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Approaches in Physical Activity: From Basic to Applied Researches 2020

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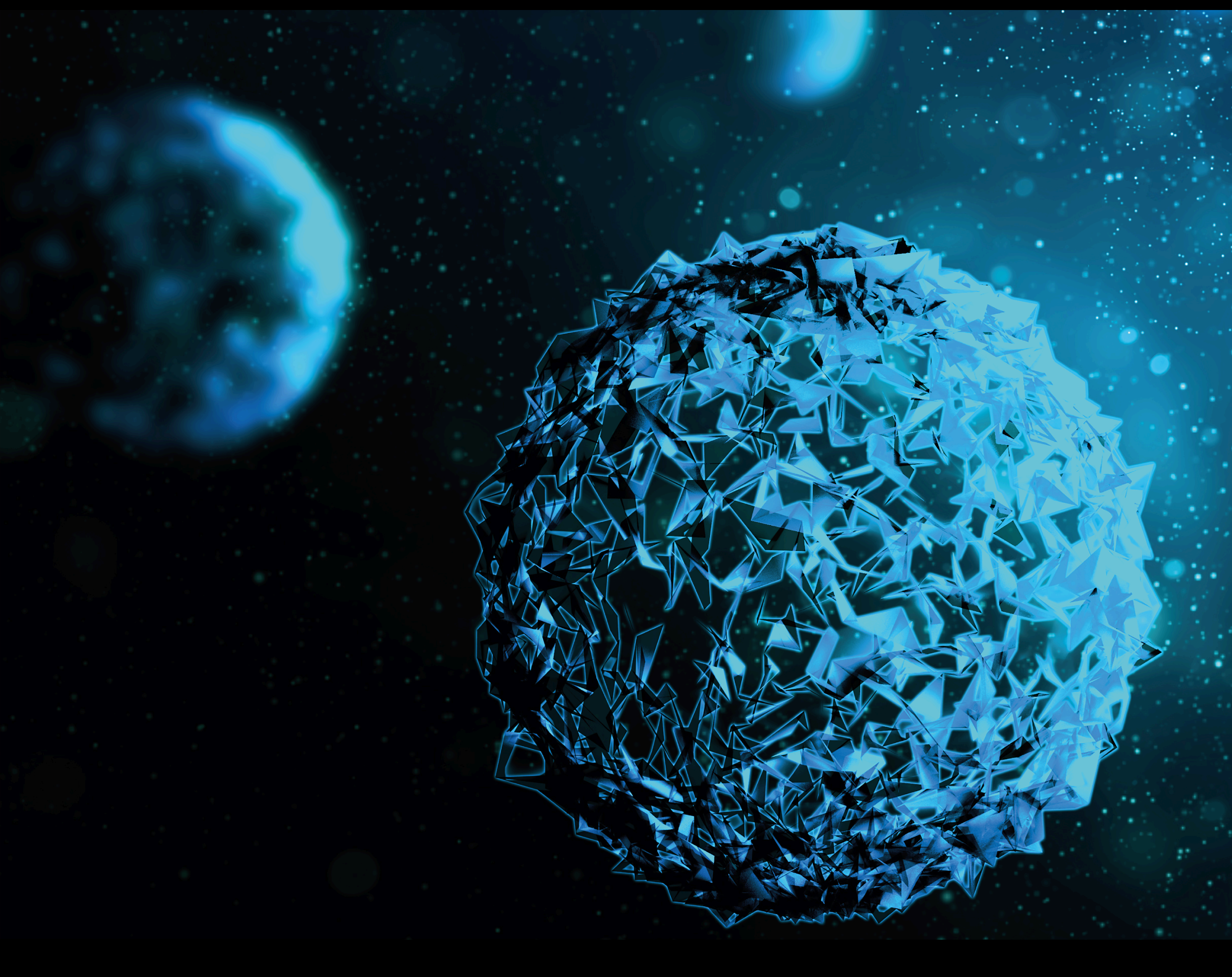

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Contents

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Research Article

Short-Term Cigarette Smoking in Rats Impairs Physical Capacity and Induces Cardiac Remodeling

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Despite the strong evidence on the cardiac and renal damages after chronic exposure to cigarette smoke, there is a paucity of data on its short-term effects. The study evaluated the short-term effects of cigarette smoking on left ventricular (LV) remodeling, *in vitro* myocardial and renal function. Female *Wistar* rats were randomized to control (C) and cigarette smoking rats for eight weeks. Physical capacity was assessed using an adapted model of exhaustive swim; left ventricle (LV) morphology and function were also evaluated. Renal function was assessed by creatinine clearance and urine protein. The *in vitro* myocardial performance was analyzed in isolated papillary muscles. Rats exhibited reduced physical capacity after short-term cigarette smoking. Although there was no change on LV function, reduced chamber diameter was found in the smoking group associated with an increased LV wall thickness. There was augmented cardiac mass compared to C that was confirmed by increased cardiomyocyte nucleus volume, but *in vitro* myocardial performance and renal function were unchanged. A short-term cigarette smoking induces cardiac remodeling without abnormalities in function. The smoking group still preserved renal function and *in vitro* myocardial performance. However, the reduced physical capacity may suggest an impairment of the cardiac reserve.

1. Introduction

Cigarette smoking is the leading cause of preventable morbidity and premature mortality at developed countries [1]. The main health disorders linked to smoking are cardiovascular diseases, cancer, and chronic obstructive pulmonary disease. In addition, smoking is an important risk factor to myocardial infarction [2] and nephropathies [3].

Studies have reported that a long-term cigarette smoke exposure may be associated with cardiac remodeling [4–6] which in turn correlates with myocardial dysfunction, heart failure, and increased mortality risk [7]. However, there are few studies [8, 9] that define the cardiotoxic effects of short-term cigarette use, specifically reporting data from myocardial mechanics, which could indicate the initial and possibly reversible changes in the cardiocirculatory system. If concerning renal implications, although long-term exposure to cigarette smoke is an independent risk factor for microalbuminuria, diuresis and proteinuria [10, 11], the short-term effects on the renal function are still poorly understood as well.

Thus, to date, a number of evidences have been reported the local and systemic effects of chronic exposure to cigarette smoke and such studies requiring prolonged exposure for several months. Therefore, the aim of this study was to evaluate the effects of short-term cigarette smoke exposure on myocardial function and remodeling and renal function and its consequences to the physical capacity of previously healthy rats.

2. Materials and Methods

Twenty female *Wistar* rats, weighing 200–230 g, were assigned to one of the following two groups: smoking animals ($n = 10$), exposed to cigarette smoke for eight weeks, and control animals ($n = 10$), allocated to the similar chamber but not exposed to tobacco smoke. The environment was controlled in terms of light (12 h light/dark cycle), clean-air room temperature (23 ± 3°C), and relative humidity (60 ± 5%). The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies [12]. All procedures performed were in accordance with the Guide for the Care and Use of Laboratory Animals (NIH) and the ethical standards of the institution (Institutional Research Ethics Committee of the Federal University of São Paulo—protocol 34/08).

2.1. Exposure to Tobacco Smoke. Rats were exposed to cigarette smoke in a chamber (dimension: 1.000 × 800 × 700 mm) connected to a smoking device according to other studies [5, 6]. The smoke was drawn out of filtered commercial cigarettes (composition per unit: 1.1 mg nicotine, 14 mg tar, and 15 mg carbon monoxide) with a vacuum pump and exhausted into the smoking chamber. In the first week, cigarette number was gradually increased from 5 to 20 cigarettes for 60 min, administered two times a day. Subsequently, 20 cigarettes were used in each smoking session, twice a day (60 min in the morning and 60 min in the afternoon) for eight weeks. The chamber carbon monoxide content was measured with a sensor Toxi Vision CO 860 (Biosystems, Prairieville, LA, USA).

2.2. Physical Capacity Swim Test. Physical capacity was assessed using an adapted model of exhaustive swimming previously reported [13]. A load equivalent to 10% of body weight was attached around the waist of each rat using a rubber band. Rats from all groups were observed to determine swimming time until exhaustion. Exhaustion was defined as the time-point when the rat could not swim up to the water surface for 10 seconds.

2.3. Renal Function. Renal function was measured after 8 wk cigarette smoking exposure as previously described [14]. Briefly, rats were placed in a metabolic cage for 24 h with water and food *ad libitum*. After urine collection, samples were stored in −20°C. Serum (SCr, mg/dL) and urinary creatinine (UCr, mg/dL) were determined by Jaffé method (Creatinina K-Colorimetrico, Picratoalcalino, Labtest Diagnostica SA, Minas Gerais, Brazil). The creatinine clearance (CrCl, mL/min) was calculated to estimate glomerular filtration rate. The urinary protein was measured by an enzymatic colorimetric assay (Sesiprot kit Labtest Diagnostica SA, Minas Gerais, Brazil) and expressed as 24-hour proteinuria (24 h Uprot) or urine protein/creatinine clearance ratio (Uprot/CrCl).

2.4. Blood Pressure Measurement. Animals were allowed to adapt to the environment for three days before the measurement of blood pressure. Animals were placed in a heated chamber at a temperature of 38-40°C for ten minutes, and blood pressure values were recorded from each animal. At the end of protocols, mean, and systolic and diastolic blood pressures were determined by a tail cuff method (LETICA, LE5002, Barcelona, Spain) in conscious rats.

2.5. Doppler Echocardiography. At the end of protocols, rats were anesthetized with ketamine (50 mg/kg) plus xylazine (10 mg/kg) by i.p. route. Transthoracic echocardiographic was performed using a HP SONOS 5500 instrument (Philips Medical Systems, Andover, MA, USA), as described elsewhere [15, 16]. The transverse images were obtained at basal (at the tip of the mitral valve leaflets), middle (at the papillary muscle level), and apical (distal to the papillary muscle but beyond the cavity cap) levels of the left ventricular (LV). The end-diastolic (LVEDD) and systolic (LVESD) LV diameters and diastolic (LVAWT) and systolic (LVPWT) LV posterior wall thicknesses were measured from the transverse parasternal view using M-mode images. The LV systolic function was defined by the fractional shortening (FS), and diastolic function was analyzed by the mitral diastolic influx velocity curve on the pulsed-wave Doppler. From the 4-chamber view, peak E-wave and A-wave velocities were acquired, and the E/A ratio was derived. Heart rate was calculated by a coupled electrocardiography.

2.6. In Vitro Myocardial Performance. Myocardial mechanic was evaluated as previously described [17, 18]. LV posterior papillary muscles were carefully dissected and vertically mounted in an organ bath heated at 29°C and filled with an oxygenated Krebs-Henseleit buffered solution 100% oxygenated and then attached to force transducer (Grass mod FT03E). Preparations were stimulated by platinum electrodes at frequency of 0.2 Hz, using square-wave pulses of 5-ms duration, and voltage adjusted to a value 10% greater than minimum required producing mechanical response. After 60 min equilibration period, the following parameters were evaluated: developed tension (DT), maximal rate of tension increase ($+dT/dt$) and decrease ($-dT/dt$), and resting tension (RT). At the end of the experiment, the muscle length was measured, and the muscular portion between the two clips was blotted dry and weighed. The cross-sectional area was estimated from the muscle weight and length by assuming a cylindrical shape and specific gravity of 1.0, and all force-related data were normalized by respective cross-sectional area and muscle mass.

2.7. Cardiac Biometry and Histomorphometry. Before the excision of the papillary muscle, atrium and ventricles were weighed separately, in order to use the chamber mass divided by the body mass as an index suggestive of hypertrophy. After papillary muscle dissection, ventricular samples were fixed in 10% buffered formalin and embedded in paraffin to evaluate nuclear volume and collagen content in histology slides [6, 16]. Briefly, 7 μm thickness sections were obtained from the LV and hematoxylin-eosin stained. Cardiac muscle fibers were visualized on a longitudinal axis using an Olympus microscope at 40x magnification, and ellipsoid nuclei were analyzed. As an estimative of myocyte hypertrophy, the average nuclear volume was determined randomly in 50 −70 myocytes cut longitudinally for each animal and calculated according to the following equation: nuclear volume = $\pi \times D \times d2/6$, where d is the shorter nuclear diameter and D is the longer nuclear diameter (15). LV collagen content was determined by picrosirius red staining using polarized light. The perivascular areas were excluded from analyzes. All histological images were visualized using an Olympus microscope at 5 randomized 40x magnification fields per animal and analyzed using Image Tool software 3.0.

2.8. Statistical Analysis. Analyses were performed using the SPSS (version 12.0, Chicago, Illinois, USA). All data are expressed as the mean ± standard error of the mean (SEM). The D'Agostino-Pearson and Levene tests were used to verify approximately normal statistic distributions and variance homogeneity, respectively. Comparisons between groups were performed by unpaired Student's t test or ANOVA two way conform necessary. Statistical significance was established at $p < 0.05$.

3. Results

As showed at Figure 1, no differences were found in physical capacity before interventions (baseline time-point). However, rats exposed to cigarette smoke for eight weeks exhibited patent exhaustion in a shorter time (before: 197 ± 7 *vs.* after: 169 ± 4 seconds), but no changes were observed in control animals (before: 199 ± 6,after: 201 ± 5 seconds).

Despite the reduced physical capacity, no significant differences were found in systolic, diastolic, or mean blood pressures between the smoking and control groups (Table 1).

Additionally, Doppler echocardiography was performed in anesthetized rats to further evaluate cardiac morphology and function. Heart rate was significantly increased in the smoking group (243 ± 28 *vs.* controls: 312 ± 18 bpm), but without changes on LV fractional shortening and on the E/A ratio of the mitral valve flow study (Figure 2). Moreover, the group exposed to cigarette smoke significantly changed the cardiac morphology assessed by echocardiography: there was a reduction in LV diameters in both diastolic and systolic phases, associated with an increased LV posterior wall thickness compared with controls (Figure 2).

To further investigate if the unchanged cardiac global function *in vivo* was associated with preserved myocardial mechanics, the contractile response of papillary muscle was evaluated *in vitro*. As showed in Table 1, systolic (DT and +dT/dt) and diastolic (−dT/dt) performances of the isolated cardiac muscle were similar between groups.

Regarding renal function, as evaluated by urine protein levels and creatinine clearance, there were no statistically significant differences between the groups by short-term exposure to cigarette smoke (Table 1), although urinary protein excretion indexed by creatinine clearance tended to increase in the smoking group ($p = 0.0552$).

Finally, the heart biometry and histomorphometry were also assessed (Figure 3), and smoking rats had increased LV mass and total cardiac mass compared with controls. Also, microscopic study indicated an increased nuclear volume of the LV cardiomyocytes from this group. In addition, myocardial interstitial collagen content was significant increased by short-term smoke exposure.

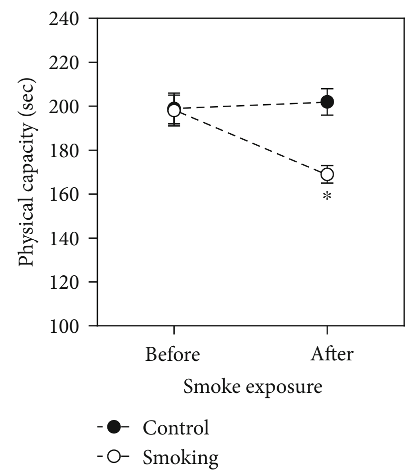

Figure 1: Physical capacity test performed by rats before and after smoke exposure in controls and smoking groups. Data expressed as mean + / − SEM. *$p < 0.05$ vs. before and control group.

Table 1: Parameters of cardiac and renal functions of animals not exposed and exposed to cigarette smoke.

	Control	Smoking	p value
Hemodynamic			
SBP (mmHg)	126 ± 2	129 ± 2	$p > 0.05$
DBP (mmHg)	84 ± 2	82 ± 3	$p > 0.05$
MBP (mmHg)	98 ± 1	98 ± 2	$p > 0.05$
Myocardial function			
DT (g/mm^2/mg)	1.11 ± 0.57	0.95 ± 0.38	$p > 0.05$
+dT/dt_{max} (g/mm^2/mg/s)	10.13 ± 3.57	8.63 ± 2.62	$p > 0.05$
−dT/dt_{max} (g/mm^2/mg/s)	−8.18 ± 5.88	−5.43 ± 1.82	$p > 0.05$
RT (g/mm^2/mg)	0.22 ± 0.17	0.19 ± 0.06	$p > 0.05$
Renal function			
SCr (mg/dL)	0.48 ± 0.05	0.47 ± 0.08	$p > 0.05$
CrCl (mL/min)	1.14 ± 0.02	1.13 ± 0.05	$p > 0.05$
Uprot (mg/24 h)	16.27 ± 1.60	20.15 ± 1.53	$p > 0.05$
Uprot/CrCl (mg/mL)	14.78 ± 1.40	18.56 ± 1.20	$p > 0.05$

Values are the mean ± SEM. Systolic (SBP), diastolic (DBP), and mean blood pressures (MBP) measured in hemodynamic study; developed (DT) and resting tensions (RT) and maximum rate of tension rise (+dT/dt_{max}) and decline (-dT/dt_{max}) of isolated cardiac muscles; serum creatinine (SCr), creatinine clearance (ClCr), 24 h urinary excretion (Uprot), and urine protein/creatinine clearance ratio (Uprot/CrCl).

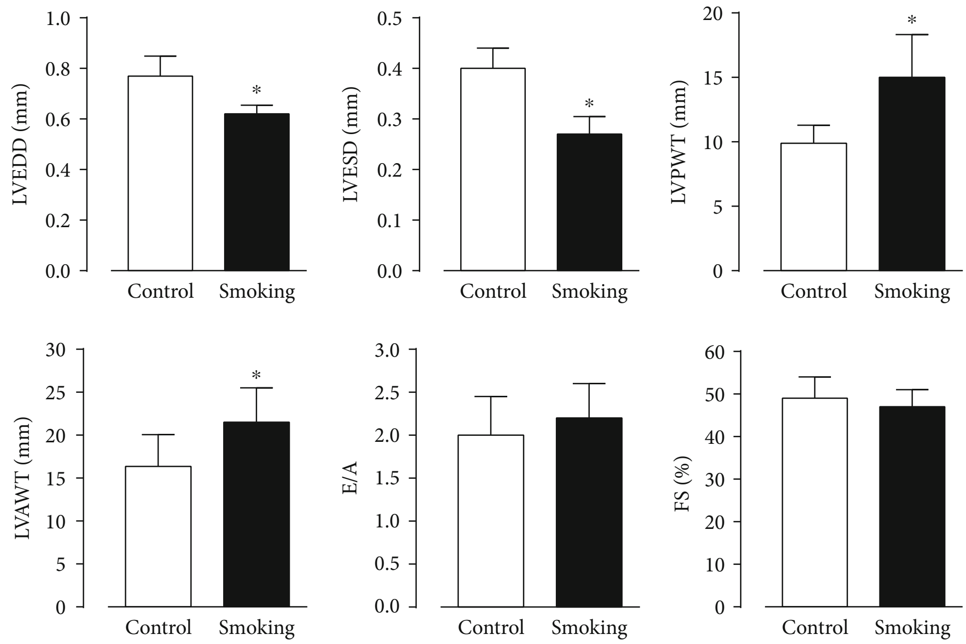

Figure 2: Morphofunctional data from Doppler echocardiography. Left ventricular end-diastolic (LVEDD) and end-systolic diameters (LVESD); LV posterior (LVPWT) and anterior wall thickness (LVAWT); relation between velocity of E and A waves (E/A ratio); and LV fractional shortening (FS). Bars are the means ± SEM. $^{*}p < 0.05$ *vs.* control.

