gait
16	72	F	Lt basal ganglia	Hemiparesis (4/5)	Manual dexterity: place battery
17	80	M	Lt superior cerebellum	Hemiparesis (4/5)	Stability of gait
18	67	M	Rt MCA	Hemiparesis (3/5)	Opening of hand

*Based on CT scan results and on clinical presentation; MCA: middle cerebral artery.

slopes). The ArmTutor makes it possible to specify the track width on a continuous scale of ArmTutor-specific units. Four exercise levels of increasing difficulty were selected for this evaluation. The difficulty of the task was mediated by narrowing the track width in even steps from 40 ArmTutor units in level 1 to 10 ArmTutor units in level 4. The ArmTutor is a tool in the arsenal of robotic rehabilitation tools developed by MediTouch Ltd. [28, 29].

4.2. Second Part. The second part did not involve the use of designated tools. The study aimed at evaluating a general relation between BEI monitoring and temporary treatment effect for different treatment goals and functional levels. Therefore we included patients and treatments of various types; the objectives of standard physiotherapy for the individual patients are presented in Table 1.

5. Experimental Protocol

5.1. First Part. Each participant was tested in two blocks in each of the four levels of difficulty (1–4). Each participant performed twice two-minute exercises at levels 1, 2, 3, and 4. A 30-second rest period was given between blocks. The ArmTutor software provided a performance grade (in %) per participant. All tests were conducted in a single session, moving consecutively from one level of difficulty to the next. The control participants were blinded with regard to their BEI level during exercise.

5.2. Second Part. Each patient underwent an initial evaluation to select a treatment goal for a specific motor function, which matched the patient's functional level. Following this evaluation, each patient completed two treatment sessions. One session involved real-time feedback, with the treating physiotherapist using the BEI; the other session involved BEI monitoring that was not available for the physiotherapist. The order of the two sessions (feedback and no-feedback) was pseudorandomized for each patient through alternate allocation. Altogether, half the patients (9/18) started with the feedback session (FB+) and half (9/18) with the no-feedback session (FB−). During the feedback session, the physiotherapist responded to BEI decreases (of more than 10%) lasting 30 seconds or more by either encouraging the patient to concentrate or by changing the difficulty level of the exercise. A change in difficulty level was based on patient performance: difficulty level was reduced if the exercise seemed to the physiotherapist too difficult for the patient and increased if the exercise seemed too easy. Figure 1 shows the intervention algorithm used by the therapist. If the BEI level did not decrease, the exercise continued unchanged. Based on these general recommendations, when the BEI level dropped, the physiotherapist did adaptations to the

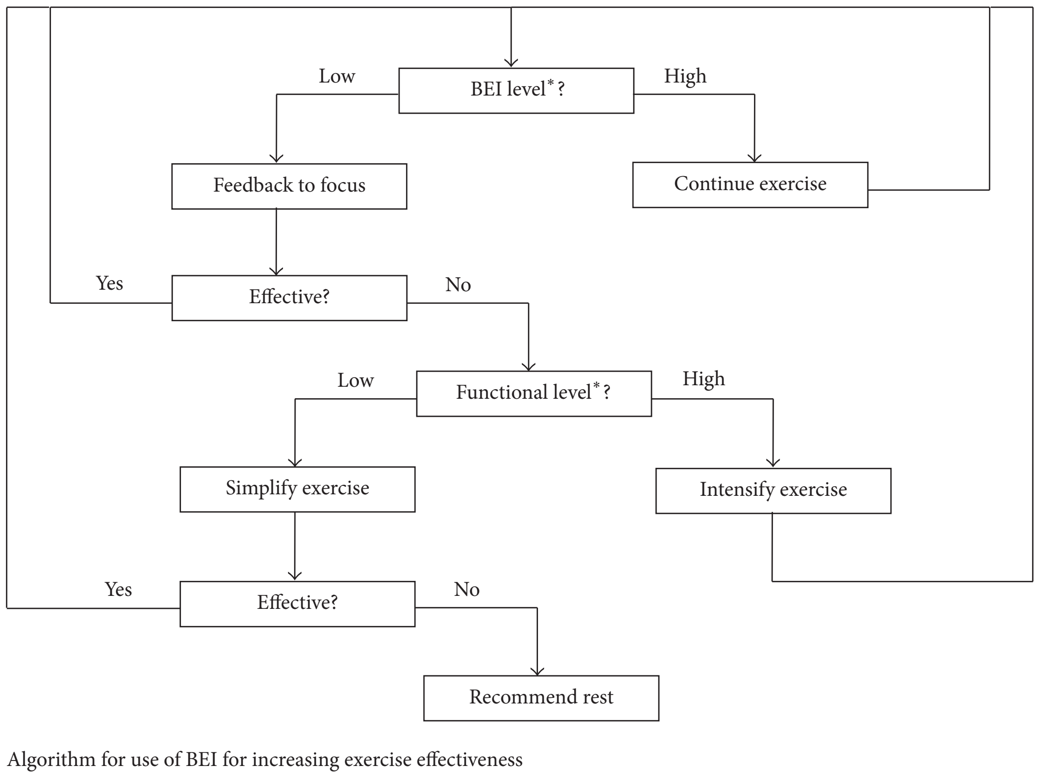

Figure 1: Algorithm for use of the BEI during treatment sessions. If the BEI level was stable, the current exercise continued. When BEI level dropped consistently below average for at least 30 seconds, the patient was first encouraged to concentrate on the exercise, and if this did not help, the therapist evaluated the exercise level. If it was too easy, the therapist intensified the exercise. If it was too difficult, the therapist reduced the intensity of the exercise. If this did not improve the BEI, the therapist suggested rest or used supportive and passive exercises for a few minutes. *Note that both BEI level and functional level are evaluated relatively for each patient.

current exercise or switched between exercises. The specific switches in exercise were selected by the physiotherapist, based on his clinical judgment. It should be emphasized that this involvement of judgment by the physiotherapist did not impact the main research question of this study. Note that the main comparison of temporary functional change is between the higher BEI session and the lower BEI session for each patient, regardless of whether feedback was used in the session or not and regardless of the specific exercises selected by the physiotherapist. For some patients the higher BEI session was the session with the feedback, while for others it was the session without the feedback.

Treatment sessions lasted on average 35 minutes. Each session was preceded and followed by a 30-second evaluation period, in which the motor function targeted by the treatment was tested and filmed. The two pairs of evaluation films (FB+ pre/post and FB− pre/post) were evaluated by two physiotherapists, who were blinded to all aspects of the session. The blinded evaluators did not know whether feedback was used and what the BEI level was for the session. Each evaluating physiotherapist was asked to quantify the functional change achieved at the end of each treatment session on a 7-point Likert scale [−3, +3]. The evaluators were instructed to focus their evaluation upon changes in the quality, range, and speed of movement. A positive score indicated improvement and a negative one deterioration. The degree of improvement or deterioration was specified on a scale ranging from 1 (minor) to 3 (major). A score of 0 indicated no significant functional change between the pre- and postsession evaluations. This method of evaluation was suggested by Altschuler et al., 1999. Video-based evaluation was employed in multiple additional studies [30, 31].

6. EEG Analysis

The Brain Engagement Index (BEI) was developed by Brain-MARC LTD and is available to researchers (see http://brainmarc.com/wp-content/uploads/2015/12/BrainMarc-Brochure.pdf). It is an embodiment of template matching between the averaged ERP signal and the raw EEG sample, which is a prevalent method in advanced EEG analysis, in which a basic template is compared with the sampled signal [21]. The BEI was computed with a moving window of 10 seconds for the period of the preceding 60 seconds. The template was a 1500 milliseconds attention-related averaged ERP delta bandpass activity [19], which was matched with a moving window of the same size in the sampled signal. The matching was performed in real-time every 10 seconds, as follows: (i) the last 60-second sample was divided into segments of 10 seconds; (ii) each segment was filtered in the delta bandpass

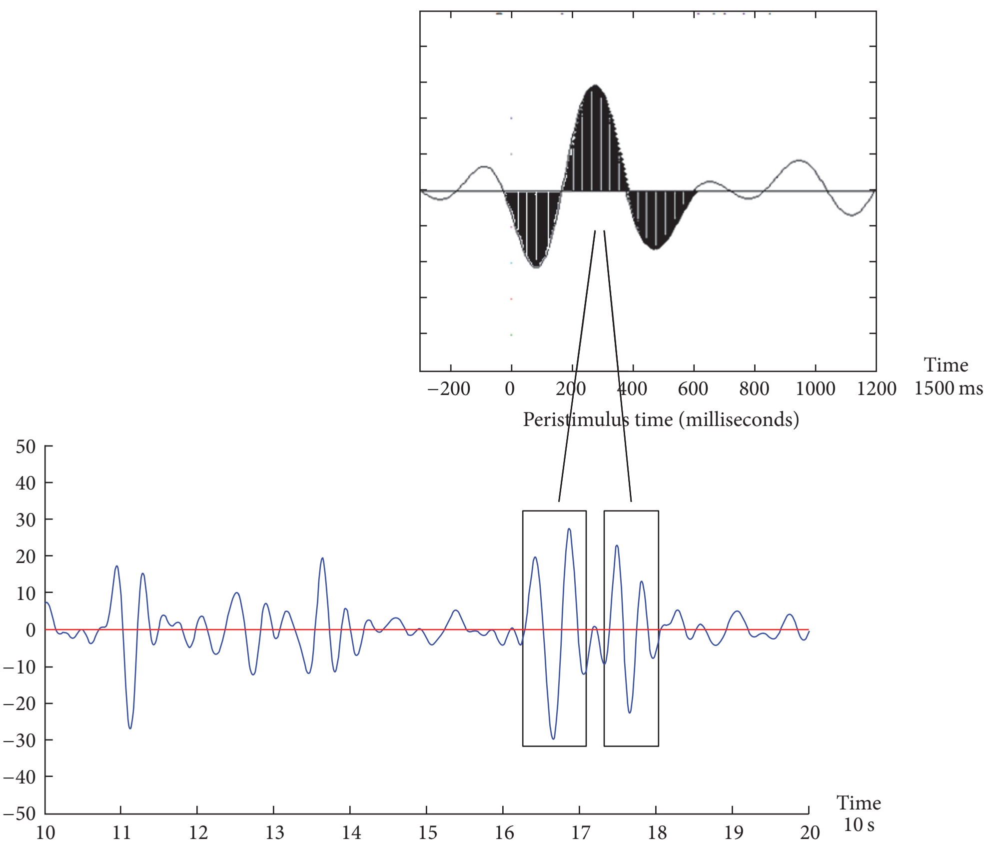

Figure 2: Demonstration of component template matching. The component template is emphasized in black in the top inset. The new sample in the bottom of the figure is scanned with a moving window, following normalization to the $[-1, 1]$ range. Whenever a match is found (in black rectangles), it is counted. The BEI is a normalization of this count to the $[0, 1]$ range.