4. Discussion

The present study demonstrates that short-term exposure to cigarette smoke was capable of inducing an adverse cardiac remodeling associated with impaired physical capacity in previously healthy female rats. The level of carbon monoxide in the exposure chamber used in the present study was ~510 ppm, similar to reported by other authors using the same protocol [5, 6, 19]. According to these authors, an exposure to smoke from 40 cigarettes/day is sufficient to increase the rate of carboxyhemoglobin to 5.3 ± 2.8% in rats, while animals that do not inhale smoke have 0.9 ± 0.7% of carboxyhemoglobin on blood. It should be noted that values of carbon monoxide of 400 ppm are sufficient to promote comparable to rates of carboxyhemoglobin found in humans considered heavy smokers [20]. Despite this, cardiac function evaluated in anesthetized animals and the myocardial performance evaluated *in vitro* still seems to be preserved after this short-term smoking.

Our data indicate that short-term exposure to smoke reduced the physical capacity of previously healthy rats. Actually, it is not possible to determine whether this physical capacity of smoking rats resulted from pulmonary, cardiovascular, or musculoskeletal abnormalities (i.e., skeletal muscle). However, it is noteworthy that the impairment of physical capacity is a well-known predictor of cardiovascular-related death [21] and that the improvement of the ability to perform exercise greatly contributes to reduce mortality due to cardiovascular disorders [22, 23]. Furthermore, exercise intolerance is a crucial point, because it directly affects self-related quality of life [24].

Regarding this, there are indications that chronic smoking impairs the physical capacity of the men [25, 26] and mitigates the tolerance to walking fatigue test [27]. Moreover, McDonough and Moffatt [28] stated that the chronically increased smoking-related blood carbon monoxide content could worsen exercise tolerance and reduce the maximal aerobic capacity, associated with an impaired glucose metabolism during exercise. An experimental study has also shown a reduction of 24% of aerobic capacity of animals exposed to carbon monoxide in similar dose to that found in individuals who smoke heavily [29]. For the authors, abnormalities in mitochondrial function in skeletal muscles can interfere with exercise capacity.

To the best of our knowledge, the impact of short-term cigarette smoking on the functional fitness and physical activity is few related by the literature. Regarding the effects of cigarette smoke on the cardiac function as a substrate for impaired physical capacity, there was proposed a possible association between smoking and functional fitness in heart failure [30]. However, given that both chronic smoking and heart failure syndrome could potentially reduce physical capacity not only by cardiac but also by peripheral changes such as pulmonary, hemodynamic, and neuro-motor functions, associated with water and salt kidney retention, our data indicates that short-term cigarette smoking may reduce functional fitness independent of heart or kidney failures.

Actually, there were no significant changes on GFR and urinary protein excretion in rats submitted to passive cigarette smoking for eight weeks, suggesting preserved glomerular and tubular functions. On the other hand, there are evidences that chronic cigarette smoking is associated with functional and structural renal changes in rats, demonstrating abnormal glomerular morphology after 16 weeks [11] and advanced hydropic degeneration of kidney after 24 weeks [31].

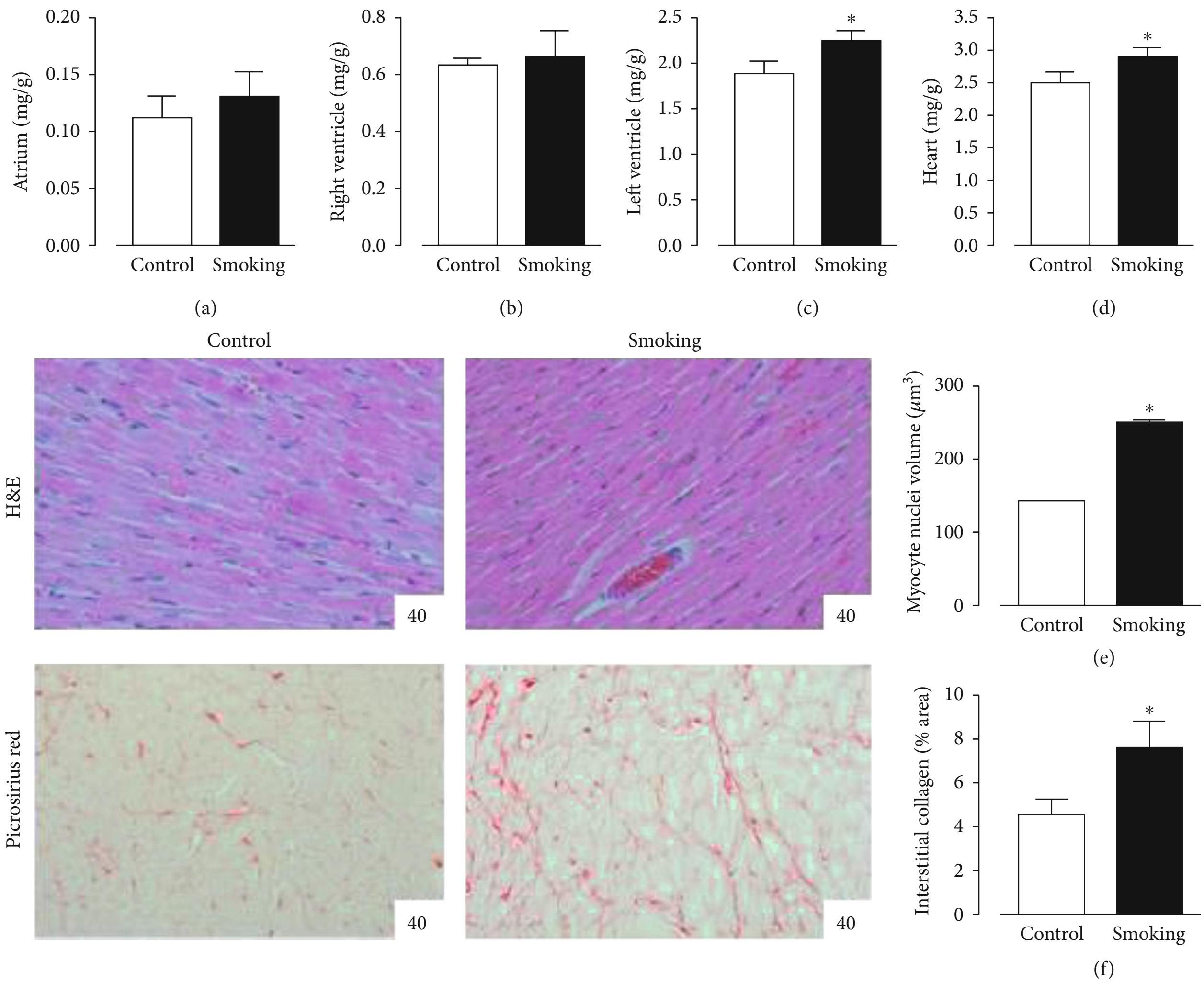

Figure 3: Cardiac biometry and histomorphometry. Atrial (a), right ventricular (b), left ventricular (c), and heart (d) masses were indexed to body mass. In the lower panels, representative microphotographies of the myocardium stained with hematoxylin-eosin (H&E) for myocyte nuclei analysis and picrosirius red for interstitial collagen evaluation. Remodeling parameters including myocyte hypertrophy (e) and interstitial fibrosis (f) are graphically demonstrated. Bars are the means ± SEM. $^{*}p < 0.05$ *vs.* control.

Conversely to previous observed in chronic smoke exposure [5, 6], but similar to described for short-term protocols [8, 9], echocardiographic data did not show ventricular systolic or diastolic dysfunction after this 8-week protocol, and no changes on blood pressure were noted as well. Moreover, cardiac muscle mechanics assessed *in vitro* was not affected, similar to also reported by Paiva et al. [19] after 4 weeks and Brooks et al. [32] after 16 weeks of smoking exposure in rats. Together, these findings could suggest that our experimental model of a short-term cigarette smoke exposure was not accompanied by cardiac dysfunction. However, about this apparent normality it is important noting that, under anesthesia or without substantial hemodynamic/mechanical loads, cardiac performance may appear unaltered, making the appropriate characterization of dysfunction difficult [15]. In spite of this supposed normality, when the hearts of smoking rats were submitted to a stress condition such as the physical capacity swim test, a significant degree of impairment was evident. Although we did not perform hemodynamic stress test and considering that noncardiac effects of smoking may also be present, we could just hypothesized that impaired physical capacity was due, at least in part, to a reduced cardiac reserve.

Notwithstanding, a previous study demonstrated that short-term of cigarette smoke induced cardiac morphological changes in rats [6] that could also be related to the reduced physical capacity. In fact, the increase in heart mass and myocyte nuclear volume and the reduced ventricular diameter after short-term cigarette smoking as suggestive of cardiac hypertrophy are not new data. There is no consensus about the hypertrophy mechanism involved in cardiac hypertrophy; however, the hypoxia caused carbon monoxide and nicotine. In the present study, the hypertrophic and fibrotic processes were not associated with changes on blood pressure, which suggests that this cardiac remodeling may be independent of hemodynamic loading. Regarding this, an important issue is the increased blood viscosity that could sustain increased cardiac afterload. Moreover, several other factors could act as additional mechanisms to trigger cardiac hypertrophic process during cigarette smoking: the generation of reactive oxygen species induced by smoking is knowingly cytotoxic to the myocardium [33]; nicotine has also been shown to be associated with myocardial remodeling [34, 35] and sympathetic hyperactivity [7], and although we did not assess sympathetic tone, heart rate was significantly elevated in the smoking group, which could play a role for the adverse cardiac remodeling; and evidence for the association between carbon monoxide/hypoxia and myocardial hypertrophy had also been showed [29, 36]. Although we did not measure plasma levels of nicotine and cotinine, it is important note that these parameters are commonly used to estimate smoking intensity. In the present work, we used the carbon monoxide content on the exposure chamber to estimate smoking intensity, similar to other studies [5, 6, 19]. Thus, it is possible to consider that the hypertrophic response was linked to multiple effects of cigarette smoking not only to nervous and cardiovascular systems, but also by neurohumoral mechanisms. For example, it is well known that smoking, or more specifically nicotine, activates the sympathoadrenal system and increases the synthesis and release of noradrenaline and adrenaline [7, 37, 38], and stimulates the renin-angiotensin-aldosterone system [39].

In conclusion, our results indicate that short-term cigarette smoke exposure in rats induced a concentric LV hypertrophy accompanied by increased in interstitial collagen. In addition, despite the apparent normal cardiac and renal functions, the smoking group has a significant impairment of the physical capacity, which could be suggested a result, at least in part, of a reduced cardiac reserve as a damaging consequence of this short-term smoking. It is noteworthy that recurrence of short-term smoking may have summative effects and thus constitute the mechanism underlying the ultimate chronic effects. Therefore, our data about the short-term effect of cigarette smoking can reflect an initial change in the pathophysiological mechanisms of smoking-induced chronic harmfulness.

Data Availability

All data are available if necessary.

Disclosure

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Conflicts of Interest

The authors declare that they have no conflict of interest.

Acknowledgments

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Research Article

Physical Training Is a Potential Modifier of Risk for Contrast-Induced Acute Kidney Injury in Diabetes Mellitus

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Background. Iodinated contrast (IC) is a leading cause of hospital-based acute kidney injury (AKI). Contrast-induced acute kidney injury (CI-AKI) is a decline in renal function due to iodinated contrast administration and occurs more frequently in individuals with increasingly common risk factors, such as diabetes mellitus (DM). Physical training (PT) can have renoprotective effects on CI-AKI in diabetic nephropathy. The aim of this study was to evaluate the injury in kidneys of diabetic rats submitted to treatment with IC, evaluating the impact of PT on hemodynamics and renal function in addition to oxidative profile in diabetic rats submitted to IC-AKI. *Materials and Methods*. Adult male Wistar rats are randomized into four groups: citrate ($n = 7$): control group, citrate buffer (streptozotocin-STZ vehicle), intravenous tail (iv), single dose; DM ($n = 7$): STZ, 60 mg/kg, iv, single dose; DM+IC ($n = 7$): DM rats treated with IC (sodium meglumine ioxithalamate, 6 mL/kg, intraperitoneal (ip), single dose); DM+IC+PT ($n = 7$): DM rats treated with IC as mentioned and submitted to physical training. Renal function parameters (inulin clearance, neutrophil gelatinase-associated lipocalin (NGAL), serum creatinine, and urinary albumin), hemodynamics (renal blood flow and renal vascular resistance), and oxidative profile (urinary peroxides, urinary TBARS, urinary nitric oxide, and renal tissue thiols) were evaluated. *Results*. It was possible to observe a decrease in inulin clearance, renal blood flow, and thiols in renal tissue accompanied by an increase in urinary flow, serum creatinine, urinary albumin, renal vascular resistance, urinary peroxides, urinary nitrate, and TBARS in the DM group compared to the citrate group. The DM+IC group showed a reduction in inulin clearance, and the renal dysfunction was also seen by the increased NGAL. Renal hemodynamics and oxidative profile compared were also worsened in the DM group. PT improved renal function by increasing renal blood flow and thiol levels in renal tissue and reduced renal vascular resistance, metabolites of reactive oxygen, nitrogen species, and lipid peroxidation in the DM+IC+PT group compared to DM+IC. *Conclusions*. Our results confirmed that DM induction increases renal vulnerability to the toxicity of IC and an association between DM with IC predisposes to severe AKI with reduced renal function alongside with renal hemodynamic alterations and oxidative mechanism of injury. The PT showed a renoprotective effect in DM animals subjected to damage with IC by modulating renal hemodynamics and oxidative profile, confirming a potential to modify the risk of CI-AKI when diabetes mellitus is present.

1. Introduction

Iodinated contrast (IC), used to improve the visibility of organs and structures in diagnostic exams, is a leading cause of acute kidney injury (AKI) [1]. Contrast-induced acute kidney injury (CI-AKI) is the third leading cause of AKI in hospitalized patients and is clinically defined by an increase in serum creatinine ≥ 0.5 mg/dL or 25% increase in serum creatinine from the baseline value 48 h past the contrast media administration [2, 3].

CI-AKI increases morbidity and mortality risk and occurs more frequently in the presence of risk factors, such as preexisting renal impairment or diabetes mellitus (DM), with prevalence estimated at approximately 30% [4, 5].

Pathophysiology mechanisms for CI-AKI are complex and remain unclear, but it is known that it involves cell damage caused by the direct cytotoxic effect of IC to renal tubular epithelial cells, renal vasoconstriction resulting in medullary hypoxia, and the formation of reactive oxygen species (ROS) [1, 6].

CI-AKI has been growing in the recent years and will probably increase its prevalence in the future with the more frequent contrast-mediated diagnostic need in old patients and with increasingly common comorbid conditions such as DM [3, 5]. There is no specific treatment for CI-AKI; therefore, strategies to recover kidney function and reduce the CI-AKI risk in the presence of DM are urgently needed [3, 6].

Physical training (PT), a nonpharmacological therapy recommended to control DM, can be promising to attenuate the complications of aggravated CI-AKI in DM because it induces beneficial adaptive responses and influences physiological biomarkers, such as oxidative stress biomarkers, nitrosative stress, and hemodynamics, which implicate in the development and progression CI-AKI [7, 8].

Recently, researchers have been investigating the role of PT on AKI and the favourable effects observed reinforce its role in preventing AKI [9–11]. Although many studies have shown the beneficial influence of PT in several diseases, the mechanisms involved are not clear and little is known about this process in the CI-AKI, which reinforces the need for further study in this field.

In this study, we have investigated the injury in kidneys of diabetic rats submitted to treatment with IC, evaluating the PT impact on hemodynamics and renal function in addition to oxidative profile in diabetic rats submitted CI-AKI.

2. Materials and Methods

2.1. Animals. Adult male Wistar rats (weighing 250-290 g) were used. The animals were obtained from the Institute of Biomedical Sciences at the University of Sao Paulo and were housed at the Experimental Laboratory of Animal Models (LEMA) at the School of Nursing at the University of Sao Paulo, in a room with controlled temperature (25°C/77°F) and alternating light/dark cycles. The rats had free access to water and rat chow. The study was carried out in accordance with international standards for the manipulation and care of laboratory animals. The protocol was approved by the Ethical Committee of Experimental Animals, University of Sao Paulo (CEEA–protocol n. no. 1277/2019).

2.2. Streptozotocin-Induced Diabetes Mellitus Model. The animals received streptozotocin (STZ; 60 mg/kg), diluted in 0.5 mL of citrate buffer (0.1 mol/L; pH 4.5) in the first day of the protocol. The injection was administrated in the caudal vein for DM induction. The control animals received only 0.5 mL of citrate buffer. Blood glucose levels were measured 48 h after the injection to confirm hyperglycemia (Accu-Chek, Roche; measurement range: 10–600 mg/dL). Animals considered hyperglycemic and included in the study were those that consistently showed a blood glucose level higher than 250 mg/dL [12]. DM induced in this protocol is considered type I DM.

2.3. Iodinated Contrast Administration. The animals received 6 mL/kg of IC (meglumine ioxithalamate and sodium) i.p., single dose on the 26th day of experimental protocols [13].

2.4. Physical Training. This protocol includes an acclimation period of 1 week to the aquatic environment after DM induction and before PT. PT consisted of daily swimming, five days/week, 60 minutes/day, with an additional load corresponding to 5% of the animal's body weight placed in the tail. This protocol is considered moderate-intensity aerobic PT [14–16].

2.5. Experimental Groups

(i) Citrate ($n = 7$): control group of chronic diabetes mellitus model, rats that received 0.5 mL of citrate buffer (STZ vehicle), intravenous (iv) tail, single dose on 1st day.

(ii) Diabetes mellitus (DM, $n = 7$): rats receiving 60 mg/kg of STZ diluted in 0.5 mL citrate buffer, iv tail, single dose.

(iii) Diabetes mellitus+iodinated contrast (DM+IC, $n = 7$): rats receiving 60 mg/kg STZ diluted in 0.5 mL citrate buffer iv tail and received 6 mL/kg of IC intraperitoneal (ip), single dose on 26th day.

(iv) Diabetes mellitus+iodinated contrast+physical training (DM+IC+PT, $n = 7$): rats receiving 60 mg/kg STZ diluted in 0.5 mL citrate buffer iv and daily swimming, five days/week, 60 minutes/day from the 6th day and received 6 mL/kg of IC ip, single dose on 26th day.