[1–4 Hz]; (iii) the data points in the filtered segment were normalized to the $[-1, +1]$ range, where -1 denoted the most negative deflection in the filtered segment and $+1$ the most positive one; (iv) filtering and normalization to $[-1, +1]$ were also performed for the 1500 ms averaged delta ERP wave, shown in Figure 2 (top inset), to generate the template; (v) the normalized sampled segment was scanned by a moving window of 1500 ms; (vi) the averaged distance between the moving window data and both the template and the template opposite (1-template) were computed; (vii) if the averaged distance was less than a threshold of 0.5 from the template (see Figure 2), the count of matches was increased, provided that no other match was found in a previous window, partly overlapping the current one; (viii) if the averaged distance was more than the threshold, the count of no-matches was increased, provided that no other no-match was found in a previous overlapping window; (ix) the BEI is the division of the counts of matches by the no-matches; the maximum BEI value is set to +1, so that the BEI scale has a range of $[0, 1]$; (x) the median of the six 10-second segment BEIs, from the last sampling minute, is taken as the current BEI (as the BEI is calculated every 10 seconds, there is a 50-second overlap in the period analyzed for consecutive BEI values); (xi) for every 1500-millisecond window, we also computed the standard deviation/mean ratio of delta activity. If this ratio was greater than 1, the sampling was likely to be noisy (based on previous analysis) and therefore this 1500-millisecond sample was rejected and not included in the above computation. If multiple (>1) nonoverlapping 1500 millisecond windows were rejected within a given 10-second segment, the entire segment was automatically rejected. At least three nonnoisy 10-second segments were required within the last 1 minute to generate a valid BEI for the entire minute. Otherwise the entire minute was rejected as noisy and no BEI was reported for it. When two consecutive BEI values were not reported (no-value was reported in the monitor graph), the therapist was asked to check and improve the contact of the NeuroSky system with the patient's head, verifying a green connection marker in the application window. Such intervention was required, on average, about 1-2 times in a treatment session. Of potential practical value is the use of dry electrodes below the hairline, Fpz referenced to earlobe. We showed previously the feasibility of extracting significant markers from this region [19]. Obviously sampling from the forehead is always susceptible to noise, especially due to eye movements, but with the use of effective noise rejection method [32] together with adjustment of the device, we were able to obtain 3–6 BEI values in ~90% of the sampling minutes.

7. Data Analysis

We used the following indices in the analysis.

7.1. First Part

(1) Start-of-exercise BEI: we used the first BEI acquired during each exercise block.

(2) End-of-exercise BEI: we used the last BEI acquired during each exercise block.

The BEI for each difficulty level was acquired by averaging the 2 blocks of the same difficulty level. In levels 1 and 2 ArmTutor performance grade of all participants was above the MediTouch recommended threshold for good performance. On level 4 all participants showed long drop in performance level below the recommended performance threshold. Level 3 was intermediate with short drops below the recommended performance threshold and thereafter correction to above threshold performance. The recommended performance threshold is used by MediTouch automatically to tune exercise difficulty, but in the current study we deactivated this automatic tuning to maintain constant level difficulties.

7.2. Second Part

(1) BEI Session. We computed BEI values every 10 seconds for both sessions of each patient. Next, we computed the mean BEI and standard deviation of all sampled values from both sessions of each patient. For each session, the number of samples above the mean + one standard deviation was counted and was divided by the total number of samples for the session. This value was used as the entire grade of the session, the BEI session. For the sake of demonstration of the computation of the BEI session, we present Figure 3, which shows the computation of the BEIs session of a representative patient. For each patient, the basic BEI samples are shown as a function of time. The mean BEI for both sessions, taken together, is shown as a dashed line. The mean + one standard deviation is shown as a thick line. The count of BEI samples above this threshold of mean + one standard deviation was divided by the total number of BEI samples from the entire session, to generate the BEI session. Thus if in one of the two sessions of a given patient there was a larger portion of BEI values above threshold than in the other session, this session received a higher BEI session.

(2) Session Temporary Functional Change Index. We used the average of the session effect evaluations of the two blinded evaluators as the session outcome index. The evaluation scores given by the two evaluators differed, but the data analysis compared the effect of the two sessions for each participant, and the difference between the two sessions was largely similar between the evaluators; the difference did not exceed 1 point for all patients included in the analysis (one patient, with greater interrater differences, was excluded from data analysis).

8. Statistical Analysis

8.1. First Part. The comparisons are based on repeated measures ANOVA with Tukey HSD correction and on paired sample t-test.

8.2. Second Part. The major comparison is based on Wilcoxon-signed ranks test of the session temporary functional change indices. Wilcoxon-signed ranks test is designed for paired-comparison of ordered scales.

A secondary post hoc evaluation was based on chi-square comparison. In this evaluation we compared patients who started with a feedback session, which was followed by a no-feedback session, with patients who started with a no-feedback session, which was followed by a feedback session.

9. Results

9.1. First Part. We noted a tendency of increase in average BEI among control participants from levels of exercise difficulty 1 and 2 to level 3. This tendency was reversed in level 4, in which average BEI dropped (Figure 4(a)). To assess the significance of the BEI change, we performed a repeated measures ANOVA between levels with a within-participant factor. We found a significant level effect ($F(2,42) = 5.99$, $p < 0.01$). Follow-up paired sample t-tests were conducted separately to compare pairs of difficulty levels and were found to be significant between the first and second levels on the one hand and the third level on the other hand (paired t-tests, both with $p < 0.05$) and between the 3rd and 4th levels (decrease) (paired t-test, $p < 0.001$). After correction for repeated measures with Tukey HSD, the difference between the 3rd level and 4th level was still significant ($F(2,11) = 4.29$, $p < 0.01$), but the difference between the 1st and 2nd levels and the third level was not significant. The significant drop in BEI between the third and fourth levels was accompanied by reduced performance as reported automatically by the ArmTutor device (Figure 4(a), inset). Participants received an average performance grade of >90% for the first three levels and of ~80% for the fourth level.

Within each level of exercise difficulty there was a decrease in the BEI value from level start to level end (Figure 4(b)). This tendency was statistically significant (paired t-test, $p < 0.0001$).

9.2. Second Part. The main comparison in this study was between sessions with higher BEI and sessions with lower BEI. As each patient participated in two sessions, one of them had by definition a higher BEI than the other. We grouped the temporary functional changes of the sessions with higher BEI and of the sessions with lower BEI across patients (Figure 5). In the figure the y-axis shows the accumulative percentage of patients with a session-induced temporary functional change index above thresholds, which are presented in the x-axis. For example, 72% of the sessions with higher BEI of the various patients were rated with temporary functional change $\geq +1$, but only 39% of the sessions with lower BEI were rated with temporary functional change $\geq +1$. The difference between sessions with higher BEI and sessions with lower

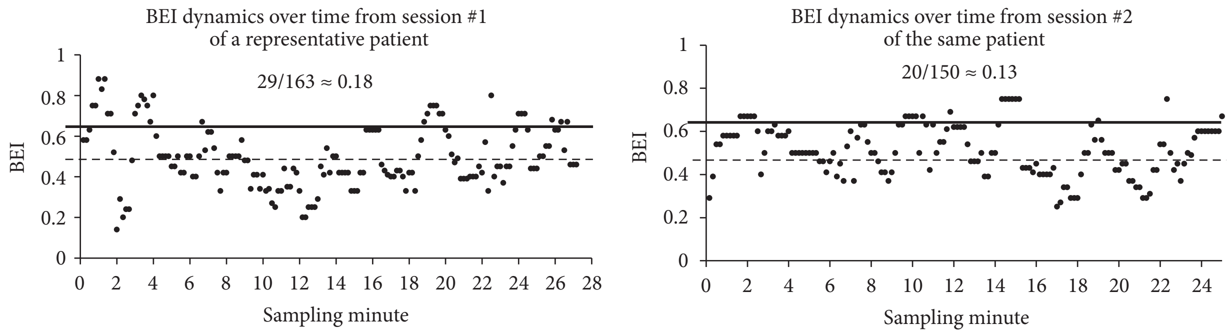

Figure 3: Computation of BEI session. For the sake of clarifying the computation of the BEI session from the basic 10 seconds BEI values, we show an example from one patient of the basic BEI values from the two sessions he underwent. BEI values were computed every 10 seconds for both sessions. The mean BEI (dashed line) and +1 standard deviation (thick line) of all sampled values obtained from *both sessions* were computed. For each session, the number of samples above the mean + 1 standard deviation was counted and was divided by the total number of samples for this session. This value was used as the BEI session, and it is shown for each of the two sessions for demonstration. The same BEI computation session was followed for all patients.

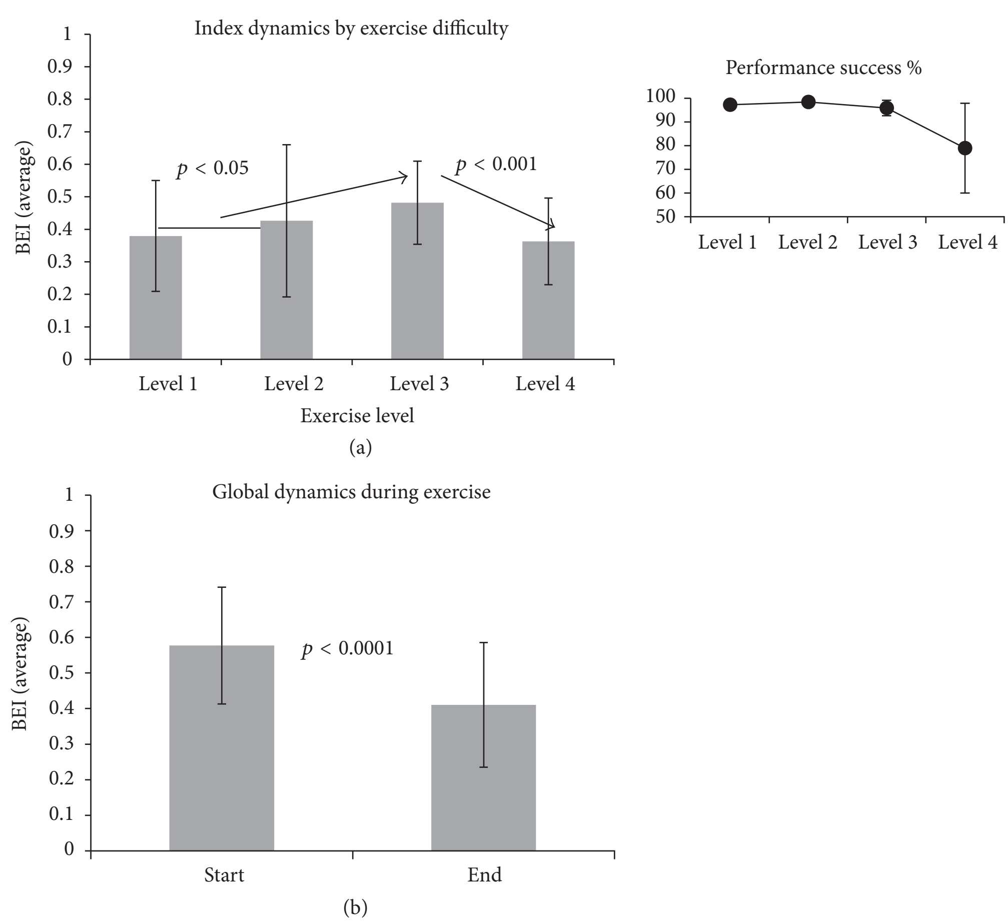

Figure 4: BEI association with exercise difficulty and practice. (a) Dynamics of BEI as a function of exercise difficulty. At each level, the BEI is averaged for both exercises over all participants (±SD). The arrows mark the tendency of BEI change between 3 exercise levels: an average of levels 1 and 2 (owing to functional similarity), level 3, and level 4. The inset shows the percent of success, reported by ArmTutor. The success rate reduced in the 4th level. (b) Dynamics of BEI between start and end of the exercises. The figure shows the decrease of the index between start-of-exercise and end-of-exercise. The start and end columns present averages (±SD) from all 4 levels of exercise (2 exercises in each level) over all 13 controls.