2.6. Procedures and Timing of Experimental Protocols. All protocols of experimental groups lasted 28 days. PT was performed until the 26th day for the animals in the trained group, while the other nonexercised animals were kept in collective cages during this period. On the 27th protocol day, the animals were allocated in individual metabolic cages for 24 hours, for collection of urine samples and determination of urinary flow.

The rats were removed from the individual metabolic cages on the 28th day of the protocol and anesthetized with 10 mg/kg xylazine and 90 mg/kg ketamine ip and tracheostomized to maintain spontaneous breathing during experiments for renal function and hemodynamic measurements, performed through a catheter inserted into the left carotid artery and in the right jugular vein (polyethylene tube PE-60). An abdominal incision was made, and the urinary bladder was cannulated (polyethylene tube PE-240).

After the surgical procedure and the obtaining of the parameters for renal hemodynamics, a blood sample was collected through a puncture of the distal abdominal aorta. Finally, animals were submitted to terminal blood collection and euthanasia according to guidelines for animal experimentation. The right kidney was removed and immediately cooled and stored at -70°C for thiol assay.

2.7. Renal Function Measurement

(i) Inulin clearance (mL/min): renal function was evaluated based on inulin clearance. Inulin was injected in the right jugular vein, with a loading dose of 100 mg/kg, followed by a continuous infusion of 0.04 mL/min. After a 30 min stabilization period, three urine samples were collected through the bladder catheter and two blood samples were then collected through the carotid catheter. The serum and urine inulin were measured using the anthrone method [17, 18]

(ii) Urinary neutrophil gelatinase-associated lipocalin (NGAL, pg/mL): urinary NGAL was determined using the Rat NGAL ELISA Kit, BioVendor, research and diagnostic products

(iii) Serum and urinary creatinine (Cr, mg/dL): serum and urinary creatinine were measured using the Jaffe method. The results were expressed in mg/dL; oxidative parameters were corrected using urinary creatinine [19]

(iv) Urinary albumin (mg/24 h): albuminuria was determined using the Rat Albumin ELISA Kit, Bethyl Laboratories

2.8. Hemodynamic Measurements

(i) Heart rate (beats per minute (bpm)): heart rate was measured through the catheter inserted into the carotid artery and was assessed using Biopac Systems MP150 (Santa Barbara, CA)

(ii) Mean arterial blood pressure (mmHg): mean arterial blood pressure was measured through the catheter inserted into the carotid artery and was assessed using Biopac Systems MP150 (Santa Barbara, CA)

(iii) Renal blood flow (mL/min): the renal artery was isolated after exposing the left renal pedicle, and a suitable probe was placed around for renal blood flow measurement, which was performed by a perivascular ultrasonic flowmeter (T402, Transonic Systems Inc., Bethesda, MD)

(iv) Renal vascular resistance (mmHg/mL/min): mean arterial blood pressure and renal blood flow were assessed, and renal vascular resistance was calculated with the usual formula: renal vascular resistance = mean arterial blood pressure/renal blood flow [17]

2.9. Oxidative Profile: Oxidative and Nitrosative Metabolites, Lipid Peroxidation, and Thiol Antioxidant Assay

(i) Urinary peroxides (nmol/g urinary Cr): the peroxides, ROS metabolites, were determined in the urinary samples by the method of ferrous oxidation of xylenol orange version 2 [20]

(ii) Urinary nitrate (μM/g urinary Cr): the urinary nitrate excretion, RNS metabolites, was measured using the Griess reaction method [21]

(iii) Thiobarbituric acid reactive substances (TBARS, nmol/g urinary Cr): urinary TBARS were evaluated as an indirect biomarker of lipid peroxidation. Urine samples were added to a mixture of 17.5% trichloroacetic acid (TCA) and 0.6% thiobarbituric acid. This mixture was heated to 95°C in a water bath for 20 min. The solution was removed from the water bath and cooled in ice, followed by the addition of 70% TCA. The solution was then incubated for 20 min, and absorbance was read at 534 nm [22]

(iv) Thiols in renal tissue (nmol/mg total protein): the soluble nonprotein thiols in renal tissue were measured by the thiol antioxidant assay using the Ellman method. The amount of soluble thiols was corrected to the total protein amount analyzed using the Bradford method [23, 24]

2.10. Statistical Analysis. Results were expressed as mean ± standard deviation. Variance was analyzed using the one-way ANOVA test, followed by Newman-Keuls (GraphPad Prism version-7 for Windows®): $^{a}p < 0.001$ vs. citrate; $^{b}p < 0.001$ vs. DM; $^{c}p < 0.001$ vs DM+IC.

3. Results and Discussion

3.1. Effects of Physical Training on Renal Function. To evaluate the effectiveness of PT on CI-AKI on diabetic nephropathy, glomerular filtration rate was assessed by inulin clearance studies and changes on urinary flow, urinary NGAL, serum creatinine, and urinary albumin.

The DM induced in this study resulted in worsening renal function as demonstrated by decreased inulin clearance and increased urinary flow, serum creatinine, and albuminuria (Table 1).

The administration of IC to diabetic rats caused an additional deleterious effect on renal function as demonstrated by increased NGAL in the DM+IC group (Table 1). Among markers of renal function, inulin clearance is the most reliable to estimate glomerular filtration rate while NGAL has been described as a sensitive and specific marker of AKI [25, 26]. Therefore, the increase of NGAL might be associated with the onset of CI-AKI in the diabetic animals.

Initially, IC acts as an osmotic diuretic, freely filtered by the glomeruli and poorly absorbed by the renal tubule [27]. However, the IC cytotoxic effect to renal cells of tubular epithelial increases the viscosity of tubular fluid, compromising its flow, which leads to further renal retention and greater cytotoxic exposure [28]. IC results in a long-term effect on perfusion and oxygenation throughout the kidney, and according to clinical observations, it has been verified that the serum Cr level in patients with CI-AKI oftentimes reaches the peak within 2–5 days after IC administration [28].

Albuminuria, which occurs due to microvascular dysfunction in DM, is a biomarker for chronic kidney disease, and it is associated with a greater risk of AKI even in patients

Table 1: Renal function.

Groups	n	Urinary flow (mL/min)	Inulin clearance (mL/min)	Urinary NGAL (pg/mL)	Serum creatinine (mg/dL)	Urinary albumin (mg/24 h)
Citrate	7	0.012 ± 0.002	0.83 ± 0.09	44.06 ± 10.15	0.30 ± 0.06	3.76 ± 0.91
DM	7	0.055 ± 0.011^{a}	0.49 ± 0.10^{a}	73.11 ± 29.24	0.92 ± 0.06^{a}	39.42 ± 8.89^{a}
DM+IC	7	0.074 ± 0.006^{ab}	0.16 ± 0.05^{ab}	163.64 ± 35.08^{ab}	1.35 ± 0.15^{ab}	71.37 ± 8.88^{ab}
DM+IC+PT	7	0.093 ± 0.019^{abc}	0.59 ± 0.05^{ac}	84.39 ± 7.36^{ac}	1.05 ± 0.07^{ac}	40.95 ± 9.44^{ac}

$^{a}p < 0.001$ vs. citrate; $^{b}p < 0.001$ vs. DM; $^{c}p < 0.001$ vs. DM+IC.

Table 2: Renal hemodynamics.

Groups	n	Heart rate (bpm)	Mean arterial blood pressure (mmHg)	Renal blood flow (mL/min)	Renal vascular resistance (mmHg/mL/min)
Citrate	7	509 ± 39	96 ± 6	7.47 ± 1.49	12.56 ± 2.19
DM	7	532 ± 48	102 ± 8	4.03 ± 0.27^{a}	25.72 ± 1.82^{a}
DM+IC	7	539 ± 44	102 ± 16	1.70 ± 0.19^{ab}	54.35 ± 6.34^{ab}
DM+IC+PT	7	464 ± 27^{c}	95 ± 5	4.20 ± 0.44^{ac}	24.02 ± 5.04^{ac}

$^{a}p < 0.001$ vs. citrate; $^{b}p < 0.001$ vs. DM; $^{c}p < 0.001$ vs. DM+IC.

Table 3: Urinary peroxides, urinary nitrate, TBARS, and thiols.

Groups	n	Urinary peroxides (nmol/g urinary Cr)	Urinary nitrate (μM/g urinary Cr)	TBARS (nmol/g urinary Cr)	Thiols (nmol/mg total protein)
Citrate	7	1.33 ± 0.82	23.71 ± 4.96	0.22 ± 0.15	24.45 ± 5.39
DM	7	11.64 ± 4.00^{a}	56.82 ± 12.73^{a}	12.91 ± 3.02^{a}	13.65 ± 1.73^{a}
DM+IC	7	19.96 ± 6.98^{ab}	75.32 ± 9.65^{ab}	20.49 ± 5.29^{ab}	8.56 ± 1.17^{ab}
DM+IC+PT	7	10.84 ± 2.75^{ac}	51.75 ± 7.66^{ac}	14.10 ± 2.31^{ac}	14.45 ± 1.88^{ac}

$^{a}p < 0.001$ vs. citrate; $^{b}p < 0.001$ vs. DM; $^{c}p < 0.001$ vs. DM+IC.

with a preserved renal function after contrasted exam [29, 30]. Lifestyle modification program, including physical exercise, demonstrated reduction of albuminuria and maintenance of glomerular filtration rate in diabetic patients [31].

In this study, IC induced a reduction in glomerular filtration rate in the animals with diabetic nephropathy as demonstrated by decreased inulin clearance. PT prevented the sharp reduction in the inulin clearance caused by IC in the diabetic animals. In addition, PT prevented the worsening of renal function as observed by lower NGAL, serum creatinine, and urinary albumin in DM+IC+PT compared with DM+IC (Table 1). This is probably due to adaptive mechanisms of renal function and to the adaptation to physical stress acquired gained with training.

Our results suggest that PT is a good, nonpharmacological strategy to preserve renal function and reduce the CI-AKI risk in the presence of diabetic nephropathy. Although studies have shown the beneficial influence of physical exercise in several diseases, the mechanisms involved are not clear. To clarify how PT could contribute to kidney protection, renal hemodynamics and renal oxidative profile were further analyzed.

3.2. Effects on Renal Hemodynamics. A statistically significant difference was not detected in the mean arterial pressure between groups. There was a significant decrease in heart rate in the DM+IC+PT group after physical training compared to the DM+IC group without training (Table 2).

DM showed a deleterious effect on renal hemodynamics with a decrease in renal blood flow and an increase in renal vascular resistance (Table 2). The use of IC worsened the effects of DM on the renal blood flow and vascular resistance (Table 2). However, PT prevented an excessive increase in vascular resistance and a decrease in renal blood flow caused by IC (Table 2).

The association of direct medullary vasoconstriction and high viscosity of IC compromises cell oxygen delivery and reduces intrarenal blood flow. Animal experiments demonstrated a reduction in renal blood flow induced by IC partly assigned by the downregulation of endogenous renal NO synthesis [28].

Renal hemodynamic dysfunctions are observed in AKI and are involved in the establishment and evolution of renal injury. Therefore, stabilization of hemodynamic parameters is crucial to the management of CI-AKI [3]. In the present study, PT attenuated renal hemodynamic changes in diabetic nephropathy animals submitted to IC damage, probably by decreasing renal vascular resistance, which resulted in improved renal blood flow.

3.3. Effects of Oxidative Profile. To determine whether the antioxidant effect of PT is involved in renal protection in the current experimental model, urinary peroxides, urinary nitrate, serum TBARS (a byproduct of lipid peroxidation), and thiol levels in renal tissue (indicative of reduced glutathione, a major endogenous antioxidant) were assessed.

It was observed a significant increase in urinary peroxides and nitrate as well as in TBARS levels in the diabetic group, whereas thiols were significantly reduced compared to the citrate group (Table 3). Additionally, IC administration worsened the oxidative profile in diabetic rats (Table 3).

The IC vasoconstriction results in hypoperfusion and decreased oxygen level in the inner stripes of the outer medulla, causing severe local hypoxia, contributing to oxidative and nitrosative stress, which is known to be mediated by ROS and reactive nitrogen species (RNS) [32]. Data demonstrated that oxidative stress, nitrosative stress, and lipid peroxidation increase in the kidney of diabetic animals were worsened after IC treatment. This could be due to the decrease in antioxidant enzymes, such as glutathione, a thiol enzyme.

The decrease in thiols in the kidney and the increase in lipid peroxidation in DM+IC were significantly improved after exercise. PT showed an improvement in oxidative profile with a significant reduction in oxidative and nitrosative metabolites (peroxides, TBARS, and urinary nitrate) and a significant increase in thiol antioxidant reserve in DM+IC+PT when compared to DM+IC (Table 3).

PT has been used to prevent or treat chronic degenerative conditions once it promotes cellular responses signaled by the physiological stress of exercise [3, 33]. Studies that analyzed the effects of moderate physical exercise with vitamin supplementations on oxidative stress in diabetic rats demonstrated that this association can strengthen the antioxidant defense system through the reduction of ROS and blood glucose levels, preventing the development of diabetic nephropathy [33].

The data collected in this study highlight PT potent antioxidant action in IC-AKI, demonstrating that PT decreases the vulnerability of the diabetic kidney to acute damage due to IC treatment, contributing to an improvement in the renal oxidative profile, with reduced oxidative and nitrosative metabolites and elevated the thiol levels.

4. Conclusions

Our results confirmed that DM induction increases renal vulnerability to the toxicity of IC. The association of DM and IC predisposes to severe AKI with reduced renal function in rats by changing renal hemodynamics and oxidative mechanism of injury. This study highlights the exercise-induced antioxidant effect on IC nephrotoxicity in diabetes mellitus in experimental settings, by modulating renal hemodynamics.

Data Availability

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

Conflicts of Interest

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

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Research Article

Effectiveness of Low-Frequency Stimulation in Proprioceptive Neuromuscular Facilitation Techniques for Post Ankle Sprain Balance and Proprioception in Adults: A Randomized Controlled Trial

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Stretching is an important part of post ankle sprain rehabilitation, as well as an effective exercise for improving general ankle-joint performance. But the combination of stretching alongside low-frequency stimulation has not yet been extensively studied. Therefore, the purpose of the present randomized controlled trial was to compare the combined effects of low-frequency transcutaneous electrical nerve stimulation (TENS) with proprioceptive neuromuscular facilitation (PNF) on strength, balance, and proprioception among individuals with post ankle sprain. Sixty male subjects with lateral ankle sprain were selected and randomly allocated to three groups: group 1, group 2, and the control group (CG). Subjects in group 1 received the PNF stretching technique combined with TENS. TENS stimulation was provided using two electrodes placed 5 cm apart directly on the triceps sural muscle of the affected leg and a biphasic current with a symmetrical waveform at 50 Hz for 15 seconds, tuned for a 3-second ramp up time and a 30-second rest time with a 250-microsecond pulse duration was given with PNF stretching. Subjects in group 2 received the PNF stretching technique alone. Both group 1 and group 2 received these treatments for 4 weeks (4 days/week); follow-up assessments were administered in the third and fifth weeks. CG received no treatment; outcome measures alone were assessed. Outcome measures comprised pain, balance, flexibility, proprioception, range of motion, muscle strength, and functional limitation. A mixed-model ANOVA showed significant interaction (time and group) and the time effect for all the outcome measures ($p \leq 0.05$). Group 1 (PNF-TENS) showed significant improvement for all the outcome variables compared to the other groups. The present study showed PNF stretching combined with TENS for the triceps sural muscle to trigger muscle contraction during the muscle contraction phase of the PNF stretch, compared against PNF stretching alone, produced significant improvements in ankle function for post ankle sprain subjects.

1. Introduction

The ankle joint plays a vital role in collecting sensory feedback as well as in controlling balance and posture [1]. Ankle sprain refers to a ligament tear in the ankle, and ligament sprains most commonly occur on the lateral side of the ankle in isolation [2]. Ankle sprains are easily diagnosed [3] because the pain, tenderness, and swelling are usually localized on the outside of the ankle for a patient who has twisted their ankle with inversion [4].

Ankle sprain not only causes damage to the structure of the ligament but also damages the surrounding structures such as the muscles, tendons, and nerves in the ankle complex. Any such injury may lead to ligament laxity of the ankle joint, muscular weakness, and deficits. This injury leads to impairment of joint proprioception, balance, firing of ankle muscles, nerve conduction velocity, cutaneous sensation, and muscle power, as well as restriction of the range of motion of the ankle, especially dorsiflexion [5]. Rehabilitation of ankle injuries requires specific activities and exercises to improve and recover normal function of muscles and ligaments. The journey towards recovering normal function after the rehabilitation phase of ankle post sprain is challenging [6].

The effectiveness of a rehabilitation program after injury or surgery often determines the success of future function and performance [7]. For example, the range of motion and muscle power should return to normal preinjury levels such that functional activities may be performed normally as per preinjury [6]. Most patients with ankle sprain recover completely, but a minority of patients report consistent pain, fear of recurrence, and functional limitation. Intervention to curb and permanently recover from an ankle sprain is still much debated and is coupled with a lack of evidence for the effectiveness of treatment designed to build confidence for patients with chronic ankle sprain [8].

In rehabilitation, the complete care of ankle injuries must include pain management, regaining full ankle range of motion, as well as improving muscle strength, proprioception, and balance [9]. These goals can be achieved by modalities that include flexibility and strengthening exercises, proprioception, and balance training. A structured program of intervention, allowing for the significant effect of time and treatment, is essential for understanding ankle rehabilitation.

Stretching is used in various therapeutic procedures that are designed to increase the length of soft tissue structures that have been shortened due to pathological causes, thereby increasing the range of motion [10]. Tight muscles of the leg are passively stretched, isometrically activated, and then further stretched to increase the ankle range of motion [11].

Proprioceptive neuromuscular facilitation (PNF) is a stretch training technique used to increase flexibility [12]. PNF uses static stretching in combination with triggering isometric muscle contraction. PNF stretch uses muscle contraction to trigger neuromuscular activity, initiate a greater stretch, and increase range of motion [13]. PNF techniques such as the "contract-relax" technique or the "hold-relax" technique can be used to achieve a range of motion (ROM) increase beyond that of traditional stretching. The hold-relax PNF technique is done using agonist contraction, initial stretching, and then isometric contraction of a muscle which is tight followed by concentric contraction to the opposite tight muscle. Hold-relax uses dynamic stretching along with the static stretches isometrically [14, 15].

The widespread knowledge about transcutaneous electrical nerve stimulation (TENS) is mainly to reduce pain and improve function in different painful conditions over the last few years and one of the primary clinical tools for managing pain [16, 17]. Because pain and restriction in the range of motion are commonly reported, the usage of TENS is shown to relieve pain in clinical practice, especially when applied before stretching and therapeutic exercises [18, 19].

It is also reported that in animals and clinical research conducted recently, TENS improved balance, muscle strength, and spasticity [20–22]. TENS is effective in relieving muscle fatigue; muscle fatigue is considered an important factor for voluntary muscle control, posture, and balance [23]. Treatment using TENS reduced knee pain effectively by increasing the quadriceps motor neuron pool and triggering the isometric quadriceps muscle activity [24]. However, the use of this TENS to trigger a muscle contraction during the phase of a muscle contraction during PNF (hold-relax) stretch has not been investigated in previous studies.

Therefore, we hypothesized that TENS application could improve and aid the stretching effect in a synergistic manner thereby increasing the range, proprioception, balance, and flexibility of the muscles. The purpose of this research was to compare pre-, post-, and follow-up effects between the PNF stretching technique combined with TENS and PNF stretching alone for post ankle sprain individuals. A second aim is to determine the treatment effect on pain, balance, flexibility, proprioception, range of motion, muscle strength, and functional limitation between the groups.

2. Materials and Methods

The clinical trial was approved by the Institutional Ethics Committee (ECM#2019-26) of King Khalid University, Saudi Arabia. A clinical trial was also registered in the Clinical Trials Registry—ISRCTN 18013941 (UK).

2.1. Participants. After obtaining written informed consent, 69 subjects were screened, consisting of both university students and staff. Of the initial group, 60 subjects had a unilateral lateral ankle sprain and were included in the study as shown in the flow chart (Figure 1), based on the following inclusion criteria: males who sprained their ankle at least 3 months before, aging between 18 and 40 years, who are unable to bend their foot upwards on the post sprain ankle as much as on the normal ankle, and who have been diagnosed by an orthopedic surgeon. Excluded were subjects with general health issues, ankle fracture, dislocation, grade 3 ankle sprains, bony limitation, swelling, neuropathies, or any other neuromuscular pathologies.

2.2. Design. The study was a single-blind randomized controlled trial. Subjects were randomly allocated to three groups using block randomization, each group with 20 subjects of the 3 blocks. Concealed allocation was achieved using a computer-generated table of block-randomized numbers. The random numbers were placed in sealed envelopes. The researcher opened the envelopes and proceeded with treatment according to the group assigned. Twenty subjects were randomly allocated to group 1 (PNF-TENS), group 2 (PNF), and the control group (CG).

Group 1 received PNF (hold-relax technique) along with TENS; group 2 received PNF stretching (hold-relax technique) only; and the CG received no treatment. In all, there were 12 treatment sessions, conducted four times per week, for three weeks, in the university clinic. All three groups were assessed at pretreatment, posttreatment in the third week, and follow-up which was recorded in the beginning of the fifth week. Outcome measures were tested by an independent evaluator not involved in providing treatment to subjects as

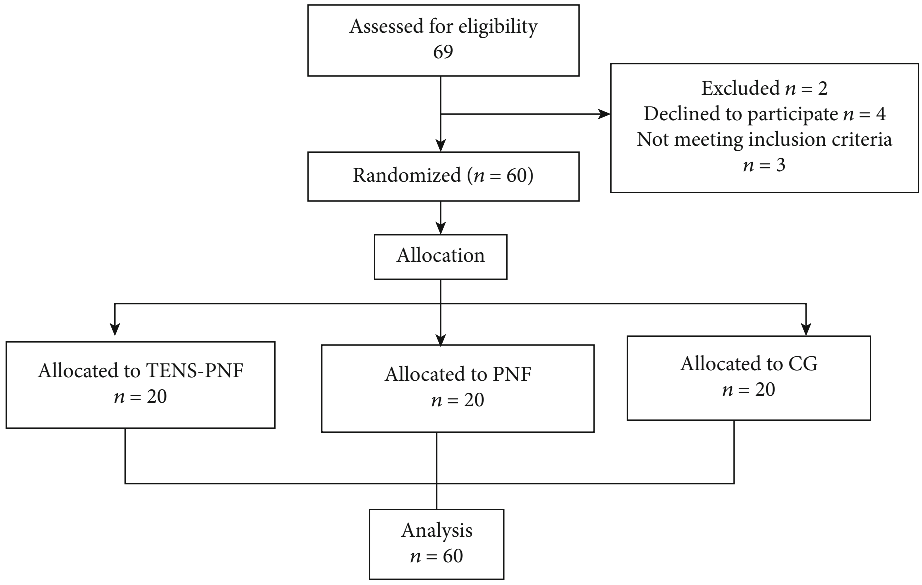

Figure 1: Flow chart enrolment for the study.

well as allocation. The outcome measures were pain, balance, flexibility, proprioception, range of motion, muscle strength, and functional limitation. The outcomes were measured in the same order throughout the study, prior intervention, at the 3rd week, and at the 5th week.

2.3. Outcome Measures

2.3.1. Pain. The visual analog scale (VAS) was recorded using a handwritten mark on a 10 cm line representing a continuum from "no pain" to "worst pain" [25].

2.3.2. Star Excursion Balance Test (SEBT). The balance was assessed using SEBT and was measured with the subjects standing barefoot at the center of a grid with eight lines extending at 45° angles. Subjects were instructed to touch the farthest point on the line with their distal part of the foot while maintaining the posture. Each subject maintained a single-leg stance and used the contralateral leg to touch as far as possible along the chosen line. The examiner marked the point touched by the foot (distance in cm) from the center of the grid to the point touched by the big toe. Subjects then returned to a bilateral stance and maintained equilibrium. Leg length was measured while subjects were in the supine position, from the anterior superior iliac spine to the distal tip of the medial malleolus in order to normalize the reach distance [26].

A valid trial was measured in the same standing posture, and when any change was detected, the subject's stance foot was repositioned to the center of the grid prior to beginning the next trial. The eight lines—anterior (A), posterior (P), medial (M), lateral (L), anterolateral (AL), anteromedial (AM), posterolateral (PL), and posteromedial (PM)—were constructed based on the direction shown in Figure 2. Reach direction order was designed using a Latin square to avoid any order sequence effect that might contaminate the data [27]. Subjects performed two practice trials in each direction with a ten-second rest break between reach trials [28]. After evaluating the primary and secondary outcome measures, the subjects were provided with treatment as per their group protocol.

2.3.3. Flexibility (Knee to Wall Test). Subjects were asked to stand facing a wall with about 10 cm between their toes and the wall. Subjects were then asked to step back a distance of one foot behind the other foot. The knee was bent to the front until it touched the wall, and the subject was asked to keep that heel in full contact with the floor. If the knee could not touch the wall without the heel coming off the floor, the front foot was moved closer to the wall. This exercise was then repeated, and the distance from the tip of the big toe to the wall was measured [29].

2.3.4. Ankle Proprioception. A digital dual inclinometer (Dualer IQ PRO Digital Inclinometer, J-TECH, Midvale, UT 84047, USA) was used to measure joint proprioception of the ankle. Subjects were asked to sit in a high sitting position with their eyes closed. A dual inclinometer was strapped to the midshaft lateral face of the tibia, and the display unit was strapped to the middle of the third lateral border of the foot. The foot was brought to the targeted angle dorsiflexion, and the subject was asked to maintain the position for 10 seconds (in order to remember this position) and then to return to the neutral position. The subject was then asked to bring the foot actively to the target angle once again [30, 31], as shown in Figure 3. The measurement was taken during three consecutive trials from both angles separately (dorsiflexion and plantar flexion). Recorded mean values (in degrees) were used for the analysis of both target positions. The error angle deviation from the target position set angle was used as the result value [32].

2.3.5. Range of Motion (ROM). The ROM was assessed using a flexi-plastic baseline (USA) standard universal goniometer

Figure 2: Star Excursion Balance Test in anterior and posterolateral directions.

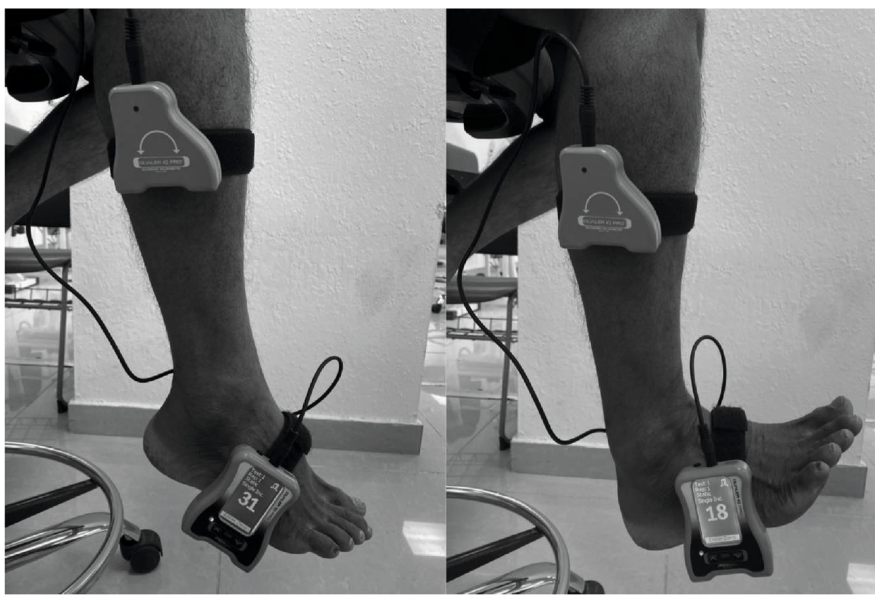

Figure 3: Proprioception of the ankle in plantarflexion and dorsiflexion.

for measuring dorsiflexion ROM and plantarflexion ROM. Subjects were seated in the high sitting position, with the fulcrum centered over the lateral malleolus of the ankle and the stationary arm parallel to the fibula and tibia. The movable arm of the goniometer followed a line parallel to the 5th metatarsal of the foot. Subjects were asked to dorsiflex and then plantarflex their ankles from the foot-relaxed starting position (considered to be the zero-neutral position), and the average of the three trials was recorded [33].

2.3.6. Muscle Strength. Isometric muscle strength was measured using a strength dynamometer (Baseline, USA). Each participant was positioned in the supine position with their feet over the edge of a plinth. The strength dynamometer was positioned against the metatarsal heads on the plantar surface of the foot to measure the strength of the plantar flexors. The strength dynamometer was positioned on the dorsal aspect of the foot proximal to the metatarsal heads to measure the strength of the dorsiflexors. Each participant performed two practice trials in order to familiarize themselves with the movements prior to testing. Three repetitions were performed for both dorsi- and plantar flexors, with a minimum rest period of 10 seconds between contractions. A single examiner performed all tests for each individual [34].

2.3.7. The Foot and Ankle Disability Index (FADI) Score. Functional limitation was assessed using FADI; all subjects completed the FADI during three different sessions (pre, week 3, and week 5). The completed survey indicated the function of the injured ankle at each session. Each item was scored from 0 (unable to do) to 4 (no difficulty at all), based on 22 questions related to functional activities and four questions related to pain. The FADI has a total of 104 points and is scored as percentages. A total of 100% indicates no dysfunction at all [35].

2.4. Intervention

2.4.1. PNF Stretching Method. The PNF technique (hold-relax) was applied for the triceps sural muscle using agonist contraction, after stretching followed by isometric contraction of the tight muscle and followed by concentric contraction to the opposite tight muscle [36]. The hold-relax PNF protocol was performed, with each subject lying prone on a plinth and the therapist resisting the subject's plantar flexion. The therapist followed the fundamental principles of the PNF method in terms of manual contact, body position and body mechanics, verbal commands, and vision [37]. The subject was asked to perform isometric triceps sural muscle contraction for 20 seconds, after which the therapist waited for four seconds before resuming the triceps sural muscle stretch, slowly and continuously, until the subject reported strong but tolerable discomfort and began to feel a stretching sensation. Once this benchmark had been reached, the stretch was maintained for approximately 30 seconds longer. This method was adopted from the previously published work by Esnault and Viel [38] and was performed four times per session on the affected lower limb.

2.4.2. Group 1: TENS-PNF. This group received PNF stretching, as described above, in the PNF stretching method combined with TENS (Trans Med from Enraf Nonius). Two electrodes (4×8 cm) were used for this procedure. The electrodes were placed in water-soaked sponge pouches and strapped on the triceps sural muscle: one was placed 5 cm distal to the popliteal fossa, and the other was placed 5 cm distal to the proximal electrode, directly on the triceps sural muscle of the affected leg as shown in Figure 4. The TENS device unit was adjusted to deliver a biphasic current with a symmetrical waveform at 50 Hz for 15 seconds, tuned for a 3-second ramp up time, and a 30-second rest time with a 250-microsecond pulse duration. The intensity was set to the maximum tolerance limit by each subject and was performed four times per session on the affected lower limb. This method was adopted from the previously published work by Pérez-Bellmunt et al. [39]. Each subject underwent this modified PNF stretching procedure four times per session on the affected lower limb, and the total intervention was 30 minutes. This combination method was applied to achieve stronger isometric contraction.

2.4.3. Group 2: PNF. For this group, the total intervention was 30 minutes and involved PNF stretching alone. The PNF stretching protocol was carried out as previously described in the PNF stretching method.

2.4.4. Group 3: Control Group (CG). Assessments alone were administered to the control group.

2.5. Sample Size Calculation. For the calculation of the minimum sample size, a priori power analysis was performed using G Power 3.1.9.4 software. Prior randomized trials [40, 41] have estimated effect sizes (0.22–0.57) for changes in plantar flexor strength among individuals with post ankle sprain. To generate the current sample size estimate, we used an effect size of 0.22 with Cohen's d, an alpha of 0.05, and power of 90%. A sample size of 20 subjects in each group was used to detect a time × group interaction.

2.6. Statistical Analysis. The normality of distribution of all variables was verified using the Shapiro-Wilk test ($p \leq 0.05$). The three group's baseline and demographic characteristics were compared using one-way ANOVA for parametric variables and chi-square test for the nonparametric variables. Levene's output was used to check the homogeneity between the groups. A mixed-model ANOVA was used to see the time effect, group effect, and time × group interaction effect between the three groups. Mauchly's test was used to test assumptions of sphericity; since the degrees of freedom were violated, it was rectified by using the Greenhouse-Geisser estimates of sphericity. The partial eta square $\eta_p{}^2$ was obtained from Greenhouse-Geisser within the subject effect. Statistical significance was indicated at $p \leq 0.05$, and the confidence interval was set at 95%. Statistical Package for the Social Sciences version 22.0 (IBM Corp., Armonk, NY, USA) was used for all the analysis.

3. Results

Pooled means and standard deviations of all outcome variables as well as p values showed no significant difference, except for the SEBT in the anterior direction, as shown in Table 1. Levene's output showed no significant differences between the three groups, indicating homogeneity between the groups. Mixed-model ANOVA revealed a significant time effect and time × group interaction effect ($p \leq 0.01$) for pain, flexibility, proprioception, ROM, muscle strength, FADI score, and balance. The group effect was significant in the anterior, posterior, posterolateral, and posteromedial directions for balance ($p \leq 0.01$). Meanwhile, functional limitation (FADI) scores ($p \leq 0.09$) and dorsiflexion ROM as well as balance in the medial, lateral, anterolateral, and anteromedial directions, did not reveal significant difference between the groups ($p \geq 0.05$) as shown in Tables 2 and 3.

The TENS-PNF group in the present study showed significant decrease in pain in the pre- to follow-up period 85.1% compared to PNF 28.2%. The TENS-PNF group showed a significant increase in balance after treatment for anterior, posterior, posterolateral, and posteromedial directions in the pre- to follow-up period (5.4%, 4.2%, 3.9%, and 5.6%) compared to PNF (1.3%, 1.2%, 0.7%, and 0.8%, respectively). The TENS-PNF group showed significant increase in flexibility after treatment in pre- to follow-up was 36.3% compared to PNF 5.9%. The TENS-PNF group also showed a significant increase for proprioception in dorsiflexion after treatment in the pre- to follow-up period (81.3%) compared to PNF (13.8%), and a similar result was seen for proprioception in plantar flexion (89.7%) compared to PNF (11.3%). The TENS-PNF showed significant increase in planter flexion ROM in the pre- to follow-up (19.7%) compared to PNF (2%). The TENS-PNF showed a significant increase in muscle strength for dorsiflexors in the pre to follow-up (25.2%) compared to PNF (4%); a similar increase was also observed for the plantar flexors (29.4%) compared to PNF (2.7%). CG did not show any significant change in time,

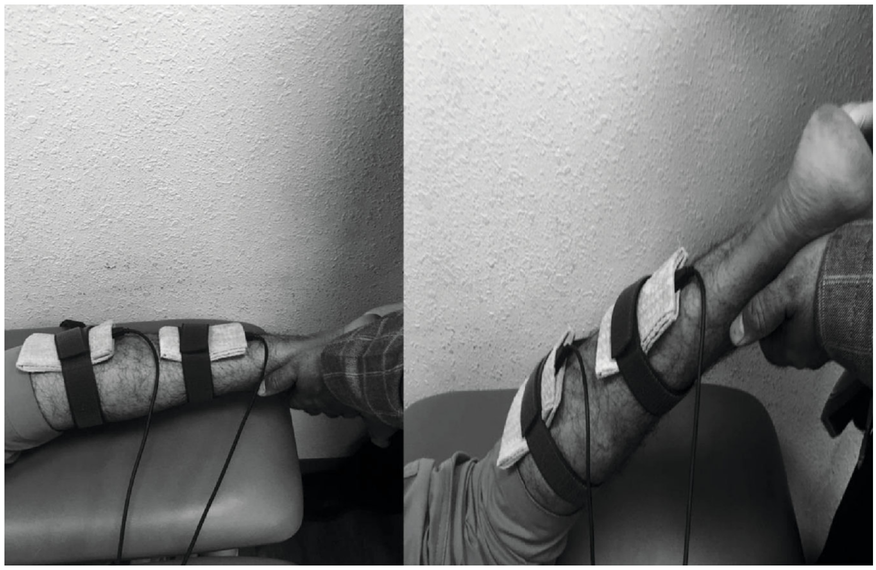

Figure 4: Application of TENS electrode placements used to activate the triceps sural muscle and simultaneous PNF stretching.

Table 1: Data (mean and standard deviation) of variables prior to intervention for each group.