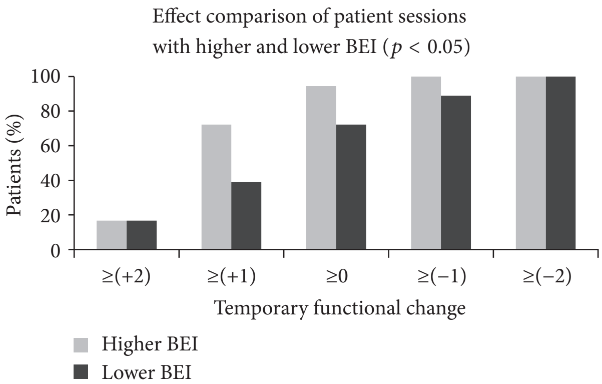

Figure 5: Comparison of the temporary functional change between the sessions in which the BEI was higher for each patient and the sessions in which the BEI was lower for each patient. As each patient participated in two sessions, one of them had by definition higher BEI than the other and the data in the figure aggregates all sessions with higher BEI and all sessions with lower BEI over patients. For some patients the session with higher BEI was the feedback session, while for other patients the session with higher BEI was the no-feedback session. The y-axis shows the percentage of patients with a session temporary functional change index above thresholds, which are presented in the x-axis. This BEI-based comparison revealed a significant difference in temporary functional change ($p < 0.05$).

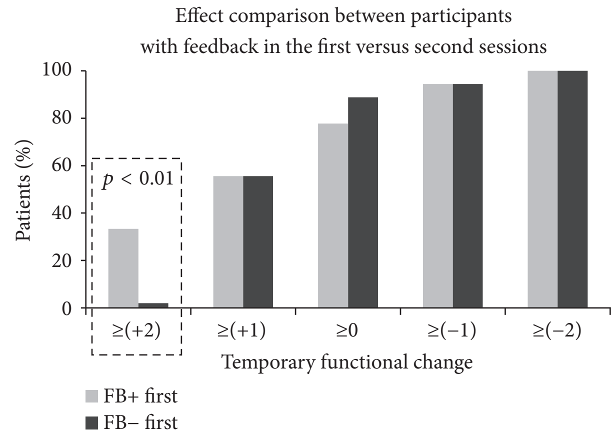

Figure 6: Accumulative histogram comparisons between patients who started with a feedback session and those who started with a no-feedback session. The y-axis shows the percentage of sessions with temporary functional change indices above the thresholds, which are presented in the x-axis. For participants who started with a feedback+ session, both the first feedback+ and the second feedback− session were included in the count. For participants who started with a feedback− session, both the first feedback− and the second feedback+ session were included in the count. Post hoc analysis of the highest possible temporary functional change (≥+2) revealed a significant difference ($p < 0.01$) between patients who started with feedback in the first session and patients who started with no feedback in the first session. This difference is emphasized with the dashed rectangle.

BEI was statistically significant (Wilcoxon-signed ranks test: $Z \approx -1.76$, $p < 0.05$). It should be noted that this comparison is independent of the physiotherapist involvement in the protocol and exercise selection. The comparison is between higher BEI sessions and lower BEI sessions, regardless of whether feedback was used in the session or not. We further computed the effect size (for categorical variables, [33]) of the higher BEI sessions compared with the lower BEI sessions. This effect size was $d \approx 0.71$.

In a secondary post hoc analysis we compared between patients whose first session was with feedback and patients whose first session was without feedback (Figure 6). For participants who started with a feedback+ session, both first feedback+ and second feedback− sessions were included in the analysis. For participants who started with a feedback− session, both first feedback− and second feedback+ sessions were similarly included in the analysis. The purpose of the comparison was to evaluate whether the use of feedback in the first session had any effect that may have been carried over to the second session. Post hoc statistical analysis showed a significant preference of the maximal temporary functional change (≥+2) for the patients with feedback in the first session in comparison with the patients with no feedback in the first session ($X^2(1, 36) \approx 7.20$, $p < 0.01$).

10. Discussion

The first part of the study suggests there might be a possible association between the BEI and exercise difficulty in a standardized protocol with control participants. BEI at least tended to be lower when the exercise level was easier and it reduced again when exercise level was too difficult and performance was compromised. Thus, BEI may be at its peak when exercise level is challenging, yet not overchallenging. The implication may be that BEI is more related to neurophysiologic processes of sustained attention than with processes of global arousal [34], which may remain high during the phase that is too difficult [35]. It seems possible to distinguish in the EEG signal between sustained attention and alertness markers [36].

Nevertheless, it should be remembered that this is only a preliminary study and more elaborative manipulations of exercise difficulty in various environments are needed in order to establish the relation between the BEI and exercise challenge. If indeed higher BEI will be established further, as related to effective exercise challenge, it may be a useful tool for neural rehabilitation. At times it might be challenging to deduce quickly from good patient performance alone whether a given exercise is sufficiently engaging and the patient works intensively and engagingly or alternatively the exercise is simple for the given patient and does not require intense work. Another required differentiation, in cases of suboptimal functional performance, is between instances in which the patient still works intensively and engagingly and instances in which suboptimal performance is related to reduced engagement. In both cases it is necessary to establish the added value of the BEI for identifying engagement, beyond deduction from performance alone, of both experienced and less experienced therapists.

Supportive evidence for the possible applicability of the BEI as an index for brain engagement comes from its reduction over time within the same level of exercise difficulty. This could be interpreted as habituation secondary to improved dexterity, which develops during practice.

In the second part of the study we evaluated the relation between the BEI of the standard rehabilitative session of post-stroke patients and the temporary functional change induced by the session. The assumption was that patient engagement is related to session effectiveness, at least in terms of temporary functional change. As expected, we found a relation between BEI level during the rehabilitative session and the temporary functional change as it was evaluated by skilled blinded observers. The design of the study was not rigorous in terms of interventions employed by the therapist [37]. Furthermore, the target treatment goal was selected individually for each patient, without any attempt at uniformity in treatment goals across patients. Instead it was more naturalistic and the therapist could have selected any intervention he employs in standard rehabilitation sessions. The individualized selection of treatment goals was also chosen because of the expected relation between the relevancy of the treatment goal and the patient's engagement [6]. The main aim was to compare two sessions for each patient. By definition one of such two sessions had a higher BEI than the other and thus it was possible to show that when BEI was higher the temporary functional change was better. The evaluation of temporary functional change had to rely on a short test (so effect will not wear out), which is applicable for multiple functional levels. We used for this purpose the method offered by Altschuler et al. [23]. Similar methods were used also by others [30, 31].

It should be stressed that the subjective involvement of the physiotherapist in the study did not affect the evaluation of the main research question of relation between BEI session and temporary functional change. This is because, all in all, each patient participated in two sessions; in one the BEI was higher than the other. For some patients the higher BEI was in the feedback session, while for others, the higher BEI was in the no-feedback session. But still, as is evident from Figure 5, higher BEI seems to be related to better temporary functional change.

The two treatment sessions for each patient were nevertheless different. In one session the therapist received real-time BEI feedback every 10 seconds and in the other session no feedback was given. The therapist was instructed to change the exercise once the BEI reduced, according to the given algorithm. This enabled post hoc analysis regarding the effect of feedback use on the temporary change in functionality. The seminaturalistic structure of the study and the lack of blinding of the therapist set heavy limitations regarding possible conclusions regarding this secondary question. Nevertheless the therapist was blinded to the type of analysis employed, which compared between patients, who started with a feedback session, and patients who started with no-feedback session. This post hoc analysis revealed that patients, who started with a feedback session, had significantly greater likelihood to demonstrate the highest possible temporary functional change ($\geq +2$). This might mean that the therapist can use the real-time feedback to learn about the best exercises for the specific patient and might further use this information to improve also the second no-feedback session.

This study is only preliminary and of limited sample size and protocol. We believe that the results obtained in such seminaturalistic settings justify further studies with larger samples. It is necessary to establish further the association between BEI and temporary functional change and particularly the use of feedback to improve the temporary functional change. Thereafter it would be of value to evaluate the effect of repetitive use of the BEI in multiple treatment sessions in terms of sustained clinical improvement. This will require a conservative study design of more homogeneous patient populations.

Abbreviations

BEI: Brain Engagement Index
ERP: Event-related potential.

Disclosure

The study was conducted in the Department of Rehabilitation, "Reuth" Rehabilitation Hospital, Tel Aviv, Israel.

Conflicts of Interest

The first author Gadi Bartur is a consultant to BrainMARC Ltd., the company which developed the BEI. The last author Goded Shahaf is the cofounder of BrainMARC Ltd., the developer of the marker used in this work. The other authors do not have any involvement with BrainMARC or any other conflicts of interest.

Authors' Contributions

Gadi Bartur, Goded Shahaf, and Sara Peleg-Shani participated in the design of the study. Katherin Joubran and Gadi Bartur collected and interpreted the data. Goded Shahaf and Gadi Bartur performed data analysis and wrote the manuscript. Jean-Jacques Vatine made a major contribution in writing the manuscript. All authors read and approved the final manuscript.

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Review Article

Effectiveness of Therapeutic Exercise in Fibromyalgia Syndrome: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Objective. The aim of this study was to summarize evidence on the effectiveness of therapeutic exercise in Fibromyalgia Syndrome. *Design*. Studies retrieved from the Cochrane Plus, PEDro, and Pubmed databases were systematically reviewed. Randomized controlled trials and meta-analyses involving adults with fibromyalgia were included. The primary outcomes considered in this systematic review were pain, global well-being, symptoms of depression, and health-related quality of life. *Results*. Effects were summarized using standardized mean differences with 95% confidence intervals using a random effects model. This study provides strong evidence that physical exercise reduces pain (−1.11 [95% CI] −1.52; −0.71; overall effect $p < 0.001$), global well-being (−0.67 [95% CI] −0.89, −0.45; $p < 0.001$), and symptoms of depression (−0.40 [95% CI] −0.55, −0.24; $p < 0.001$) and that it improves both components of health-related quality of life (physical: 0.77 [95% CI] 0.47; 1.08; $p < 0.001$; mental: 0.49 [95% CI] 0.27; 0.71; $p < 0.001$). *Conclusions*. This study concludes that aerobic and muscle strengthening exercises are the most effective way of reducing pain and improving global well-being in people with fibromyalgia and that stretching and aerobic exercises increase health-related quality of life. In addition, combined exercise produces the biggest beneficial effect on symptoms of depression.