Variables	Group 1 TENS-PNF ($n = 20$)	Group 2 PNF ($n = 20$)	Control group (CG) ($n = 20$)	p value
Age (years)	25.8 ± 5.7	25.7 ± 5.6	25.9 ± 6.2	0.991
Height (meters)	1.6 ± 0.0	1.7 ± 0.0	1.7 ± 0.0	0.276
Weight (kg)	65.9 ± 14.1	72.6 ± 15.4	68.9 ± 13.6	0.346
BMI	23.0 ± 5.5	24.5 ± 4.5	23.1 ± 4.2	0.573
Leg length (cm)	83.4 ± 10	85.0 ± 5.4	86.3 ± 6.3	0.483
SEBT anterior	78.2 ± 2.5	68.5 ± 3.9	70.5 ± 5.9	0.01*
SEBT posterior	92.4 ± 3.1	91.2 ± 4.6	90.7 ± 5.4	0.494
SEBT medial	95.7 ± 3.5	96.9 ± 3.7	96.6 ± 3.5	0.576
SEBT lateral	89.1 ± 5.9	92.9 ± 4.7	91.6 ± 5.5	0.090
SEBT anterolateral	74.9 ± 4.7	75.1 ± 3.9	75.8 ± 4.1	0.091
SEBT anteromedial	84.2 ± 5.8	83.1 ± 5.7	83.8 ± 5.7	0.843
SEBT posterolateral	95.1 ± 3.0	95.6 ± 2.9	94.9 ± 2.8	0.711
SEBT posteromedial	96.9 ± 2.6	96.8 ± 2.8	96.9 ± 3.3	0.998
VAS	2.7 ± 1.0	2.3 ± 1.0	2.2 ± 0.9	0.270
KNEE to wall (cm)	7.5 ± 1.8	6.7 ± 0.8	7.0 ± 0.8	0.180
Dorsi proprioception	2.1 ± 1.2	1.8 ± 1.0	1.9 ± 1.0	0.599
Plantar proprioception	2.5 ± 1.7	2.2 ± 1.9	2.4 ± 1.2	0.722
Dorsi ROM	15.9 ± 1.5	16.4 ± 1.8	16.7 ± 1.7	0.336
Plantar ROM	36.4 ± 3.9	38.5 ± 3.3	37.3 ± 4.0	0.224
Dorsi MS (kg)	11.1 ± 1.8	11.2 ± 0.8	11.1 ± 0.8	0.971
Plantar MS (kg)	13.2 ± 1.7	14.5 ± 0.9	14.1 ± 1.4	0.020
FADI score	94.3 ± 2.5	94.7 ± 3.5	95.3 ± 3.8	0.665

VAS: Visual Analogue Scale; BMI: Body Mass Index; ROM: range of motion; MS: muscle strength. *Significant ($p \leq 0.01$).

Table 2: Summary of statistical results of the mixed ANOVA and pooled means and standard deviations of all variable measures.

Variables	Group 1 (TENS-PNF) Group 2 (PNF) Control group (CG)	Mean (standard deviation) Pre (1)	3rd week (2)	5th week (3)	Mixed ANOVA (p value) Interaction (group and time) effect η_p^2 (p value)	Group (G) effect η_p^2 (p value)	Time (T) effect η_p^2 (p value)
	TENS-PNF	2.7 ± 1.0	0.5 ± 0.6	0.4 ± 0.5			
Pain VAS (cm)	PNF	2.3 ± 1.0	1.6 ± 0.8	1.6 ± 0.8	0.608 (0.01)*	0.192 (0.002)*	0.674 (0.01)*
	CG	2.2 ± 0.9	2.0 ± 0.8	2.0 ± 0.8			
	TENS-PNF	7.5 ± 1.8	10.1 ± 1.2	10.2 ± 1.2			
Knee to wall (cm)	PNF	6.7 ± 0.8	7.5 ± 0.9	7.2 ± 1.0	0.661 (0.01)*	0.482 (0.01)*	0.661 (0.01)*
	CG	7.0 ± 0.8	7.1 ± 0.8	7.1 ± 0.8			
	TENS-PNF	2.1 ± 1.2	0.5 ± 0.5	0.4 ± 0.5			
Dorsi proprioception	PNF	1.8 ± 1.0	1.5 ± 1.0	1.5 ± 1.0	0.438 (0.01)*	0.141 (0.01)*	0.390 (0.01)*
	CG	1.9 ± 1.0	1.8 ± 1.0	1.8 ± 1.0			
	EG 1	2.5 ± 1.7	0.2 ± 0.5	0.2 ± 0.5			
Plantar proprioception	PNF	2.2 ± 1.9	1.9 ± 1.0	1.9 ± 1.1	0.520 (0.01)*	0.244 (0.01)*	0.439 (0.01)*
	CG	2.4 ± 1.2	2.4 ± 1.3	2.4 ± 1.2			
	TENS-PNF	15.9 ± 1.5	18.6 ± 1.8	18.7 ± 1.8			
Dorsiflexion ROM	PNF	16.4 ± 1.8	17.2 ± 1.9	18.7 ± 1.8	0.655 (0.01)*	0.064 (0.15)#	0.622 (0.01)*
	CG	16.7 ± 1.7	16.8 ± 1.9	16.8 ± 1.8			
	TENS-PNF	36.4 ± 3.9	43.5 ± 3.7	43.6 ± 3.9			
Plantarflexion ROM	PNF	38.5 ± 3.3	39.9 ± 3.4	39.3 ± 3.0	0.729 (0.01)*	0.148 (0.01)*	0.693 (0.01)*
	CG	37.3 ± 4.0	37.5 ± 4.1	37.5 ± 4.3			
	TENS-PNF	11.1 ± 1.8	13.9 ± 1.7	13.9 ± 1.7			
Dorsiflexion MS	PNF	11.2 ± 0.8	11.7 ± 0.7	11.6 ± 0.6	0.741 (0.01)*	0.298 (0.01)*	0.736 (0.01)*
	CG	11.1 ± 0.8	11.3 ± 0.8	11.3 ± 0.8			
	TENS-PNF	13.2 ± 1.7	17.1 ± 1.7	17.1 ± 1.7			
Plantarflexion MS	PNF	14.5 ± 0.9	15.1 ± 0.9	14.9 ± 1.0	0.594 (0.01)*	0.218 (0.01)*	0.541 (0.01)*
	CG	14.1 ± 1.4	14.3 ± 1.5	14.2 ± 1.5			
	TENS-PNF	94.3 ± 2.5	98.4 ± 1.9	98.6 ± 1.7			
FADI score	PNF	4.7 ± 3.5	5.3 ± 3.4	95.3 ± 3.4	0.678 (0.01)*	0.078 (0.098)#	0.651 (0.01)*
	CG	5.3 ± 3.8	5.5 ± 3.7	95.5 ± 3.7			

VAS: Visual Analogue Scale; ROM: range of motion; MS: muscle strength; FADI: the Foot and Ankle Disability Index score. *Significant effect ($p \leq 0.05$). #Nonsignificant.

group, or time × group interaction effect for the variables. There comparison before and after treatment showed a significant difference between the time and measurements, as shown in Figures 5 and 6 for all the variables.

4. Discussion

Many studies have reported various types of stretching techniques and methods to address musculoskeletal problems and the impacts those problems have on sports performance and disability testing [42]. Studies reported that a minimum of 2-minute stretching of the gastrocnemius significantly produces an ROM increase and a decrease of stiffness in the muscle-tendon unit [43]. Several reports which indicated stretching conditions and methods of application have also examined time parameters [44]. Furthermore, many protocols based on the published results of previous studies have been found to contradict the results of those studies; therefore, the authors of this study selected a PNF stretching protocol from previously published research [45].

In a study conducted on young anterior knee pain subjects using TENS and PNF technique, it was concluded that pre- to postintervention the pain pressure threshold values decreased corresponding to pain similar to other studies, and also an increase in ROM values proved muscle relaxation and the significant change they observed from pre to 6-minute posttreatment values was in functional vertical jump demonstrating the effect on muscle performances for both the TENS group and the PNF group [46]. Various studies have provided mixed conclusions on the effect of

Table 3: Summary of statistical results of the mixed ANOVA and means and standard deviations of balance.

Balance	Group 1 (TENS-PNF) Group 2 (PNF) Control group (CG)	Mean (standard deviation)			Mixed ANOVA (p value)		
		Pre	3rd week	5th week	Interaction (group and time) effect η_p^2 (p value)	Group (G) effect η_p^2 (p value)	Time (T) effect η_p^2 (p value)
SEBT anterior	TENS-PNF	78.2 ± 2.5	81.9 ± 3.1	82.5 ± 2.6	0.613 (0.01)*	0.593 (0.01)*	0.670 (0.01)*
	PNF	68.5 ± 3.9	70.2 ± 4.1	69.4 ± 4.2			
	CG	70.5 ± 5.9	70.7 ± 7.0	70.8 ± 7.3			
SEBT posterior	TENS-PNF	92.4 ± 3.1	96.1 ± 3.1	96.3 ± 3.1	0.655 (0.01)*	0.136 (0.01)*	0.710 (0.01)*
	PNF	91.2 ± 4.6	92.4 ± 4.5	92.3 ± 4.7			
	CG	90.7 ± 5.4	90.9 ± 5.3	91.0 ± 5.2			
SEBT medial	TENS-PNF	95.7 ± 3.5	99.8 ± 4.1	100.1 ± 4.1	0.727 (0.01)*	0.043 (0.28)#	0.758 (0.01)*
	PNF	96.9 ± 3.7	98.3 ± 3.5	98.1 ± 3.7			
	CG	96.6 ± 3.5	96.8 ± 3.3	96.7 ± 3.4			
SEBT lateral	TENS-PNF	89.1 ± 5.9	92.1 ± 5.9	92.2 ± 5.7	0.607 (0.01)*	0.033 (0.38)#	0.624 (0.01)*
	PNF	92.9 ± 4.7	93.9 ± 4.2	93.4 ± 4.1			
	CG	91.6 ± 5.5	91.8 ± 5.4	91.8 ± 5.1			
SEBT anterolateral	TENS-PNF	74.9 ± 4.7	77.0 ± 4.6	77.3 ± 4.7	0.653 (0.01)*	0.001 (0.96)#	0.671 (0.01)*
	PNF	75.1 ± 3.9	76.4 ± 3.8	75.6 ± 4.0			
	CG	75.8 ± 4.1	76.1 ± 4.0	76.1 ± 4.0			
SEBT anteromedial	TENS-PNF	84.2 ± 5.8	88.1 ± 5.9	88.7 ± 5.8	0.562 (0.01)*	0.062 (0.15)#	0.602 (0.01)*
	PNF	83.1 ± 5.7	84.3 ± 5.7	84.2 ± 5.4			
	CG	83.8 ± 5.7	84.1 ± 5.8	84.1 ± 5.8			
SEBT posterolateral	TENS-PNF	95.1 ± 3.0	98.6 ± 2.4	98.9 ± 2.4	0.678 (0.01)*	0.118 (0.02)*	0.703 (0.01)*
	PNF	95.6 ± 2.9	96.7 ± 3.2	96.3 ± 3.4			
	CG	94.9 ± 2.8	95.1 ± 2.9	95.1 ± 2.9			
SEBT posteromedial	TENS-PNF	96.9 ± 2.6	102.1 ± 4.0	102.3 ± 4.0	0.633 (0.01)*	0.181 (0.01)*	0.638 (0.01)*
	PNF	96.8 ± 2.8	98.3 ± 3.2	97.7 ± 3.3			
	CG	96.9 ± 3.3	97.2 ± 3.0	97.1 ± 3.0			

SEBT: Star Excursion Balance Test. *Significant effect ($p \leq 0.05$). #Nonsignificant.

PNF stretching and the permanence of ROM gains. For example, one study reported that ROM improvements were not immediately significant 6 minutes after 5 repetitions of PNF stretching [47].

Another study, however, concluded that even after a single repetition of PNF stretching, ROM was significantly higher than baseline values. This improvement was evident 90 minutes after cessation of intervention for the muscle groups stretched [48]. Several other studies have also noted that ROM increments decrease quite sharply once intervention ceases [47, 49] and therefore recommend that PNF stretching should be conducted at least once or twice weekly. The present study's results show that ROM significantly increased when combining the TENS and PNF intervention 4 times per week for 3 weeks, and the gained ROM did not decline, which was observed in the follow-up assessment. Karasuno et al.'s [18] results support the present study; they concluded that TENS combined with stretching is effective in reducing pain and decreasing the muscle hardness, ultimately increasing the ROM.

TENS causes elicited muscle contractions and also allows for the activation of a greater proportion of type II muscle fibers compared to volitional exercise at comparable intensity [50–52]. Kang et al. [53] suggested that TENS, when applied directly to the skin overlying the gastrocnemius (calf muscle), is effective in improving balance for healthy adults, which concurs with the results of the present study. TENS not only improves strength but also increases joint position sense and balance [54]. The present study used TENS in combination with PNF stretching and found significant improvement in strength, balance, and proprioception compared to PNF and CG.

The results of a randomized controlled trial for children with hamstring syndrome who were given stretching combined with TENS indicated that the said combination produced better results than a protocol without TENS combinations [55]. A similar study also proved that TEN-PNF significantly improved flexibility of the hamstring muscles [39]. Another study applied TENS combined with PNF stretching for the hamstring muscles in volleyball players,

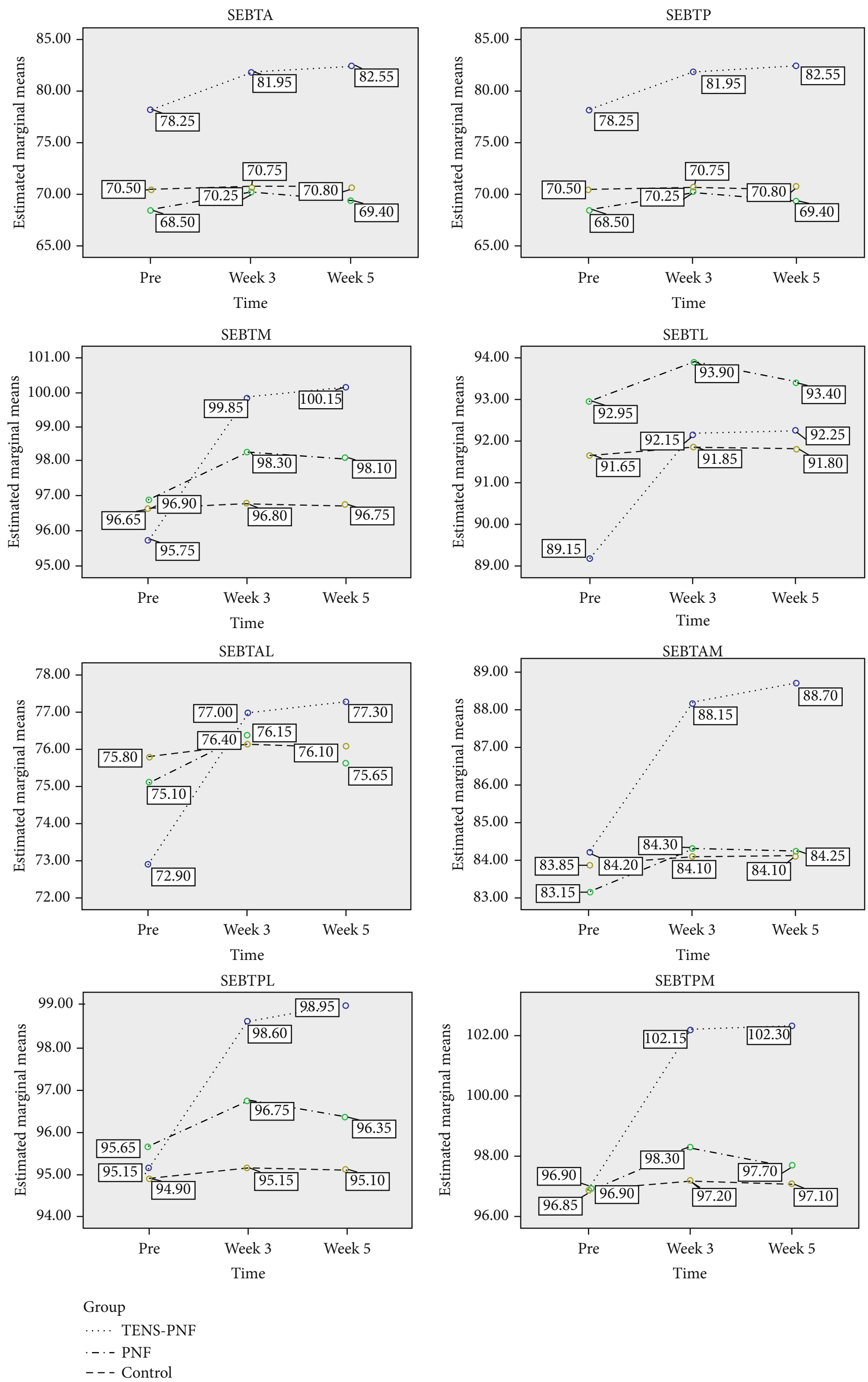

FIGURE 5: Mean values of the group and time interaction effect of the outcome variables measured at the pre, 3rd week, and 5th week for Star Excursion Balance Test (SEBT). A: anterior; P: posterior; M: medial; L: lateral; AM: anteromedial; AL: anterolateral; PM: posteromedial; PL: posterolateral.

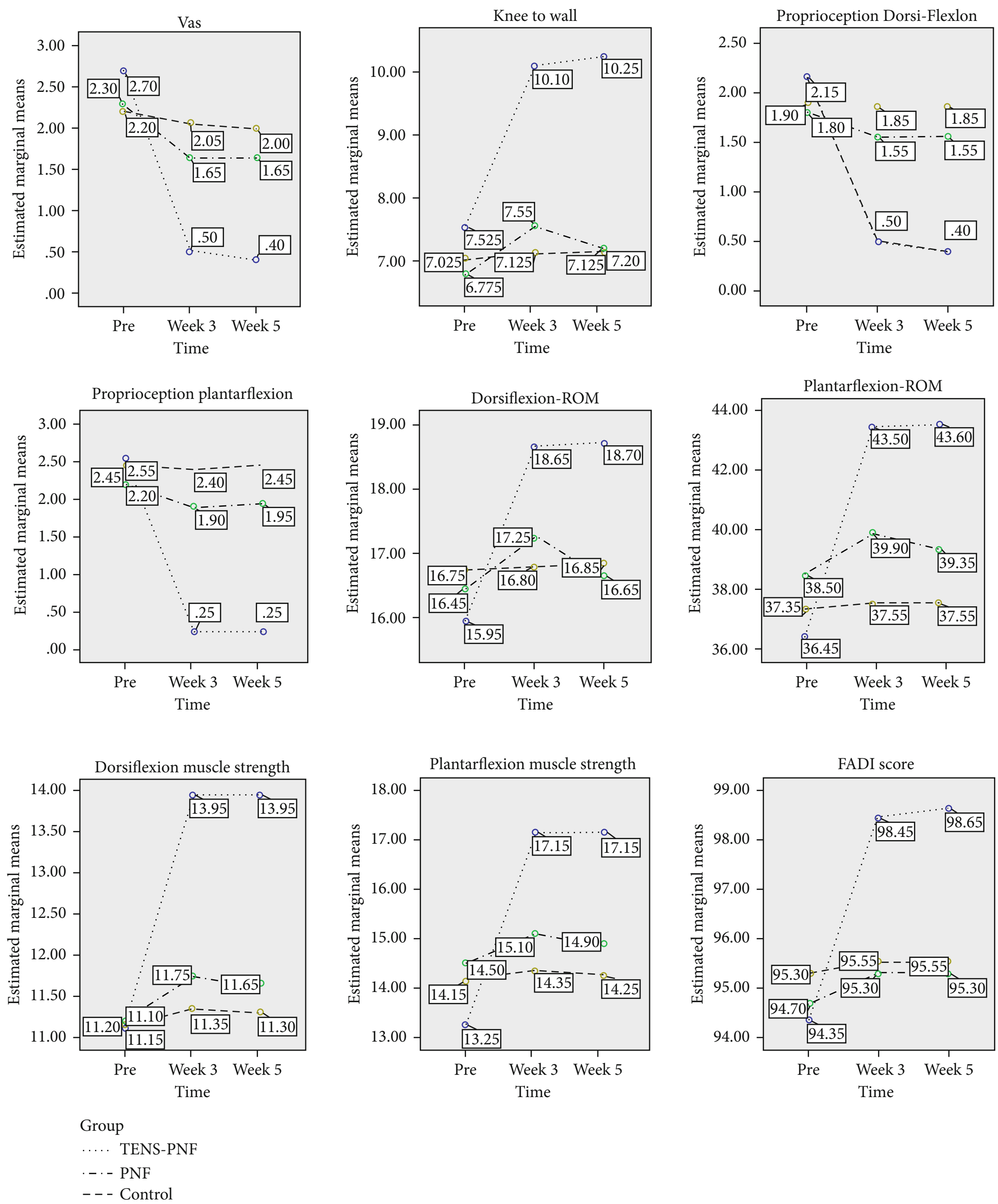

Figure 6: Mean values of the group and time interaction effect of the outcome variables measured at pre, 3rd week, and 5th week for pain, flexibility, proprioception, range of motion, muscle strength, and functional limitation. VAS: Visual Analogue Scale; ROM: range of motion.

following a very similar design [56]. Similar results were found in a study conducted for healthy women to achieve flexibility gains on their hamstrings that found that there was no increase in muscle flexibility compared to the group which did not receive TENS; based on their findings, they concluded that the combination of TENS and stretching decreases the resistance imposed by neurological and visco-elastic properties and will significantly increase muscle flexibility compared to an isolated technique [57]. The present study results also concur with the previous studies, proving that flexibility significantly improved with combination of TEN-PNF.