1. Introduction

Fibromyalgia Syndrome (FMS) is a rheumatic disease of unknown etiology [1] which is characterized by widespread pain and associated with multiple other symptoms including fatigue, anxiety, and depression [2]. The global mean prevalence of FMS in the general population is 2.7% with a female-to-male ratio of 3 : 1 [3] and the diagnosis is most often made in the middle age [4].

There is evidence from randomized controlled trials (RCTs) that some treatments, for example, pharmacotherapy, patient education, behavioral therapy, and physiotherapy, are effective in reducing symptoms [5]. Physiotherapy techniques used with this patient group include massage therapy, kinesiotherapy, electrotherapy, hydrotherapy, and therapeutic exercise (TE). TE seems to be effective, but there is no consensus on the type, frequency, duration, and intensity of physical activity which is beneficial to this population [6].

The aims of TE include the prevention of dysfunction and the development, restoration, or maintenance of strength, aerobic resistance, mobility, flexibility, coordination, balance, and functional abilities [7–9].

Methods used in TE include aerobic training, coordination and balance training, posture stabilization, body mechanics, flexibility exercises, gait training, relaxation techniques, and muscle strengthening exercises [10–12].

The aim of this meta-analysis was to summarize evidence on the effectiveness of therapeutic exercise in FMS.

2. Methods

This review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [13] and the recommendations of the Cochrane Collaboration [14, 15].

2.1. Data Sources and Searches. A systematic review of publications retrieved from the Cochrane Plus, PEDro, and Pubmed databases was performed. A manual search of the journals FisioterapiaandCuestiones de Fisioterapia was also carried out. The search strategy is detailed in Additional File (see Supplementary Material available online at https://doi.org/10.1155/2017/2356346). Only fully published material in Spanish or English was reviewed. The keywords used in database searches were "fibromyalgia", "physical activity", "exercise", and "exercise therapy". The search strategy was adapted as necessary for each database. This comprehensive search was performed from April 2016 to May 2017.

2.2. Study Selection. The search was conducted by two authors (DS, SN) who screened the titles and abstracts of potentially eligible studies. DS and SN also independently examined the full text of articles which passed the initial screening in order to determine whether they met the selection criteria. Cases where there was a discrepancy between the two reviewers were reevaluated and a consensus decision was achieved by discussion.

2.3. Eligibility Criteria

2.3.1. Type of Study. RCTs comparing types of therapeutic exercise or comparing therapeutic exercise with a control group receiving another intervention or standard care were included.

2.3.2. Participants. Studies with participants older than 18 years, diagnosed with FMS in the absence of significant comorbidity, were included.

2.3.3. Type of Intervention. Studies using aerobic, strengthening, or stretching exercises or a combination of these were considered. Studies of exercise interventions based on activities such as yoga or tai-chi were excluded.

2.3.4. Comparisons. All included studies compared the effect of at least one type of exercise with a control treatment, either another form of physical activity or standard care.

2.3.5. Outcomes Measures. All included studies assessed at least one key domain of FMS symptoms (pain; symptoms of depression; global well-being; health-related quality of life (HRQOL)).

2.4. Data Extraction. Two authors (DS, TG) extracted the data independently using standard extraction forms. Data collected included participants, sample sizes, duration of studies, interventions, outcomes, results, and methods to measure outcomes. Discrepancies were rechecked and consensus was achieved by discussion.

Data extracted after treatment were considered an experimental group and values presented by the patients before treatment as a control group. When two different treatments were compared in the same study they were treated as independent studies for the purposes of the meta-analysis, because the aim of this study was to compare the effects of various therapies.

On the other hand, for each variable two subgroups were differentiated depending on whether the analysis by intention-to-treat or per protocol was performed in the study. When standard deviations (SDs) were not reported in the publication, they were calculated based on what was published from t-values, confidence intervals, or standard errors or used the mean of the SDs from other studies using the same outcome scale.

2.5. Data Items. The following items were extracted: author/year, design of the study, participants, interventions, comparisons, outcomes studied in this meta-analysis, and conclusions.

When researchers reported more than one indicator for an outcome a predefined order of preference for analysis was used. These preferences were predefined according to the specificity of each outcome measure (in descending order):

Pain. Visual Analogue Scale (VAS), VAS, from Fibromyalgia Impact Scale (FIQ), and Multidimensional Pain Inventory subscale

Global Well-Being. FIQ total score

Symptoms of Depression. Beck Depression Inventory (BDI), Hospital Anxiety and Depression Scale (HAD), and VAS from FIQ

HRQOL. Total SF-36 questionnaire (SF-36) score.

2.6. Risk of Bias within Studies and Methodological Quality. Two pairs of reviewers (DS, SN and TG, DP) worked independently to assess the methodological quality in accordance with the CONSORT 2010 [16] statement (Consolidated Standards of Reporting Trials), which contains 25 items scored as zero or one. Only studies that scored over 15 on the CONSORT checklist were included. In addition, the Cochrane Collaboration's tool was used to assess the risk of bias. Sequence generation, allocation concealment, blinding, completeness of outcome data, and absence of selective outcome reporting were also assessed. Risk of bias was classified as low, unclear, or high in each domain.

2.7. Data Synthesis and Analysis

2.7.1. Summary Measures. The meta-analysis was conducted using the Review Manager Analysis software (RevMan 5.3) from the Cochrane Collaboration. Standardized mean differences (SMDs) were calculated from the means and SMDs for each intervention. The SMD used in RevMan software is the measure of effect size known as Hedge's (adjusted) g, which is the difference between the 2 means divided by the pooled SD, with a correction for small sample bias. Hedge's (adjusted) g was chosen because most of the studies included in this meta-analysis were small (<40 subjects per group). As it uses quantitative measures and continuous variable, the statistical analysis method used was the inverse variance [15].

The combined results were assessed using a random effects model, which is more conservative than a fixed effects model and incorporates both within- and between-study variance. Cohen's g was used to evaluate the magnitude of the effect size, calculated as SMD, using the following criteria: $g > 0.2$ to 0.4 small effect size; $g > 0.4$ to 0.8 medium effect size; $g > 0.8$ large effect size. Overall effects were assessed using the Z statistic; $p < 0.05$ was the criterion for rejection of the null hypothesis, that is, concluding that a systematic effect had been demonstrated [17]. The results of the meta-analysis were classified using the following modified level of evidence descriptors: strong = consistent results in at least two RCTs of moderate quality; moderate = consistent results in at least two low quality RCTs and/or one moderate quality RCT; limited = results in low quality RCTs; conflicting = inconsistent results in multiple RCTs; without evidence = no RCT evidence available.

2.7.2. Planned Methods of Analysis. Heterogeneity was assessed using the I^2 statistic: $I^2 < 40\%$ heterogeneity might not be important; $I^2 = 30$–60% may represent moderate heterogeneity; $I^2 = 50$–90% may represent substantial heterogeneity; $I^2 = 75$–100% may represent considerable heterogeneity. The significance of I^2 depends on the magnitude and the impact of heterogeneity tests (e.g., Chi-squared test). Cochran's Q statistic was also calculated. This statistic is associated with the chi-squared statistic of heterogeneity with $k - 1$ degrees of freedom, where k is the number of included studies. If Q is significant, $p < 0.10$, it is likely that at least one of the included studies is different from the others.

In the random effects model tau^2 (t^2) is also used to estimate the variance in the distribution of effects across studies. If $t^2 = 0$ the results of random effects meta-analysis would be almost identical to those of a fixed effects analysis, indicating that there is no heterogeneity [15].

2.7.3. Sensitivity Analysis. In order to examine the influence of individual studies on the overall results, pooled analyses were conducted with each study individually deleted from the model. This enabled us to investigate causes of heterogeneity [15].

2.7.4. Subgroup Analysis. The effects of the various types of exercise (aerobic, strengthening, stretching, and combined) were also analyzed separately.

2.7.5. Risk of Bias across Studies. Potential publication bias was assessed by visually inspecting the funnel plot (plots of effect estimates against standard error) produced by the RevMan Analysis software. Publication bias tends to result in asymmetrical funnel plots [15, 18]. Data on all variables from intention-to-treat analysis were combined to produce the funnel plot.

3. Results

3.1. Study Selection. The literature search produced 704 citations, of which 262 were double hits (studies found in at least two data sources). Screening of title and abstracts resulted in exclusion of 393 studies. After reading the full text of the remaining articles, 33 studies were excluded. 16 RCTs were included in the qualitative synthesis, but only 14 were included in the quantitative analyses because the required measures were not available for 2 studies (Figure 1).

3.2. Study Characteristics. General characteristics of included studies are detailed in Table 1. One study was conducted in Norway [19], one was in United Kingdom [20], two were in Brazil [21, 22], three were in Spain [23–25], three were in the United States [26–28], three were in Sweden [29–31], and two were in Turkey [32, 33]. Patients were recruited by a fibromyalgia association in two studies [19, 23], by local newspaper advertisement in three [29–31], through a rehabilitation center in three [26, 28, 30], by a support group in two [24, 25], and through a hospital rheumatology service in four [21] and one study did not specify how participants were recruited [22]. Analysis by intention-to-treat was performed in ten studies [19–21, 24–26, 28–31].

3.3. Participants. The number of groups compared in the studies varied: one study compared four groups (two exercise groups, one self-help course group, and a combination of exercise and self-help course group) [28], two studies compared three groups [19, 21, 24] (two interventions groups and a control group), two studies compared one type of exercise with a control group [20, 31], and four studies [26, 27, 32, 33] compared two different types of exercise without a control group; one of them was identified as an equivalence study [26]. In total 715 participants were studied before and after treatment. Three studies included men in the sample, in total 15 men of 165 patients. Almost all the participants were women ($n = 700$, 97.90%); there were 15 (2.10%) male participants. The average age of participants was 42.36 years.