It can be held that TENS-PNF showed a significant difference and improvement attributable to the autogenic inhibition reflex, which is the reflex produced when a Golgi organ registers an increase in muscle tension. In our case, contraction in the PNF later provokes a reflex relaxation of the muscles [58]. This reflex may be triggered more when using the TENS because of its unique electrical stimulation that can trigger a tetanic contraction, simultaneously improving muscle strength and increasing tension in the Golgi organ [59]. Considering the evidence indicating that TENS could play an important role in stretching programs, the present study contributes to the existing evidence in favor of PNF combined with TENS for the triceps sural muscle, and the results of the present study support these earlier works.

The results of the present randomized controlled trial suggest that the use of TENS low-frequency currents improved the results of PNF stretching when applied directly to the triceps sural muscle and, therefore, that the results obtained with this stretching modality are significant. The study was conducted with male subjects only. A comparison study with females to understand the response to PNF stretching, with and without low-frequency electrical stimulation, should also be examined. The present study was only conducted for subjects participating in recreational sports; results may differ for professional athletes.

5. Conclusions

The present study showed that a 12-session treatment program, spread over 3 weeks, triceps sural muscle PNF stretching combined with TENS triggered muscle contraction during the muscle contraction phase of the PNF stretch, compared against PNF stretching, produced significant improvements in balance, proprioception, strength, and range of motion, while also yielding reducing pain for post ankle sprain subjects. It was also demonstrated that the treatment effect was sustained even after cessation of treatment to the follow-up assessment in the 5th week. For this reason, this treatment procedure will likely be helpful in rehabilitating post ankle sprain patients by improving overall function and helping build confidence in capacity for physical activity.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

All the authors declare that they have no conflicts of interests.

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Research Article

Measurement of Bone Mineral Density in Children with Cerebral Palsy from an Ethical Issue to a Diagnostic Necessity

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Introduction. Due to concerns about cumulative radiation exposure in the pediatric population, it is not standard practice to perform dual-energy X-ray absorptiometry (DXA) analysis in the diagnostic process of musculoskeletal disorders, such as cerebral palsy (CP). This study aimed to evaluate the bone mineral density (BMD) in children with CP and the ethical justification of applying DXA analysis in these children. *Material and Methods*. In this monocentric retrospective analysis, data were collected from children and adolescents with CP who were treated for a primary illness for three years. A clinical examination, which included a DXA analysis, recommended by the multidisciplinary team, was performed. After applying inclusion and exclusion criteria, 60 scans remained for statistical analysis. BMD and Z-scores for the lumbar spine (LS), and hip right and left femoral neck (RFN and LFN, respectively), and total hip (TH) were recorded. *Results*. The average age of children with CP when DXA analysis was first performed was about 7 years. The BMD (mean ± SD) at LS (LS-BMD) of all patients was 0.612 ± 0.12, at RFN 0.555 ± 0.11, at LFN 0.572 ± 0.1, and at TH (TH-BMD) 0.581 ± 0.13. The values of the Z-score (mean ± SD) at LS of all patients were -2.5 ± 0.22, at RFN -2.2 ± 0.21, at LFN -2.25 (SD = 0.2), and at TH -2.3 (SD = 0.23). There was no statistical significance between age and gender; however, BMI, walking ability, fracture history, and pattern of CP had a significant impact on BMD and Z-score values of these children. *Conclusion*. The results of our study clearly indicate that children with CP have a higher risk of low BMD, osteoporosis, and bone fractures, which makes it ethically justifiable to perform the DXA analysis in these children.

1. Introduction

The current standard for measuring bone mineral density (BMD) is dual-energy X-ray absorptiometry (DXA), due to its availability, accuracy, ease of repetition, and patients' low X-ray exposure [1]. Using DXA analysis in pediatric population is complex, because of the bone mineral density changes during the process of growth and development. Children have not achieved their final bone mineral density; thus, every obtained result needs to be compared to the average value for the same sex and age (Z-score), which means that the results vary at different ages, unlike adults, whose measured BMD value is compared to one standard, an "ideal" value for a grown, mature person (T score) [2]. Children of the same age can differ in skeletal maturity, which further adds complexity to the interpretation of DXA results. In children who have musculoskeletal disorders, e.g., cerebral palsy (CP), DXA analysis becomes even more challenging [3, 4].

CP is a term used for describing abnormal motor development of central origin, and it is the most prominent neurological disorder that occurs in childhood and continues into adulthood [5]. In developed countries, the incidence of this disorder is about 2 per 1000 live births. 70-80% of cases have a prenatal, unknown cause, while a smaller percentage occurs due to labor complications and problems in the early neonatal period [6]. CP patients have lower life expectancy compared to the general population, especially when severe complications and comorbidities are present [7]. Children with CP face numerous complications during their development: gastroesophageal reflux, aspiration syndromes, respiratory infections, seizures, and muscle contractures. In addition, aging-associated diseases like atherosclerosis, osteoporosis, sarcopenia, osteoarthritis, and dementia are more pronounced and occur earlier in CP patients, due to their static lifestyle. It is known that bone fractures are not a direct cause of death; however, their influence on morbidity is high [8]; therefore, measuring BMD is an important diagnostic procedure [9, 10]. For low BMD-related fracture risk, osteoporosis assessment, and therapeutic possibilities are less defined, compared to adult population. However, in the last years, there has been progress regarding diagnostics and diagnostic classification of reduced BMD in children. International Society of Clinical Densitometry (ISCD) defined parameters for osteoporosis in children in 2008 [11].

In children, osteoporosis diagnosis is based on two criteria: (1) the presence of low BMD with a Z-score lower than -2.0 and (2) presence of fracture history (long bones of the upper and lower extremities, compression fractures of the vertebrae) [11, 12]. Certain researchers consider that the term "osteopenia" should be avoided in children and that referring to Z-score results between 0 and -2 as "low BMD" is more appropriate [11]. Risk factors for low BMD values in children with CP are low weight, anticonvulsive therapy, poor nutrition, and inadequate sun exposure [10–12]. The incidence of bone fractures in children with a severe form of CP is 7-9.7% per year, with fractures of the lower extremity of the femur being the most common.

Every pediatric X-ray exam, especially in those with psychomotor development impairments, represents an ethical dilemma, and the benefit of a diagnostic or therapeutic procedure must outweigh the risks of the procedure itself [13]. Applying the principles of informed consent in pediatric healthcare involves consent by the parent/guardian, as well as the consent of a child older than 15. Consent should be the result of a continuous interactive communication between the health care providers, the child, and the parent/guardian. In the process of obtaining consent, health care providers are obliged to include the child in decision-making, according to its maturity and cognitive abilities, and provide the child, as well as the parent/guardian, with a form and amount of information that would be comprehensive and clear. Older children and adolescents, without cognitive deficits, have a right to independently consent to a suggested medical procedure, provided they are adequately informed about all the aspects of it by the health care provider. In the case of them declining the medical procedure, the health care provider is obliged to ask the patient's legal guardian for consent [13].

In case of DXA analysis, for spinal and femoral scanning, the effective radiation dose varies between 0.5 μSv and 15 μS for adults, while, in children, these values are higher and can reach 20 μS [14]. By comparison, the average effective dose acquired by each individual from natural sources is about 10 μS. The usual duration of a scan for cooperative children is about 1 minute for the lumbar spine and 5-7 minutes for the whole body [10, 14].

Numerous studies have shown that physical exercise can improve bone metabolism, increase BMD and BMC, provide good bone structure and strengthen bone mass [15–17]. Therefore, physical and kinesitherapy treatment, which is an integral part of the treatment of these children, is very important, both because of the stimulation of motor development and the improvement of BMD.

This study aimed to evaluate the BMD in children with CP and ethical justification of applying DXA analysis in these children. Our hypothesis was that the obtained data would show significantly low values of BMD and Z-score, which increases the risk of bone fractures and that it would highlight the need for an adequate treatment, which is aimed at damage prevention. Our results may favor the need for exercise and kinesiotherapy in children with CP.

2. Material and Methods

2.1. Study Design and Population. The present study is a monocentric retrospective analysis. Data were collected from children and adolescents with CP who were treated for a primary illness in a Center for Regeneration and Rehabilitation at Novi Pazar, Serbia, during a three-year period, from March 2017 to March 2020. A detailed clinical and radiological examination, which included a DXA analysis, recommended by the multidisciplinary team, physiatrist, child neurologist, radiologist and pediatrician, was carried out prior to the start of physical treatment in these children. This study was approved by our local institutional review and ethical board. All patients/caregivers provided a written informed consent to participate. All of the investigations have been conducted according to the ethical principles suggested in the Declaration of Helsinki. Measures have been made to protect the privacy of research subjects and the confidentiality of their personal information.

During the course of three years, 70 children with CP were treated in our Center. 65 DXA scans were performed. In 5 children, the analysis could not be done due to poor compliance. The inclusion criteria were diagnosis of CP, Caucasian ethnicity, age 3 to 18 years, and written informed consent to full medical examination from patients, when possible, or from their parents/caregivers. The exclusion criteria were diseases primarily involving bone metabolism or familial history of bone metabolism disorders; chronic diseases with stunted growth, e.g., renal failure; and corticosteroid or growth hormone medication. The exclusion criteria were evaluated on the basis of patient records, due to the retrospective design of the study; this represents an important limitation of our study. After applying inclusion and exclusion criteria, 60 scans remained for statistical analysis. In 2 cases, kidney disease was the reason for exclusion from this study, 3 patients had previously received corticosteroid or growth hormone medication (Figure 1).

The CP patterns were classified as hemiplegic, diplegia, triplegia, or quadriplegic, in accordance with the criteria of the Surveillance of Cerebral Palsy in Europe [18].

2.2. Anthropometry. In children who were able to stand, body length was assessed with a stadiometer (SECA®, model No. 213, Hamburg, Germany) in 0.1 cm increments. In children who were unable to stand, a retractable metal tape was used.

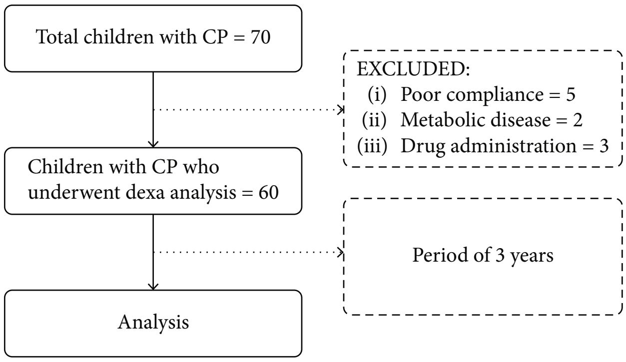


Figure 1: Participant flow diagram.

The body weight was measured by a digital scale in 0.1 kg increments. Body mass index (BMI) was calculated as a person's weight in kilograms divided by the square of their height in meters (kg/m^2).

2.3. DXA Measurement and Data Acquisition. DXA scans were obtained using a HOLOGIC densitometer, model Discovery Ci, by a single medical technician. Subjects' DXA scans over a 3-year period were utilized, as this corresponded to the time that studies at our institution were performed on a single machine, modeled on the study of our colleagues from Germany and USA [19, 20]. The lumbar spine and both hips were imaged, when possible, and analyzed with the manufacturer's software. A daily calibration of the machine was done with the spine and whole body phantom and weekly calibration with the tissue bar and air scan; DXA precision determination with current staff demonstrates a coefficient of variation of ≤1.0% at the spine and ≤2.0% at the femoral neck.

Quality control assurance measurements were performed according to the manufacturer's recommendations. Positioning on the device and clothing of the patients were executed according to the manufacturer's instructions (Figure 2). Only measurements that were considered evaluable, e.g., without movement artifacts, were included in the analysis. BMD and Z-scores for the lumbar spine (LS), and right and left femoral neck (RFN and LFN, respectively), and total hip (TH) were recorded.

2.4. Statistical Analyses. Descriptive statistics were obtained, and the Shapiro-Wilk test was used to evaluate the normal distribution of the data. Subjects' demographic, functional, and bone density characteristics were summarized by mean (SD) for continuous variables, frequency (percentage) for nominal variables, and rates for percentage change. For group comparison, two-sample t-test was used for continuous variables. For gender, differences in BMD and Z-scores between girls and boys were evaluated. One-way ANOVA analysis with Bonferroni correction of variance was used to evaluate if there is a significant difference in BMD or Z-scores among the BMI groups (underweight vs. health weight vs. overweight vs. obese) and walking ability groups. Morever, a comparison between quadriplegic and other patterns of CP was performed. Changes in BMD and Z-scores

Figure 2: Positioning on the device and clothing of the patient was executed according to the manufacturer's instructions. Photographing and publishing a photograph of a child in this scientific paper is approved by the parents. The principles of the United Nations "Convention on the Rights of the Child" (UNCRC) and "Reporting guidelines to protect at-risk children" were respected. The rights to the photo are reserved by the authors.

Table 1: Participants characteristics.

	Total (N = 60)
Age at first DXA, years M (range)	7.6 (3.9–10.1)
≤11 years—prepubertal, N = 42 (SD)	5.2 (2.4)
>11 years—pubertal, N = 18 (SD)	13.8 (4.2)
Sex	
Boys, N (%)	28 (46.67)
Girls, N (%)	32 (53.33)
Anthropometrics	
Weight (kg), M (SD)	25.4 (8.1)
Height (cm), M (SD)	125 (44)
BMI (kg/m^2), M (SD)	16.6 (5.6)
Underweight (less than 5th percentile), N (%)	12 (20)
Healthy weight (5th-85th percentile), N (%)	31 (51.67)
Overweight (85th-95th percentile), N (%)	14 (23.33)
Obesity (greater than 95th percentile), N (%)	3 (5)
Walking ability	
Complete immobility, N (%)	41 (68.33)
Use of walking aids, N (%)	10 (16.67)
Independent walk, N (%)	9 (15)
Fracture history	
Yes, N (%)	14 (23.33)
No, N (%)	46 (76.67)

M: mean; N: number; SD: standard deviation; BMI: body mass index.

was calculated only in subjects who did not receive pharmacologic treatment (beyond optimization of vitamin D and calcium intake).

3. Results

Demographic and medical information is presented in Table 1. The average age of children with CP when DXA analysis was first performed was about 7 years. The youngest patient was 3, and the oldest was 17 years old. Puberty, as a crucial period in the growth and maturation of children, was used to classify the children in prepubertal and pubertal

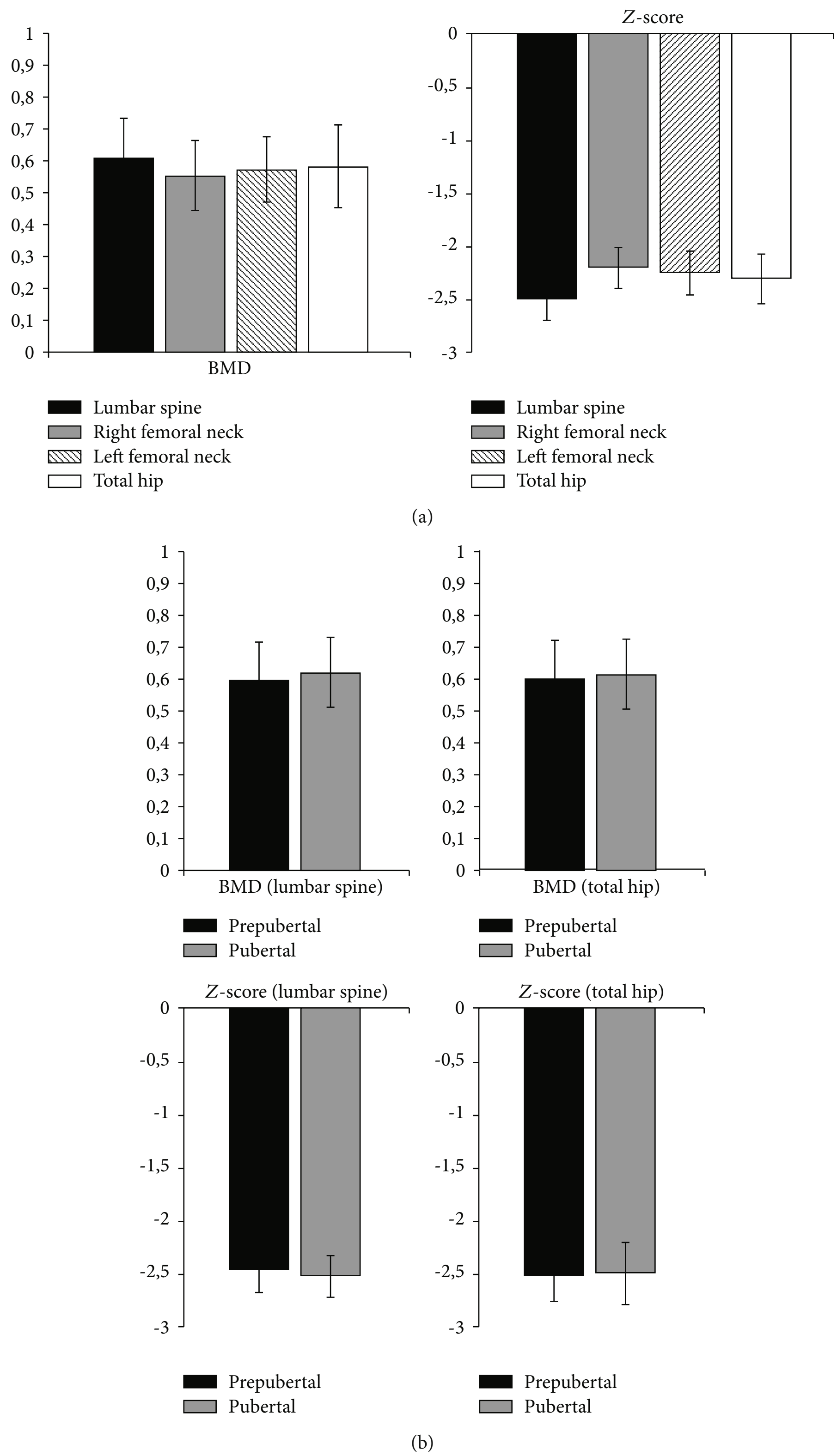


FIGURE 3: BMD (g/cm^2) and Z-score of all patients (a) and in relation to puberty (b).