3.4. Interventions. Nine studies [19, 20, 22, 26, 28, 29, 32–34] investigated the effects of aerobic exercise, either walking [21, 24, 28, 30], exercise on a cycloergometer [20, 26], or exercise on a treadmill [20, 32, 33]. Seven studies [21, 22, 26, 27, 29, 31, 33] investigated muscle strengthening and two studies investigated stretching [22, 27]. Four studies [23–25, 28] investigated the effects of a combination of types of exercise (aerobic, strengthening, and stretching exercises). Control groups performed relaxation exercises [20, 29, 31], balance exercises [32], and low intensity aerobic exercise [30] or received standard care [19, 21, 23, 25]. However, in this meta-analysis data after treatment were considered an experimental group and values presented by the patients before treatment as a control group. Seven studies compared two exercise treatments (aerobic versus strengthening; [21, 33] combined versus aerobic [24, 25]; strengthening

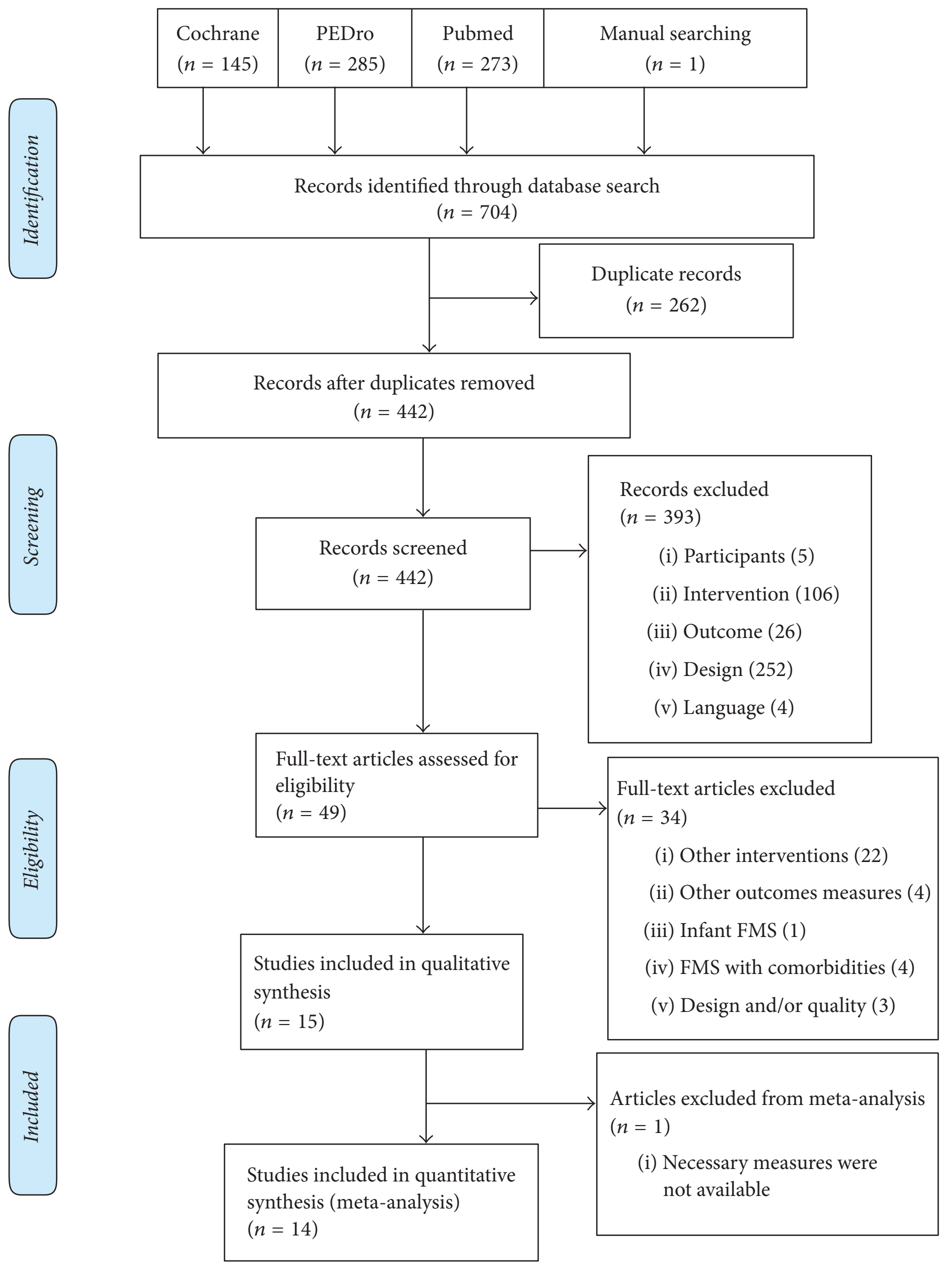


Figure 1: Flow diagram of procedure for selection of studies.

versus stretching [22, 27]; and aerobic versus strengthening [26]), as well as comparing both exercise treatments with a control condition; these studies thus had three groups [21, 24]. In the remaining seven studies, one type of exercise treatment was compared with a control group [19, 20, 23, 25, 29–31].

3.5. Variables. There was much variability in the outcome measures used in the included studies. Pain intensity was assessed using the VAS in five studies [19, 21, 22, 26, 33], and two used the SF-36 pain subscale [23, 25], one the Multidimensional Pain Inventory [26], and three the FIQ pain scale [27, 28, 30].

FMS severity was evaluated using the FIQ in eleven studies [20–25, 27–30, 32]. HRQOL was assessed with the SF-36 in seven studies [21–25, 29, 33]; symptom of depression was evaluated with the BDI in four studies [22, 24, 25, 28], by Hospital Anxiety and Depression Scale in three [30, 31, 33], and by VAS in one [19].

3.6. Risk of Bias within Studies and Methodological Quality. After critical review of each study included, it was concluded that all the studies included in this exceeded minimum thresholds for methodological and scientific quality.

However, since it is impossible to blind participants to group assignment in exercise intervention protocols, all studies were considered to be at a high risk of bias with respect to blinding of participants and personnel (Table 2) (Figure 2).

Table 1: General characteristics of included studies.

Author/year	Design	Participants	Intervention/comparison	Outcomes	Conclusions
Wigers et al. 1996 [19]	RCT	AE: 18 women and 2 men ($n = 20$) with FMS SMT: 18 women and 2 men ($n = 20$) with FMS CG: 19 women and 1 man ($n = 20$) with FMS	*Intervention:* aerobic exercise (AE) and stress management treatment (SMT) *Comparison:* usual care (CG) *Duration:* AE: 3 days a week (45 minutes) for 14 weeks. SMT: 2 days a week (90 minutes) for 6 weeks and 1 day a week (90 minutes) for 8 weeks	(i) Pain (ii) Symptoms of depression	Aerobic exercise was the overall most effective treatment.
Jones et al. 2001 [27]	RCT	EG: 28 women with FMS CG: 28 women with FMS	*Intervention:* muscle strengthening (EG) *Comparison:* stretching exercises (CG) *Duration:* 2 days a week (60 minutes) for 12 weeks	(i) Pain (ii) FMS impact	Muscle strengthening produces an improvement in overall disease activity.
Richards and Scott 2002 [20]	RCT	EG: 62 women and 5 men ($n = 67$) with FMS CG: 64 women and 5 men ($n = 69$) with FMS	*Intervention:* aerobic exercise (EG) *Comparison:* relaxation (CG) *Duration:* EG: 2 days a week (12–50 minutes) for 12 weeks. CG: 2 days a week (60 minute) for 12 weeks	(i) FMS impact	Aerobic exercise is an effective treatment for FMS.
Rooks et al. 2007 [28]	RCT	AE: 35 women with FMS ST: 35 women with FMS FSHC: 27 women with FMS ST-FSHC: 38 women with FMS	*Interventions:* aerobic exercise (AE), strength training, aerobic exercise and stretching (ST), fibromyalgia self-help course (FSHC), and a combination of ST and FSHC (ST-FSHC) *Duration:* AE and ST: 2 days a week (60 minutes) for 16 weeks. FSHC: 120 minutes every two weeks	(i) Pain (ii) FMS impact	Progressive walking, simple strength training movements, and stretching activities improve functional status, key symptoms, and self-efficacy in women with FMS.
Bircan et al. 2008 [33]	RCT	AE: 13 women with FMS SE: 13 women with FMS	*Interventions:* aerobic exercise (AE) and strengthening exercise (SE) *Duration:* 3 days a week (30–40 minutes) for 8 weeks	(i) Pain (ii) Symptoms of depression	AE and SE are similarly effective at improving symptoms, depression, and quality of life in FMS.
García-Martínez et al. 2010 [23]	RCT	EG: 14 women with FMS CG: 14 women with FMS	*Intervention:* exercise combined protocol (aerobic, strengthening, and stretching exercises) (EG) *Comparison:* normal daily activities (CG) *Duration:* 3 days a week (60 minutes) for 12 weeks	(i) Pain (ii) HRQOL (iii) FMs impact	The GE improved quality of life, psychological state, and physical functioning.

Table 1: Continued.

Author/year	Design	Participants	Intervention/comparison	Outcomes	Conclusions
Sañudo et al. 2010 [24]	RCT	EG1: 22 women with FMS EG2: 21 women with FMS CG: 20 women with FMS	*Interventions:* aerobic exercise and combined exercise (EG1 and EG2) *Comparison:* Normal daily activities (CG) *Duration:* GE1: 2 days a week (45–60 minutes) GE2: 2 days a week (35–45 minutes), 24 weeks	(i) FMS impact (ii) HRQOL (iii) Symptoms of depression (iv) Pain	An improvement from baseline in total FIQ score was observed in the exercise groups and was accompanied by decreases in BDI scores. Relative to nonexercising controls, CE evoked improvements in the SF-36 physical functioning and bodily pain domains and was more effective than AE for evoking improvements in the vitality and mental health.
Mannerkorpi et al. 2010 [30]	RCT	EG: 34 women with FMS CG: 33 women with FMS	*Intervention:* Nordic walking moderate to high intensity (EG) *Comparison:* low intensity walking (CG) *Duration:* EG: 2 days a week (10–20 minutes), 15 weeks. CG: 1 day a week	(i) Pain (ii) FMS impact	The Nordic walking group had better FIQ physical scores.
Sañudo et al. 2011 [25]	RCT	EG: 18 women with FMS CG: 20 women with FMS	*Intervention:* combined exercise (aerobic, strength, and flexibility) (EG) *Comparison:* routine care (CG) *Duration:* 2 days a week (45–60 minutes) for 24 weeks	(i) HRQOL (ii) FMS impact (iii) Symptoms of depression	A combined program of long-term exercise improves psychological and health status by increasing the quality of life.
Kayo et al. 2012 [21]	RCT	WPG: 30 women with FMS SMG: 30 women with FMS GC: 30 women with FMS	*Interventions:* walking program (WPG) and muscle strengthening (SMG) exercises *Comparison:* medication only or conventional treatment (CG) *Duration:* WPG and SMG: 3 days a week (60 minutes) for 16 weeks	(i) Pain (ii) FMS impact (iii) HRQOL (iv) Use of drugs	Both modalities (WP and PSM) provided better pain relief for people with FMS than medication only or conventional treatment.
Hooten et al. 2012 [26]	RET	AE: 32 women and 4 men ($n = 36$) with FMS SE: 33 women and 3 men ($n = 36$) with FMS	*Intervention:* aerobic exercise (AE) and strengthening exercise (SE) *Duration:* AE: 10–30 minutes each day for 3 weeks SE: 25–30 minutes each day for 3 weeks	(i) Pain severity	Strengthening exercises and aerobic exercise are similarly effective in reducing pain intensity.
Gavi et al. 2014 [22]	RCT	MSE: 35 women with FMS SE: 31 women with FMS	*Intervention:* muscle strengthening exercise (MSE) and stretching exercises (SE) *Duration:* 2 days a week (45 minutes) for 16 weeks	(i) Pain (ii) HRQOL (iii) FMS impact (iv) Symptoms of depression	Both groups experienced a reduction in pain, which was more noticeable and had an earlier onset in the strengthening exercise group. Both groups experienced improvements in functionality, depression, and quality of life.

Table 1: Continued.

Author/year	Design	Participants	Intervention/comparison	Outcomes	Conclusions
Duruturk et al. 2015 [32]	RCT	BE: 12 women with FMS AE: 14 women with FMS	*Intervention:* balance exercise (BE) and aerobic exercise (AE) *Duration:* 3 days a week (20–45 minutes) for 6 weeks	(i) Pain (ii) FMS impact	Both groups showed an improvement in pain intensity and FIQ functionality; there was no group difference on either measure.
Larsson et al. 2015 [29]	RCT	RE: 67 women with FMS CG: 63 women with FMS	*Intervention:* resistance exercise (RE) *Comparison:* relaxation exercises (CG) *Duration:* RE: 2 days a week (60 minutes) for 15 weeks. CG: 2 days a week (25 minute) for 15 weeks	(i) HRQOL (ii) Pain intensity (iii) FMS impact	Resistance exercise group reduced pain intensity.
Ericsson et al. 2016 [31]	RCT	EG: 67 women with FMS CG: 63 women with FMS	*Intervention:* resistance exercise (EG) *Comparison:* relaxation therapy (CG) *Duration:* 2 days a week (60 minutes) for 15 weeks	(i) Pain (ii) Symptoms depression	Resistance exercise improves some symptoms in women with FMS.

RCT: randomized clinical trial; RET: randomized equivalence trial; EG: exercise group; CG: control group; FMS: Fibromyalgia Syndrome.

Table 2: Risk of bias within studies.

	Wigers et al. 1996	Jones et al. 2002	Richards and Scott 2002	Rooks et al. 2007	Bircan et al. 2008	Duruturk et al. 2015	García-Martínez et al. 2012	Gavi et al. 2014	Hooten et al. 2012	Kayo et al. 2012	Larsson et al. 2015	Mannerkorpi et al. 2010	Sañudo et al. 2010	Sañudo et al. 2011	Ericson et al. 2016
Random sequence generation	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Allocation concealment	Low risk	Low risk	Low risk	Low risk	Risk unclear	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Blinding of participants and personnel	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk	High risk
Blinding of outcome assessment	Risk unclear	Low risk	Low risk	Risk unclear	Risk unclear	Low risk	Risk unclear	Low risk	High risk	Risk unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Incomplete outcome data	Low risk	High risk	Low risk	Low risk	High risk	Low risk	High risk	High risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Selective reporting	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Other bias	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

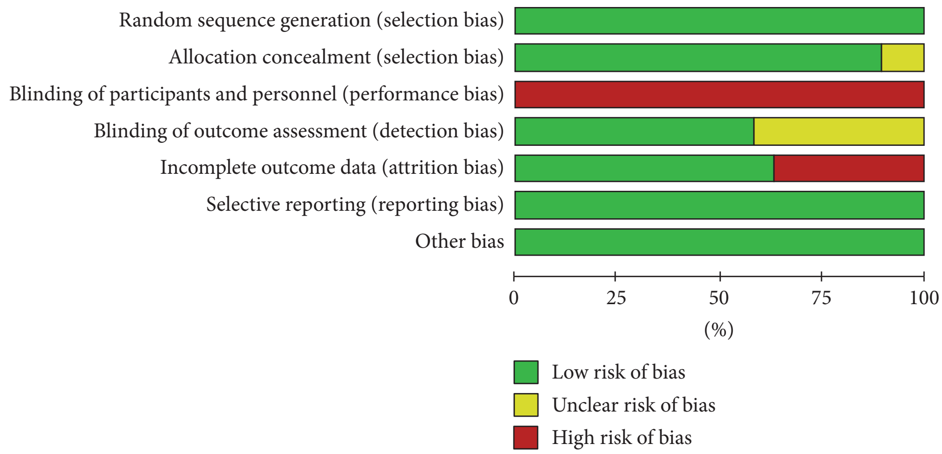


Figure 2: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

3.7. Results of Individual Studies. The means, SDs, sample sizes, and effect estimates for all studies can be seen in the forest plot (Figures 3(a)–3(e)).

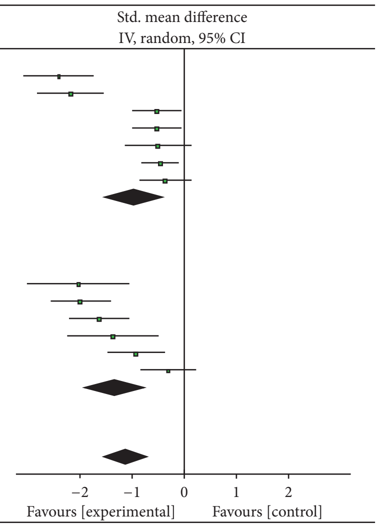
3.8. Synthesis Results. Results are reported as SMDs (95% confidence interval). In the case of pain scales, FMS impact, and depression a negative result indicates that the treatment produced an improvement in patients' condition; but the opposite is true for HRQOL, where a positive effect of treatment is indicated by a positive SMD. There is strong evidence from intention-to-treat and per protocol analysis that exercise reduces pain (−1.11 [95% CI] −1.52, −0.71; overall effect $p < 0.001$), severity of FMS (−0.67 [95% CI] −0.89, −0.45; $p < 0.001$), and symptoms of depression (−0.40 [95% CI] −0.55, −0.24; $p < 0.001$) and increases both the physical and mental component of HRQOL (physical: 0.77 [95% CI] 0.47, 1.08; $p < 0.001$; mental: 0.39 [95% CI] 0.52, 0.27; $p < 0.001$). Values of Cohen's g suggested that exercise had a large effect on pain, medium effect on FMS impact and both the physical and mental component of HRQOL, and small effect on symptoms of depression.

3.9. Subgroup Analysis. There was strong evidence on the basis of intention-to-treat and per protocol analysis that *aerobic exercise* produces a large reduction in pain (−1.05 [95% CI] −1.78, −0.33; overall effect $p < 0.001$), small effect on symptoms of depression (−0.39 [95% CI] −0.77, −0.01; overall effect $p < 0.05$), and a medium reduction in FMS severity as assessed by FIQ (−0.65 [95% CI] −1.14, −0.16; overall effect $p < 0.02$). However, there was moderate evidence from per protocol analysis that aerobic exercise does not improve both the physical and mental component of HRQOL (0.71 [95% CI] −0.09, 1.50; overall effect $p > 0.05$ and 0.71 [95% CI] −0.14, 1.45; overall effect $p > 0.05$, resp.). There was strong evidence from intention-to-treat and per protocol analysis that *muscle strengthening* decreases pain (−1.39 [95% CI] −2.16, −0.62; overall effect $p < 0.001$), produces a reduction in FMS severity (−0.84 [95% CI] 1.23, −0.45; overall effect $p < 0.001$), and has a beneficial effect on symptoms of depression (−0.37 [95% CI] −0.61, −0.13; overall effect $p < 0.02$). In addition, muscle strengthening improves both components of HRQOL (physical: 0.72 [95% CI] 0.23, 1.21; overall effect $p < 0.02$ and mental: 0.44 [95% CI] 0.17, 0.71; overall effect $p < 0.02$). The effect size was large for the variables pain and FMS severity, medium for the physical and mental component of HRQOL, and small for the symptoms of depression. There was a strong evidence from per protocol analysis that *stretching exercises* are not effective in decreasing pain (−0.94 [95% CI] −2.24, 0.35; overall effect $p > 0.05$) and do not produce a reduction in FMS severity (0.53 [95% CI] −1.19, 0.14; overall effect $p > 0.05$). There was moderate evidence that stretching exercises improve both components of HRQOL (physical: 1.15 [95% CI] 0.61, 1.69; overall effect $p < 0.001$ and mental: 0.57 [95% CI] 0.06, 1.08; overall effect $p < 0.05$). In addition, there was strong evidence from per protocol analysis that this type of exercise reduces symptoms of depression (−0.36 [95% CI] −0.72, −0.00; overall effect $p < 0.05$). The effect size was large for the variable physical component of HRQOL, medium for mental component of HRQOL, and small for symptoms of depression.

There was moderate evidence on the basis of intention-to-treat analysis that *combined exercise* produces a large decrease in pain (−0.51 [95% CI] −0.99, −0.44; overall effect $p < 0.05$). In addition, there was strong evidence that this type of exercise produces a medium reduction in symptoms of depression (−0.47 [95% CI] −0.85, −0.10; overall effect $p < 0.05$). There was strong evidence from intention-to-treat and per protocol analysis that combined exercise produces a medium reduction in FMS severity (−0.64 [95% CI] −1.06, −0.22; $p < 0.02$) The effect on HRQOL was only assessed by per protocol analysis; this provided that this type of exercise does not improve HRQOL (physical: 0.58 [95% CI] −0.24, 1.40; overall effect $p > 0.05$ and mental 0.60 [95% CI] −0.12, 1.42; overall effect $p < 0.05$, physical HRQOL (−0.58 [95% CI] −0.24, 1.40; $p > 0.05$) and mental HRQOL (0.60 [95% CI] −0.22, 1.42; $p > 0.05$)). The effect sizes were large for pain and medium for symptoms of depression, FMS severity, and physical and mental HRQOL.