groups, which were then compared by their BMD and Z -score values. The age of 11 years was taken as the limit [21], and there were 42 prepubertal children and 18 older than 11 years. Of the total number of children examined, there were 28 boys (46.67%) and 32 girls (53.33%). When it comes to anthropometric measures, the average body weight of children was about 25 kg, height (or length in immobile patients) 125 cm, and BMI in 51.67% of patients was normal. Overweight (85th-95th percentile) was present in 23.33% of the children tested, with several extreme cases, 12

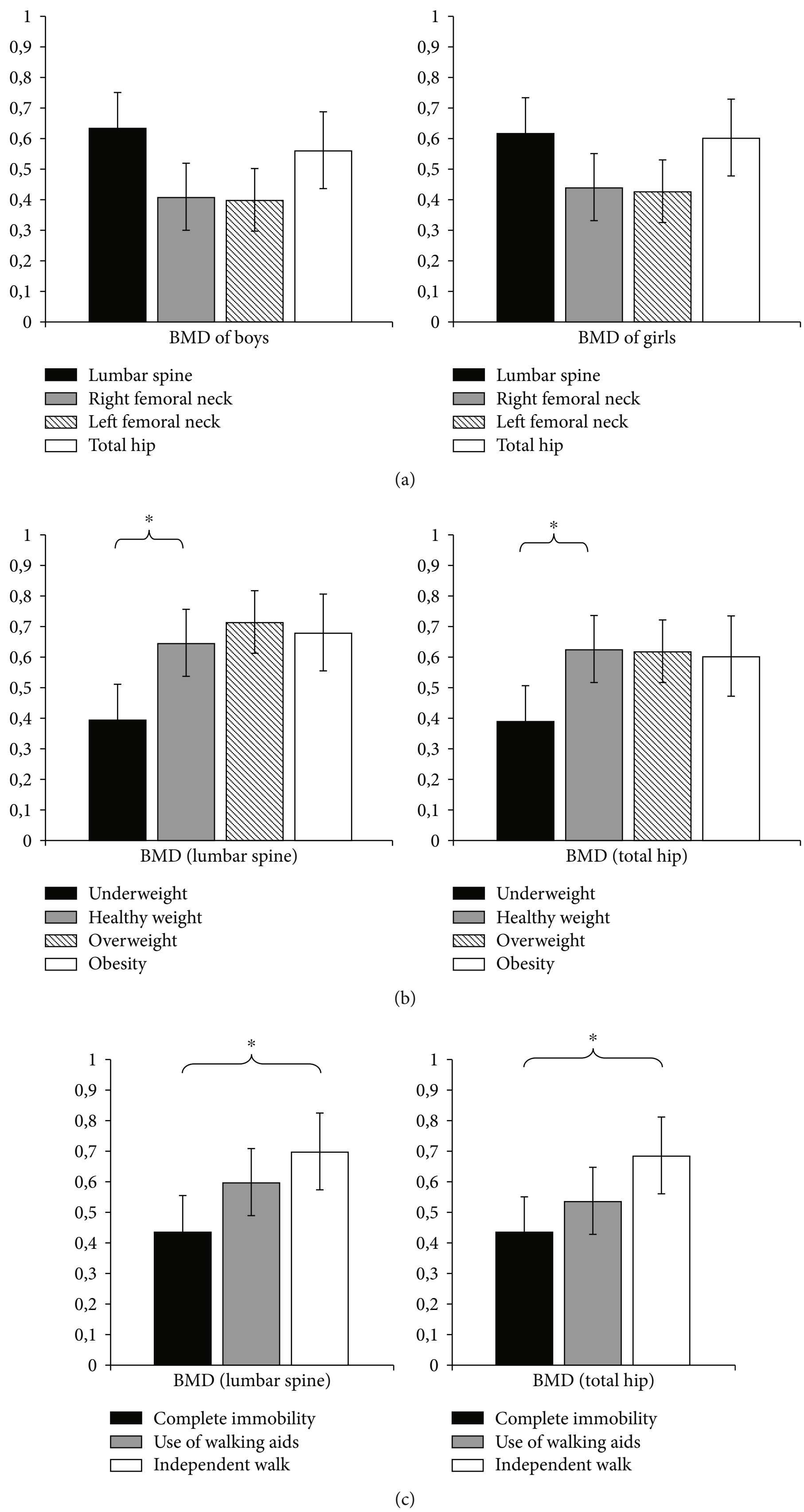
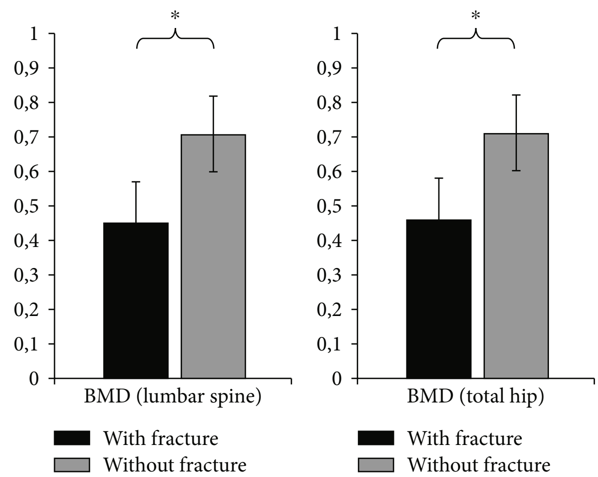


Figure 4: Continued.



(d)

Figure 4: BMD (g/cm^2) of children with CP according to patient characteristics: (a) sex, (b) weight, (c) walking ability, and (d) fracture history; $^*p < 0.05$.

underweight children (less than 5th percentile) and 3 children with obesity (greater than 95th percentile).

Walking ability is an important factor for proper development of the musculoskeletal system. Unfortunately, as many as 68.33% of the surveyed children did not walk, 16.67% of the children had mobility with the help of various aids, and only 15% of the respondents walked independently. There were 14 (23.33%) children with a history of fracture, and 46 (76.67%) had no bone fracture before or during the study (Table 1).

In our study, the BMD (mean ± SD) at LS (LS-BMD) of all patients was 0.612 ± 0.12, at RFN 0.555 ± 0.11, at LFN 0.572 ± 0.1, and at TH (TH-BMD) 0.581 ± 0.13. The values of the Z-score (mean ± SD) at LS of all patients were -2.5 ± 0.22, at RFN -2.2 ± 0.21, at LFN -2.25 (SD = 0.2), and at TH -2.3 (SD = 0.23) (Figure 3(a)). These values did not significantly deviate from previous literature data [8, 10, 15]. A comparison of the obtained values at LS and TH regions with respect to puberty is shown in Figure 3(b). It can be seen that there was no statistically significant difference between children in prepubertal and pubertal period (Figure 3(b)).

Likewise, a comparison of BMD with respect to gender was done. There was also no statistical significance between boys and girls (Figure 4(a)). In underweight children, LS-BMD (0.388 ± 0.12) was significantly lower than that in children with healthy, overweight, and obesity values ($p < 0.05$) (Figure 4(b)). Similar values were observed for the TH region. Complete immobility has proven to be an important parameter for BMD values. Children who were not mobile had significantly lower LS-BMD (0.433 ± 0.12) and TH-BMD (0.431 ± 0.12) than children who used aids or were walking independently ($p < 0.05$) (Figure 4(c)). Statistical significance between the LS-BMD and TH-BMD values in children who had fractures (0.45 ± 0.12 and 0.46 ± 0.12, respectively) and those without fractures (0.71 ± 0.11) was expected and is shown in Figure 4(d) ($p < 0.05$).

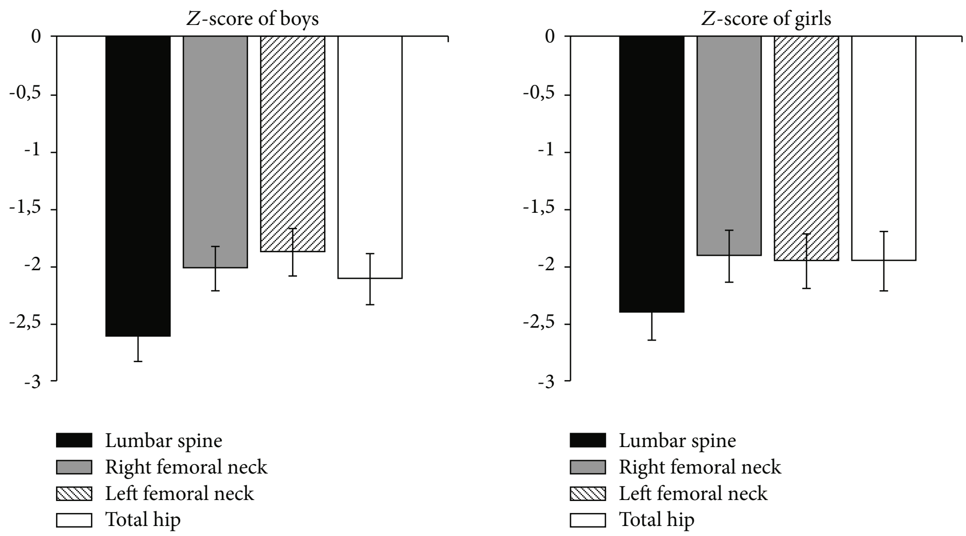
Analyzing the obtained values of Z-score against the same parameters, there was also statistical significance in patients with reduced BMI and immobility, as with those who have had fractures in the past. There was no statistically significant difference in Z-scores between boys and girls (Figure 5(a)–5(d)).

Finally, we compared values of BMD and Z-score in patients who had different clinical patterns of CP. Figure 6(a) shows that most were children with quadriplegia, as much as 56%. Diplegia was present in 20% of cases, hemiplegia was 14%, and triplegia was only 10%. Statistical analysis showed that the BMD and Z-score values were lower in children with quadriplegia (LS-BMD 0.388 ± 0.12; TH-BMD 0.389 ± 0.12; and LS-Z-score -2.55 ± 0.22; TH-Z-score -2.45 ± 0.25), compared to children with hemiplegia ($p < 0.05$), and there was no difference in comparison with triplegia and diplegia (Figure 6(b)).

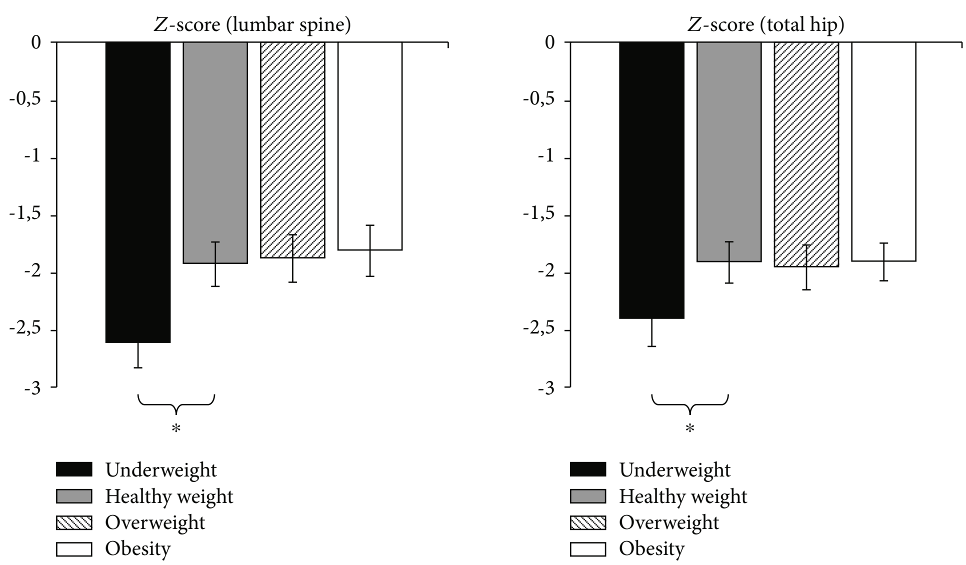
4. Discussion

Reduction in BMD was first reported in 1994, in nine nonambulant patients with CP [22]. Several further studies have shown low BMD values in children with CP, with results ranging from 68% to 97% of the examined children [23–27]. In our study, based on the latest recommended diagnostic criteria [23, 26, 27], all of the examined children had osteopenia, i.e., reduced BMD, and 23.33% of them had osteoporosis. A percentage this high could be explained, by the families of the patients living in less-developed areas of our country, and that the majority of patients grew in poor conditions, which had a significant impact on nutrition and care of the children [28, 29].

In childhood and adolescence, around 50% of the complete adult bone mass is formed [30]. In a 2015 Chinese child and adolescent health study, insufficient bone mineral content (BMC) is a result of insufficient physical activity and inadequate nutrition [31]. Calcium, as the main component of BMC, is one of the most-researched nutrients related to bone health [32]. Children with CP have various difficulties breastfeeding, swallowing, and/or chewing, which reflect



(a)



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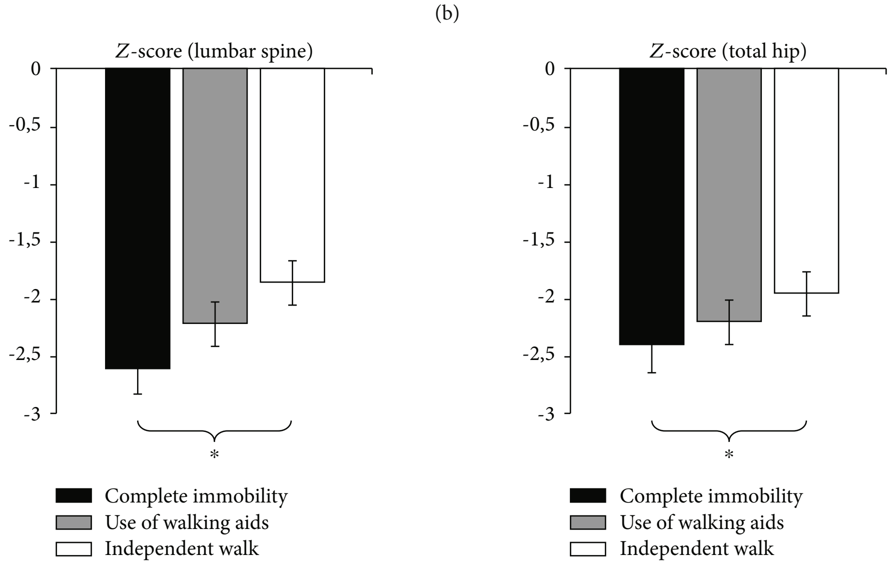
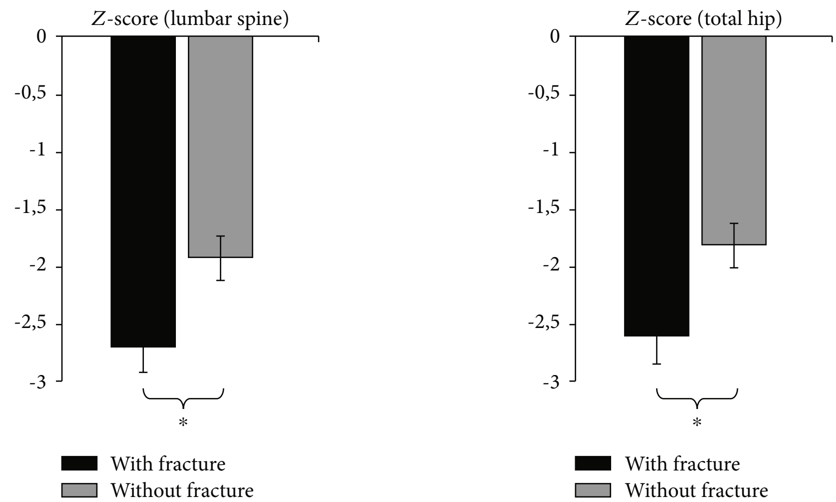


(c)

Figure 5: Continued.



(d)

FIGURE 5: Z-score of children with CP according to patient characteristics: (a) sex, (b) weight, (c) walking ability, and (d) fracture history; $^{*}p < 0.05$.

itself on quality and adequate food intake and BMI. Alternative feeding methods are often used: nasogastric tube or gastrostomy [33]. Our results have shown that 20% of children had a reduced body mass and total BMI (below 5th percentile for - underweight), which significantly affected the BMD and our results.

Increasing evidence shows that BMD is related to muscle function in healthy children [16]. Physical activity is of extreme importance when it comes to bone mass accumulation in children and adolescents, and it is observed that, in a certain degree, physical exercise can compensate for the lack of calcium intake [34]. Regular medium to high-intensity physical activity has a positive impact on bone health in young population [35, 36]. In a recent American Physical Activity Guidelines Advisory Committee Report, it is recommended that children and adolescents, ages 6-17 years, have 60 minutes or more of medium to high-intensity physical activity on a daily basis [37]. The 2016 Chinese physical activity guideline for children recommends at least 60 minutes of medium-high intensity physical activity per day, as well [38]. It is noted that the degree of physical activity is in direct correlation with BMD level [27, 34], which our study confirms. Children with quadriplegia had very low values of BMD and Z-score, and there was a statistical significance even when compared to children with only a certain degree of motor skills. Chen et al. [16] compared the results of two studies in which the results indicate that high-level physical activity with antigravity muscle training under safety control (such as jumping under supervising and necessary support), probably produces greater bone strains (≥1,500–2,500 microstrains) or eight times the body weight in ambulatory children with CP [39, 40]. Our finding supports the hypothesis that lower motor capacity and lesser mobility existing in this group of pediatric patients can affect BMD independently of the other risk factors. In addition, weakened muscle function and lack of mechanical load, present in our patients, result in inadequate forming and modeling of the muscle tissue, which consequently leads to reduced muscular strength and abnormal bone geometry and mineral content [41]. The meta-analysis published in late 2017 shows that weight-bearing exercise significantly improved the BMD in the femur compared with pretreatment values but had no effect on the BMD of the lumbar spine [42]. Mechanical stress on bone is a determinant of bone morphology, BMD, and bone strength [42, 43]. In children with CP who have difficulties in maintaining an upright position, less mechanical force is transmitted to the femurs than the lumbar spine, because mechanical stress can be imposed on the lumbar spine in a seated position.