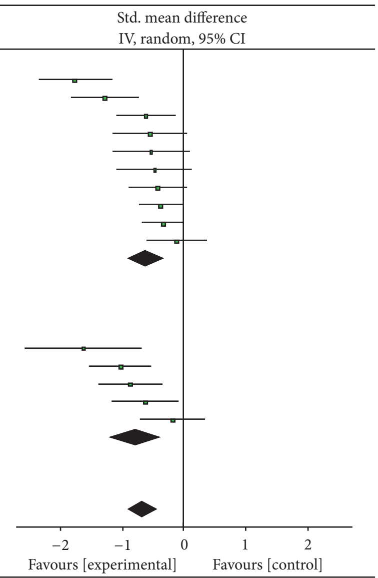
3.10. Sensitivity Analysis. Heterogeneity (measured as I^2) in data on pain from both intention-to-treat and per protocol analysis was eliminated by excluding from analysis the studies

Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, random, 95% CI
1.2.1 Pain. Analysis by intention-to-treat								
Kayo et al. 2012. Muscle strengthening	4.73	1.63	30	8.67	1.63	30	7.4%	−2.39 [−3.06, −1.71]
Kayo et al. 2012. Aerobic exercise	5.1	1.61	30	8.62	1.61	30	7.5%	−2.16 [−2.80, −1.51]
Rooks et al. 2007. Aerobic exercise	4.8	2.5	35	6	2.1	35	8.2%	−0.51 [−0.99, −0.04]
Rooks et al. 2007. Combined exercise	4.8	2.5	35	6	2.1	35	8.2%	−0.51 [−0.99, −0.04]
Wigers et al. 1996. Aerobic exercise	62	21	20	72	19	20	7.6%	−0.49 [−1.12, 0.14]
Larsson et al. 2015. Muscle strengthening	3.86	2.39	56	4.93	2.39	67	8.7%	−0.44 [−0.80, −0.09]
Mannerkorpi et al. 2010. Aerobic exercise	57.7	14.5	34	63.9	21.2	29	8.1%	−0.34 [−0.84, 0.16]
Subtotal (95% CI)			*240*			*246*	*55.8%*	*−0.95 [−1.50, −0.39]*
Heterogeneity: $\tau^2 = 0.49$; $\chi^2 = 48.97$, df = 6 ($p < 0.00001$); $I^2 = 88\%$								
Test for overall effect: $Z = 3.33$ ($p = 0.0009$)								
1.2.2 Pain. Analysis per protocol								
Bircan et al. 2008. Aerobic exercise	2.19	1.88	13	6.07	1.86	13	6.1%	−2.01 [−2.98, −1.04]
Gavi et al. 2014. Muscle strengthening	4.8	1.51	35	7.81	1.51	35	7.8%	−1.97 [−2.55, −1.39]
Gavi et al. 2014. Flexibility	6	1.46	31	8.38	1.46	31	7.8%	−1.61 [−2.19, −1.03]
Bircan et al. 2008. Muscle strengthening	2.65	1.41	13	5.21	2.18	13	6.5%	−1.35 [−2.22, −0.48]
Jones et al. 2002. Muscle strengthening	4.61	2.06	28	6.5	2.06	28	7.9%	−0.90 [−1.46, −0.35]
Jones et al. 2002. Stretching	7	2.43	28	7.68	2.17	28	8.0%	−0.29 [−0.82, 0.24]
Subtotal (95% CI)			*148*			*148*	*44.2%*	*−1.32 [−1.90, −0.74]*
Heterogeneity: $\tau^2 = 0.40$; $\chi^2 = 24.09$, df = 5 ($p = 0.0002$); $I^2 = 79\%$								
Test for overall effect: $Z = 4.48$ ($p < 0.00001$)								
Total (95% CI)			*388*			*394*	*100.0%*	*−1.11 [−1.52, −0.71]*
Heterogeneity: $\tau^2 = 0.46$; $\chi^2 = 81.19$, df = 12 ($p < 0.00001$); $I^2 = 85\%$								
Test for overall effect: $Z = 5.37$ ($p < 0.00001$)								
Test for subgroup differences: $\chi^2 = 0.84$, df = 1 ($p = 0.36$), $I^2 = 0\%$								



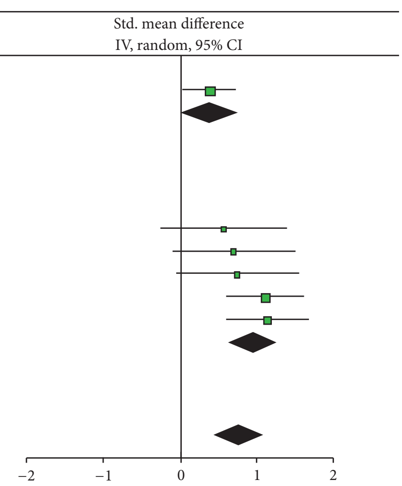
(a) Forest plot: effect of exercise on pain. SD: standard deviation; IV: inverse variance; CI: confidence interval

Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, random, 95% CI
2.1.1 FIQ. Analysis by intention-to-treat								
Kayo et al. 2012. Aerobic exercise	36.76	14.74	30	63.06	14.74	30	6.1%	−1.76 [−2.36, −1.16]
Kayo et al. 2012. Muscle strengthening	42.21	15.88	30	62.8	15.7	30	6.4%	−1.29 [−1.85, −0.73]
Rooks et al. 2007. Aerobic exercise	40.2	15.1	35	48.4	11.2	35	7.2%	−0.61 [−1.09, −0.13]
Sañudo et al. 2010. Aerobic exercise	52.1	15.95	22	60.9	15.95	22	6.0%	−0.54 [−1.14, 0.06]
Sañudo et al. 2011. Combined exercise	54.9	12.5	21	63.1	17.4	21	5.9%	−0.53 [−1.15, 0.09]
Sañudo et al. 2010. Combined exercise	53.4	18.55	21	62.5	19.25	21	5.9%	−0.47 [−1.09, 0.14]
Rooks et al. 2007. Combined exercise	38.3	19.9	35	44.9	9.3	35	7.3%	−0.42 [−0.89, 0.05]
Larsson et al. 2015. Muscle strengthening	54.4	18.2	56	60.5	14.4	67	8.5%	−0.37 [−0.73, −0.02]
Richards and Scott 2002. Aerobic exercise	55	13.74	69	59.6	12.49	69	8.7%	−0.35 [−0.68, −0.01]
Mannerkorpi et al. 2010. Aerobic exercise	59.9	12.3	29	61.7	18.3	34	7.1%	−0.11 [−0.61, 0.38]
Subtotal (95% CI)			*348*			*364*	*69.1%*	*−0.62 [−0.89, −0.34]*
Heterogeneity: $\tau^2 = 0.13$; $\chi^2 = 27.94$, df = 9 ($p = 0.0010$); $I^2 = 68\%$								
Test for overall effect: $Z = 4.40$ ($p < 0.0001$)								
2.1.2 FIQ. Analysis per protocol								
García-Martínez et al. 2010. Combined exercise	50.2	12.9	12	72.1	13.1	12	3.7%	−1.63 [−2.57, −0.68]
Gavi et al. 2014. Muscle strengthening	51.15	18.38	35	67.85	13.37	35	7.0%	−1.03 [−1.53, −0.53]
Gavi et al. 2014. Flexibility	51.15	18.38	31	66.78	17.24	31	6.8%	−0.87 [−1.39, −0.34]
Jones et al. 2002. Muscle strengthening	37.81	16.93	28	48.08	15.34	28	6.6%	−0.63 [−1.16, −0.09]
Jones et al. 2002. Stretching	43.36	19.58	28	47.14	20.64	28	6.8%	−0.19 [−0.71, 0.34]
Subtotal (95% CI)			*134*			*134*	*30.9%*	*−0.79 [−1.18, −0.40]*
Heterogeneity: $\tau^2 = 0.11$; $\chi^2 = 9.32$, df = 4 ($p = 0.05$); $I^2 = 57\%$								
Test for overall effect: $Z = 3.94$ ($p < 0.0001$)								
Total (95% CI)			*482*			*498*	*100.0%*	*−0.67 [−0.89, −0.45]*
Heterogeneity: $\tau^2 = 0.12$; $\chi^2 = 39.03$, df = 14 ($p = 0.0004$); $I^2 = 64\%$								
Test for overall effect: $Z = 5.90$ ($p < 0.00001$)								
Test for subgroup differences: $\chi^2 = 0.50$, df = 1 ($p = 0.48$), $I^2 = 0\%$								



(b) Effect of exercise on FMS severity. SD: standard deviation; IV: inverse variance; CI: confidence interval

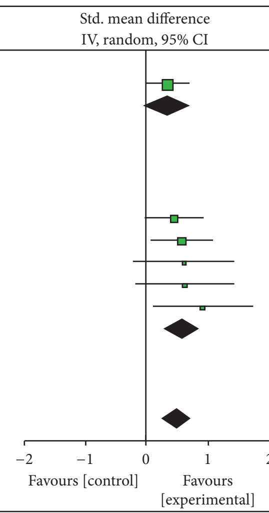
Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, random, 95% CI
3.1.1 Physical component of HRQOL. Analysis by intention-to-treat								
Larsson et al. 2015. Muscle strengthening	34.5	9.1	56	31.2	7.9	67	28.0%	0.39 [0.03, 0.75]
Subtotal (95% CI)			*56*			*67*	*28.0%*	*0.39 [0.03, 0.75]*
Heterogeneity: not applicable								
Test for overall effect: $Z = 2.12$ ($p = 0.03$)								
3.1.2 Physical component of HRQOL. Analysis per protocol								
García-Martínez et al. 2010. Combined exercise	36.4	12.9	12	30	8	12	10.7%	0.58 [−0.24, 1.40]
Bircan et al. 2008. Aerobic exercise	38.92	6.11	13	34.49	6.02	13	11.1%	0.71 [−0.09, 1.50]
Bircan et al. 2008. Muscle strengthening	45.44	7.71	13	38.66	9.78	13	11.1%	0.75 [−0.05, 1.55]
Gavi et al. 2014. Muscle strengthening	35.65	7.8	35	27.01	7.61	35	20.3%	1.11 [0.60, 1.61]
Gavi et al. 2014. Flexibility	34.15	9.2	31	24.37	7.58	31	18.8%	1.15 [0.61, 1.69]
Subtotal (95% CI)			*104*			*104*	*72.0%*	*0.95 [0.66, 1.24]*
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.29$, df = 4 ($p = 0.68$); $I^2 = 0\%$								
Test for overall effect: $Z = 6.46$ ($p < 0.00001$)								
Total (95% CI)			*160*			*171*	*100.0%*	*0.77 [0.47, 1.08]*
Heterogeneity: $\tau^2 = 0.05$; $\chi^2 = 8.09$, df = 5 ($p = 0.15$); $I^2 = 38\%$								
Test for overall effect: $Z = 4.94$ ($p < 0.00001$)								
Test for subgroup differences: $\chi^2 = 5.80$, df = 1 ($p = 0.02$), $I^2 = 82.8\%$								



(c) Effect of exercise on physical component of HRQOL. SD: standard deviation; IV: inverse variance; CI: confidence interval

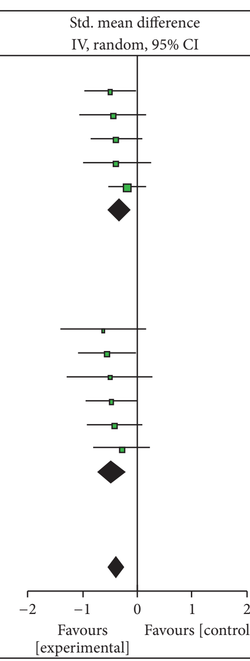
Figure 3: Continued.

Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, random, 95% CI
4.1.1 Mental component of HRQOL. Analysis by intention-to-treat								
Larsson et al. 2015. Muscle strengthening	42	12.6	56	37.7	12.2	67	37.8%	0.35 [−0.01, 0.70]
Subtotal (95% CI)			*56*			*67*	*37.8%*	*0.35 [−0.01, 0.70]*
Heterogeneity: not applicable								
Test for overall effect: $Z = 1.89$ ($p = 0.06$)								
4.1.2 Mental component of HRQOL. Analysis per protocol								
Gavi et al. 2014. Muscle strengthening	39.16	12.64	35	33.47	12.3	35	21.4%	0.45 [−0.02, 0.93]
Gavi et al. 2014. Flexibility	44.55	13.6	31	36.98	12.73	31	18.7%	0.57 [0.06, 1.08]
García-Martínez et al. 2010. Combined exercise	45	12.7	12	37.9	9.9	12	7.2%	0.60 [−0.22, 1.42]
Bircan et al. 2008. Aerobic exercise	41.07	8.53	13	35.81	7.92	13	7.7%	0.62 [−0.17, 1.41]
Bircan et al. 2008. Muscle strengthening	43.01	7.02	13	35.81	8.26	13	7.3%	0.91 [0.10, 1.72]
Subtotal (95% CI)			*104*			*104*	*62.2%*	*0.58 [0.30, 0.86]*
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.93$, df = 4 ($p = 0.92$); $I^2 = 0\%$								
Test for overall effect: $Z = 4.07$ ($p < 0.0001$)								
Total (95% CI)			*160*			*171*	*100.0%*	*0.49 [0.27, 0.71]*
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.94$, df = 5 ($p = 0.86$); $I^2 = 0\%$								
Test for overall effect: $Z = 4.37$ ($p < 0.0001$)								
Test for subgroup differences: $\chi^2 = 1.01$, df = 1 ($p = 0.31$), $I^2 = 1.3\%$								



(d) Effect of exercise on mental component of HRQOL. SD: standard deviation; IV: inverse variance; CI: confidence interval

Study or subgroup	Experimental Mean	Experimental SD	Experimental Total	Control Mean	Control SD	Control Total	Weight	Std. mean difference IV, random, 95% CI
5.1.1 Analysis by intention-to-treat								
Rooks et al. 2007. Combined exercise	9	8	35	13	8	35	10.8%	−0.49 [−0.97, −0.02]
Sañudo et al. 2011. Combined exercise	28.9	13.6	21	35.1	14.1	21	6.5%	−0.44 [−1.05, 0.17]
Rooks et al. 2007. Aerobic exercise	13	10	35	17	10	35	11.0%	−0.40 [−0.87, 0.08]
Wigers et al. 1996. Aerobic exercise	24	22	20	34	29	20	6.3%	−0.38 [−1.01, 0.25]
Ericsson et al. 2016. Muscle strengthening	6.3	3.7	67	7	3.9	56	19.4%	−0.18 [−0.54, 0.17]
Subtotal (95% CI)			*178*			*167*	*54.1%*	*−0.34 [−0.56, −0.13]*
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 1.32$, df = 4 ($p = 0.86$); $I^2 = 0\%$								
Test for overall effect: $Z = 3.15$ ($p = 0.002$)								
5.1.2 Analysis per protocol								
Bircan et al. 2008. Muscle strengthening	5.69	3.28	13	8.23	4.51	13	3.9%	−0.62 [−1.41, 0.17]
Jones et al. 2002. Muscle strengthening	7.11	5.93	28	10.78	7.03	28	8.6%	−0.56 [−1.09, −0.02]
Bircan et al. 2008. Aerobic exercise	6.39	3.79	13	8.39	3.97	13	4.0%	−0.50 [−1.28, 0.28]
Gavi et al. 2014. Muscle strengthening	18.49	12.35	35	25.83	17.36	35	10.9%	−0.48 [−0.96, −0.01]
Gavi et al. 2014. Flexibility	16.39	9.46	31	22.77	18.56	31	9.7%	−0.43 [−0.93, 0.08]
Jones et al. Stretching	8.8	6.4	28	10.64	6.35	28	8.9%	−0.28 [−0.81, 0.24]
Subtotal (95% CI)			*148*			*148*	*45.9%*	*−0.46 [−0.69, −0.23]*
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 0.75$, df = 5 ($p = 0.98$); $I^2 = 0\%$								
Test for overall effect: $Z = 3.90$ ($p < 0.0001$)								
Total (95% CI)			*326*			*315*	*100.0%*	*−0.40 [−0.55, −0.24]*
Heterogeneity: $\tau^2 = 0.00$; $\chi^2 = 2.60$, df = 10 ($p = 0.99$); $I^2 = 0\%$								
Test for overall effect: $Z = 4.96$ ($p < 0.00001$)								
Test for subgroup differences: $\chi^2 = 0.53$, df = 1 ($p = 0.46$), $I^2 = 0\%$								



(e) Effect of exercise on symptoms of depression. SD: standard deviation; IV: inverse variance; CI: confidence interval

Figure 3

by Kayo et al. and Jones et al. [21, 27]. Once these studies had been eliminated, there was still strong evidence that exercise produces a large reduction in pain (−0.97 [95% CI] −1.39, −0.55; overall effect $p < 0.001$). Using the same study-by-study exclusion procedure it was found that heterogeneity in data on FMS severity was eliminated by excluding the same studies. Eliminating the Kayo et al. and Jones et al.'s studies [21, 27] the effect size was increased and there was still strong evidence that exercise produces a large decrease in FMS severity (−1.04 [95% CI] −1.37, −0.70; overall effect $p < 0.001$).

The remaining data on outcome variables were homogeneous and therefore other sensitive analyses were not necessary.

3.11. Risk of Bias across Studies. On visual inspection, the funnel plot of posttreatment outcomes was symmetrical and there was thus no evidence of publication bias. Due to heterogeneity produced by Kayo et al.'s study, data from this study were excluded for this analysis (Figure 4).

4. Discussion

The use of various exercise interventions in the studies presented above notwithstanding any physical activity is damaging for people with FMS.

This is the first meta-analysis to assess the most effective exercise for improving some symptoms or conditions in fibromyalgia.

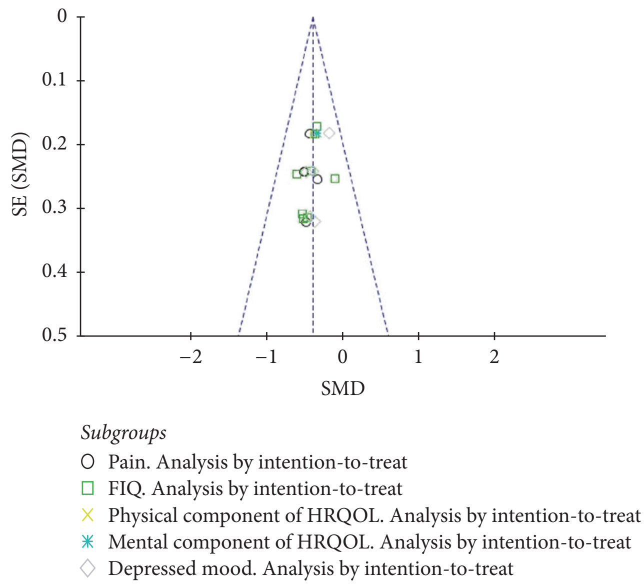


Figure 4: Funnel plot of publication bias. SE: error standard; SMD: standardized mean difference; FIQ: fibromyalgia impact questionnaire; HRQOL: health-related quality of life.

Aerobic exercise for 30 to 60 minutes at an intensity of 50–80% of maximum heart rate 2 or 3 times per week for a period of 4–6 months and muscle strengthening exercises (1 to 3 sets of 8–11 exercises, 8–10 repetitions with a load of 3.1 kg or 45% of 1 repetition maximum (RM)) seem to be most effective in decreasing the pain and severity of FMS. Stretching the major muscle groups and aerobic exercise can improve the physical and mental component of HRQOL, respectively. Combined exercise programs consisting of aerobic exercise, muscle strengthening, and stretching exercises performed for 45–60 minutes 2 or 3 times per week for 3–6 months seem to be the most effective in reducing the symptoms of depression. The findings of this research are consistent with two previous equivalence studies [21, 26] which concluded that aerobic and strengthening exercise have similar effects on pain intensity and FMS severity. In addition, like in this study, Kayo et al. [21] and Bircan et al. [33] also found that both aerobic and strengthening exercise were equally effective in improving HRQOL. However, this meta-analysis found that stretching exercise produces a greater improvement in the physical component of HRQOL than the rest of types of exercise that were studied whereas aerobic and combined exercise seem to be better at improving mental quality of life. Kayo et al. [21] noted that after 12 weeks without exercise the group who had performed muscle strengthening exercises had experienced recurrence of symptoms, whereas the beneficial effects of aerobic exercise persisted longer.

The results of other meta-analyses were also considered. In 2010, Häuser et al. [34] compared various types of aerobic exercise and found that exercising in the water and on dry land was similarly effective, this one being mild to moderate intensity, with a frequency of 2-3 times per week for 20–30 minutes at least for 4 weeks. Like García-Martínez et al. [23] Häuser et al. concluded that for the effects on physical condition and depression to persist the patients must maintain the exercise regime and therefore need to be motivated [34].

In another meta-analysis published by Kelley et al. [35] in the same year, seven studies were collected, to investigate the effects of physical activity, consisting of 15–60-minute sessions of aerobic and/or muscle strengthening exercises 2 or 3 times per week for a period of 12–23 weeks. The meta-analysis by Kelley et al. [35], like this study, suggested that physical activity improves the general well-being of women with FMS.

This meta-analysis had several limitations, one of which is the sample size of the included studies; most used relatively few participants. In addition, studies included in this meta-analysis were performed predominantly in women due to the fact that fibromyalgia is a syndrome with a significant female predominance [3]. This could be a limitation of the present study because it is not known whether the results obtained could be extrapolated to the male population suffering from fibromyalgia.

Unlike pharmacological studies, which are easily blinded, behavioral and physical treatment requiring the active participation of patients is virtually impossible to be blinded.

It is also important to take into account the heterogeneity of the studies, primarily due to the inclusion of the studies of Kayo et al. and Jones et al. [21, 27]. This heterogeneity should be taken into consideration when drawing conclusions from the analysis of this study.

Another important limitation is that each type of therapeutic exercise was investigated in only a small number of studies. Aerobic exercise is the most commonly studied type of exercise treatment for FMS.

5. Conclusions

Exercise is beneficial for people with FMS but it is unable to draw any conclusions about what type of exercise is most effective because not enough studies were included in this meta-analysis. There is some evidence to suggest that muscle strengthening and aerobic exercise are most effective in reducing the pain and severity of the disease whilst stretching and aerobic exercise produce the biggest improvements in HRQOL. Combined exercise is the most effective way of reducing symptoms of depression. Although there is still no consensus, it seems that 2 or 3 sessions of mild to moderate intensity physical activity lasting 30–45 minutes each are effective.

It would be interesting to conduct primary research into the type of exercise likely to yield the highest rate of adherence to an exercise treatment regime using a larger sample, because for the effects to be sustained the patients must continue with regular physical activity.

It would also be interesting to investigate whether group and individual physical activity have similar psychological benefits.

Disclosure

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

Authors' Contributions

M. Dolores Sosa-Reina and Susana Nunez-Nagy equally contributed to this study.

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