Low BMD is asymptomatic by itself. However, fractures that can occur cause pain and significantly contribute to the comorbidity present in this pediatric population [8]. The most common location for these is the diaphysis of long bones, e.g., the distal extremity of the femur. In our study, 14 children had fractures in their medical history, which classified them as children with osteoporosis. Considering the existing issues regarding insufficient drug efficiency and difficulties in establishing optimal dosage, as well as potential adverse reactions to drugs, pathological fractures add even more complexity to the already challenging treatment course [44].

In our study population, we found no correlation between the gender and age of children with low BMD results (Figures 3–5). On the contrary, in previous studies, it was often reported that the sex and age (prepubertal and pubertal period) were correlated with low BMD in children with CP [45, 46], most probably due to differences in sex hormone levels. We have no other explanation for these characteristics having no impact on BMD in our study population, except that the hormone effect (at this age) probably had not yet begun.

Taking into account the abovementioned facts, as well as the results of our study, it is clear that children with CP have a higher risk of low BMD, osteoporosis, and bone fractures. Children with CP require radiologic diagnostic procedures more often, due to the need to monitor their hip migration in order to prevent dislocation, frequent injury, and bone/joint deformities. However, exposing them

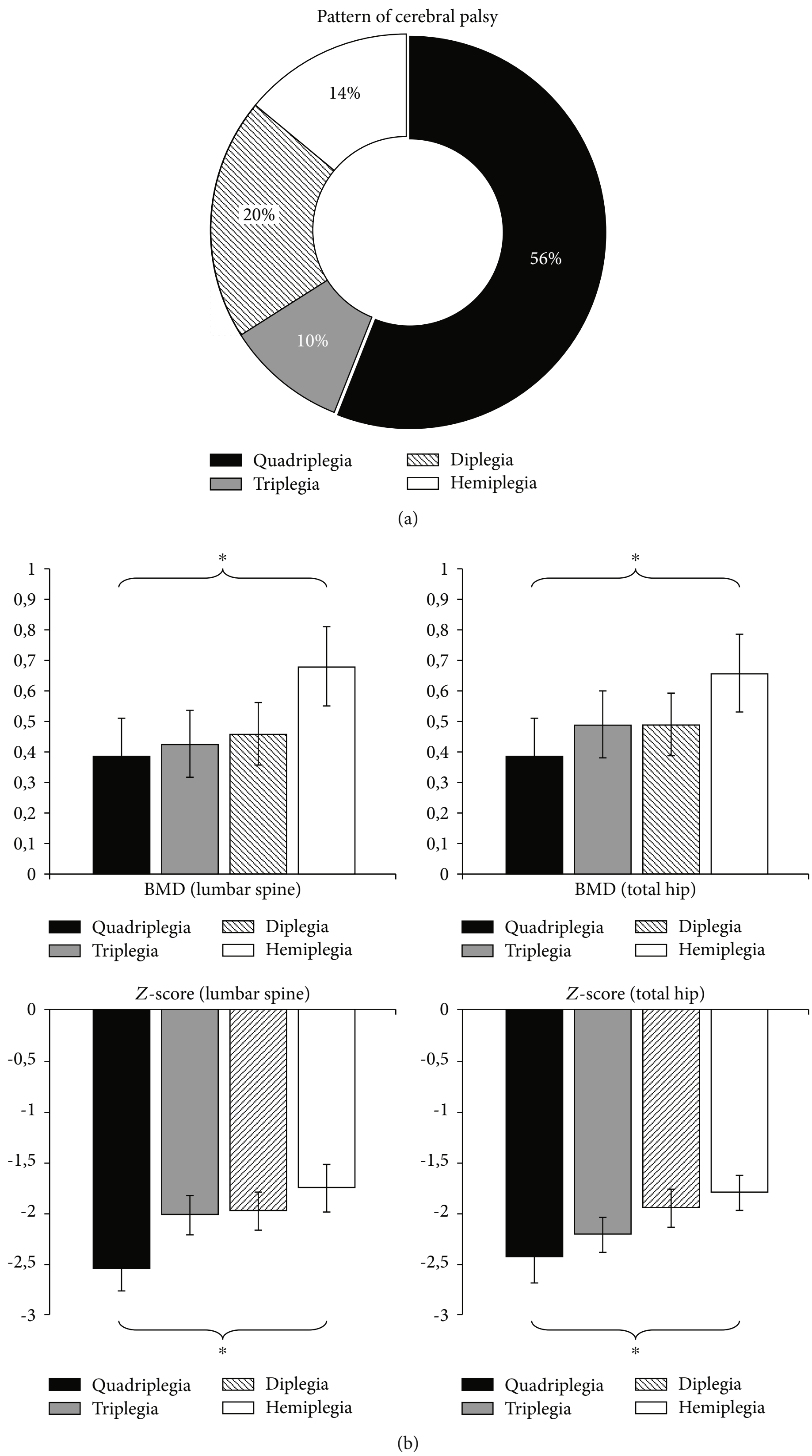


Figure 6: Percent of pattern of CP (a), and BMD (g/cm^2) and Z-score of all patients and in relation to pattern of CP (b); $^*p < 0.05$.

to additional X-radiation during nonstandard procedures, such as DXA analysis, represents an ethical question. Exposure to X-radiation carries a greater risk of malignancy, especially leukemia and thyroid cancer, in children than in adult population [47]. Previous studies have shown that many healthcare providers, including clinicians, even radiologists, are unaware of potential radiation-related risks in case of excessive and unnecessary diagnostic tests [48]. In practice, the patients often undergo tests before or without consenting to a procedure. In addition, alternative diagnostic procedures intentionally remain undiscussed. The fact that it takes the effects of the procedures 5 to 20 years to manifest them adds even more complexity to the issue [49]. Medical situations most frequently provoke multiple medical and ethical principles simultaneously and require moral and ethical judgment and commitment. Given that this study adequately and in line with the legislation of the Republic of Serbia [47] applies the ethical concept of informed consent in the pediatric patient population, the medical situation involving the diagnostic application of DXA analysis in this group of pediatric patients is ethically analysed here through the double effect phenomenon, due to the above highlighted concerns about cumulative radiation exposure in the pediatric population. The "double effect" of syntagm in medical ethics describes those practices of medical professionals that are known to have, in addition to the positive, simultaneously or successively negative consequences [50]. Led by the results of this study, which open the door to great and significant therapeutic opportunities in the field of practical prevention in this patient population, we can conclude that the benefit of this diagnostic procedure outweighs the risks of the procedure itself.

According to that, the use of DXA analysis in the pediatric population of patients with CP for the purpose of determining BMD is considered as one of those medical situations where the ethical principle of beneficence (*Salus aegroti suprema lex*—well-being of the patient is the supreme law) becomes more binding than the principle of no maleficence (*Primum non nocere*—do no harm), which were simultaneously provoked.

Its rational application in this patient population, as a positive balance of benefits and harms from it, opens the possibilities for further significant action of medical professionals who achieve the best final results for their health. It is an active action of medicine towards the prevention and reduction of the risk of further damage to health, the onset of pain and suffering, a significant deterioration in the quality of life and an additional shortening of the life expectancy of vulnerable pediatric patients with CP. Therefore, according to the result of our study, we strongly recommend this diagnostic procedure in the clinical monitoring of children with CP.

There are several limitations to our study. As in similar studies of this kind [19], the present study is a retrospective analysis of data obtained as part of a standard clinical care during an intensive rehabilitation treatment. There may be selection bias because the sample of all children with CP is not representative. In addition, anamnestic or heteroanamnestic fracture data could not be fully verified. Lower limb contractures and deformities, a common finding in children with CP, can affect the height measurement and thus the BMI calculation in the study.

5. Conclusion

The present study has confirmed that CP may worsen bone health in children and adolescents. BMD and Z-score values in children with CP were significantly lower than the reference limits. Furthermore, BMI, walking ability, fracture history, and pattern of CP had a significant impact on BMD and Z-score values of these children. All this confirms our hypothesis that CP increases the risk of bone fractures and that timely diagnosis and ensuring regular and persistent kinesiotherapy would be necessary in this pediatric population. Therefore, the use of DXA analysis outweighs the potential detrimental effect of X-radiation and we strongly recommend it in the clinical monitoring of children with CP.

Data Availability

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to restrictions, their containing information that could compromise the privacy of research participants.

Conflicts of Interest

All authors state that they have no conflicts of interest.

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Research Article

Computer Kinesiology: New Diagnostic and Therapeutic Tool for Lower Back Pain Treatment (Pilot Study)

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The aim of this study was to demonstrate the effectiveness of the diagnostic and therapeutic medical information system Computer Kinesiology in physiotherapy in patients with low back pain who were not responding to conventional therapy. Computer Kinesiology is primarily intended for the diagnostics and therapy of functional disorders of the locomotor system. This pilot study population included 55 patients (Group 1) with acute and chronic back pain and 51 persons (Group 2) without back pain. The third group was a control group of 67 healthy volunteers with no evidence of musculoskeletal pathologies and no back pain. All 173 subjects were examined three times by the diagnostic part of the Computer Kinesiology method. Groups 1 and 2 were treated after every diagnostics. Group 3 was not treated. The effect was evaluated by H score. Improvements after therapy were defined by reducing the H score by at least 1 point. In Group 1, the H score decreased by at least 1 point in 87.3% (95% CI: 75.5-94.7) and in Group 2 in 78.4% (95% CI: 64.7-88.7). There was no change of distribution of H Score grade in Group 3. The improvement neither depended on gender, age, and BMI nor was it influenced by the length of the therapy. This study demonstrated a high therapeutic efficacy of the Computer Kinesiology system in patients with back pain (Group 1) and in persons without back pain (Group 2) who used the Computer Kinesiology system for primary and secondary prevention of back pain.

1. Introduction

The issue of back pain is currently a worldwide epidemic. In the United States of America, up to 100 million adults suffer from chronic back pain and their care including work incapacity and disability costs 635 billion US dollars per year [1]. Traditionally, back pain can be divided into an acute, subacute, and chronic. Nevertheless, epidemiological data show that back pain has usually a recurrent, intermittent, episodic character [2].

Prevalence and incidence of the difficulties are as follows: 50-80% of adults have their own experience with back pain during their life, and 40% of the population suffer from back pain once a year. Back pain is one of the most frequent reasons for work incapacity. Currently, back pain appears also in 12% of adolescents at the age of 11. At the age of 15, the number increases up to 50% [2].

In medicine, back pain is referred to by different names or diagnoses such as vertebrogenic algic syndrome, lumbago, sciatica, and degenerative changes of spine. The disease may have motor, sensitive, and vegetative symptoms. The stage of the disease is crucial for every condition. Acute pain lasts up to four weeks, subacute pain lasts for 4-12 weeks, and chronic pain lasts for more than 12 weeks [1, 2]. The latest recommendation of the NIH Task Force on Chronic Back Pain Standard 2015 suggests that after 40 years of examining the causes of LBP (low back pain), the diagnosis according to pathophysiological and/or pathoanatomic criteria are not beneficial [1].

In an acute phase, an accurate diagnosis can be made in less than 15% of patients. This means that 85% of back pain in the past was usually treated with nonspecific care. Simultaneous division of back pain into three groups seems sufficient. These are severe spinal pathologies, nerve root problems, and mechanical back pain—this include 85% of the patients with nonspecific back pain (©The McKenzie Institute International). Thanks to precise subjective and objective examination, an educated physiotherapist is able to distinguish this nonspecific back pain more precisely. Specification is easier thanks to the so-called centralization phenomenon which appears in 70% of acute patients and in 50% of chronic patients with LBP. The use of the centralization phenomenon for the determination of the preferred direction of movement in the therapy testifies to the quality of the care. Terminologically, *centralization phenomenon* is defined as migration of the pain from a distal segment into a proximal one, while *centralization* is defined as a complete removal of peripheral radicular pain as a reaction to applied therapy (position, movements, and mobilization) [3–11].

Conservative treatment of back pain can take a variety of forms, from therapy procedures of spinal manipulative therapy [12, 13], motor control exercises [14], and stabilization exercises [15] to directional preference therapy based on the abovementioned centralization phenomenon, which is a basis of McKenzie's therapy. Classification of patients according to McKenzie's system is based on motion analysis, identification of centralization, directional preference, and mechanical diagnosis [16–19]. If a physiotherapist suspects structural causes of LBP, it is necessary to refer the patient to a consultant or another specialist. Functional blockades of segments [20], muscle imbalance, postural problems, and other problem subgroups are the most frequent problems with the vertebral column [21–23]. Preference of the stabilization exercises against other therapies is not fully justified because their higher efficiency has not been demonstrated [24, 25].

Given the increasing incidence of back pain, the following general recommendations should be taken as a form of prevention: reduction of hypomobility and diversion from passive treatment methods to a patient's motivation to participate actively in prevention and treatment programs, including maintenance of daily regimen measures (drinking regimen, weight maintenance or weight reduction, and sleep patterns, as well as ergonomics of daily activities and work processes).

The aim of the current approach to address LBP growth is primary prevention and secondary prevention of back pain. Primary prevention (educational programs) is focused mainly on endangered adolescents, risk groups with postural difficulties associated with one-sided work and sport load. Secondary prevention is focused mainly on patients with recurrent back pain.

The basic characteristics of the physiotherapy discipline consist in focusing on diagnostics, treatment, and prevention of functional disorders of the motor apparatus and prevention of the development of structural disorders. Physiotherapy uses two basic principles: a good functional form of an organ and long-term disorders of a function (dysfunction) may lead to structural disorders [26–28]. In the current era of evidence-based medicine (EBM), it is necessary in physiotherapy to cope with the critical opinions of clinical medical disciplines towards subjective evaluation of disorders of the motor system functions. These facts are the prompt for searching the options of objectivization and quantification of reflex changes in the locomotor system soft tissues.

Currently, Medical Expert Information System Computer Kinesiology (MEIS CK) seems to be a new and suitable therapeutic aid for the treatment of low back pain (described in our study) that is not responding to conventional therapy (e.g., hospitalization in departments like neurology, orthopedics, and rehabilitation; complex pharmacotherapy treatment; infusion therapy; local injection under CT control; contraindications for operations; and patient's preference of conservative treatment). Primarily, this system is used for the therapy of functional locomotor disorders. Medical MEIS CK meets in a validated manner the EBM requirements for diagnostics of the motor apparatus. MEIS CK supports LBP NICE guidelines for a patient's autotherapy and individual workout [29].

Evaluation of functions in the locomotor system results in numerical outputs and graphs. The procedure of data collection in the MEIS CK system includes examination of a patient mostly in a postural load, but a part of the examinations of lower limbs is performed in a supine position on a bed. Diagnostics include 46 standard physiotherapeutic tests in total (23 on the right and 23 on the left), out of which 10 are active movements, 16 are passive movements with the limbs [30], and 20 examinations are focused on soft tissues (HAZ and trigger points) (for a more detailed description, see Materials and Methods) [31, 32]. Results of examinations were written manually in a computer application as three grades, and each test was graded with one grade (A = normal function; B = less than 50% dysfunction (slight dysfunction); or C = more than 50% dysfunction (severe dysfunction) (significant limitation of movement extent, wrong moving stereotype or inability to perform a movement, or significant changes in soft tissues). After entering all values of the tests ($n = 46$) into a computer, these were processed by a mathematical model included in the software program of Computer Kinesiology. The outputs of the analyses were represented by numerical values and graphs interpreting the number of reflexes coupled with a single spinal segment (the so-called horizontal concatenation of dysfunctions) and at the same time by the movement of muscular chains (the so-called vertical concatenation of dysfunctions) [31–36]. Based on the diagnostic part output, the MEIS CK system suggests therapy by manual correction (massage—performed by a trained physiotherapist) and an individual combination of daily home exercises for the patient.

In 2001, teaching MEIS CK in the postdoctoral study of physiotherapists and physicians in the Institute for Postgraduate Medical Education (Prague, Brno) was approved by the Czech Medical Chamber. MEIS CK is suitable for locomotor system dysfunction objectivization and statistical data processing. It is also used for the evaluation of spa therapy effect in spa Bohdaneč, Františkovy Lázně, Jeseník, Košumberk, Luhačovice, Mariánské Lázně, and Slatinice. In the long term, repeated examinations could be used for the evaluation of treatment progress/regress [37]. In 2017, this was done in the spa Jeseník study evaluating the effect of spa rehabilitation care. In this study, in order to evaluate our findings before and after treatment, we used a diagnostic part of MEIS CK. The results of CK diagnostics were correlated to neurohormonal levels and to Knobloch N5 questionnaire results [38–41].

The aim of this study was to demonstrate the effectiveness of the diagnostic and therapeutic Medical Expert Information System Computer Kinesiology in physiotherapy in patients with low back pain who were not responding to conventional therapy. This was carried out in two selected groups, i.e., patients with acute and chronic back pain and healthy participants without back pain. It is the first study that evaluates the effectiveness of the MEIS CK therapy in low back pain.

2. Materials and Methods

2.1. Characteristics of the File. The study was realized during years 2014-2018. The Ethics Committee of the Third Faculty of Medicine approved the study, and written informed consent was obtained from all participants (no. 20190001/H/1). The patients with acute or chronic back pain who were previously treated by physicians and physiotherapists without any effect (reported in the patient's medical history) and who actively sought a Computer Kinesiology (CK) workplace were placed in Group 1. The persons without back pain, who chose MEIS CK for primary prevention of musculoskeletal disorders and actively sought a CK workplace were included in Group 2. The control group, Group 3, was composed of healthy volunteers who actively sought a CK workplace. All persons were from the Czech Republic population.

A total number of 173 participants (57 men and 116 women) in this study was divided into three groups. Group 1 consisted of 55 patients with acute and chronic back pain who were treated with MEIS CK. From this group, 23 patients suffered from radicular syndrome unilaterally in the lower limbs, and 17 had evidence of intervertebral disc prolapse on MRI or CT. In Group 1, there were 24 men and 31 women; the average age was 43.7 ± 9.7; BMI was 26.4 ± 4.5; and the duration of therapy/follow-up was 70.5 ± 51.7days. The participants from Group 2 (51 persons) chose MEIS CK for primary prevention of LBP and were treated by it. In Group 2, there were 12 men and 39 women; the average age was 47.4 ± 13.5; BMI was 25.6 ± 5.3; and the duration of therapy/follow-up was 140.9 ± 90.3 days. Group 3 consisted of 67 healthy volunteers (control group) who were not treated during this study. In Group 3, there were 21 men and 46 women; the average age was 36.5 ± 15.7; BMI was 25.0 ± 4.5; and the duration of follow-up 99.8 ± 65.4 days (Table 1).

Exclusion criteria for the participation in the study covered the following spinal conditions: infection, fracture, tumor, cauda equina syndrome, spinal cord compression and/or inflammatory disease, pregnancy, history of stroke or infarction, and multiple sclerosis. Anamnesis of all participants was acquired during the first entrance examination by a physiotherapist. Subjective assessment of the efficacy of the treatment by VAS (Visual Analogue Scale) was not performed because it could not be applied in Groups 2 and 3 (there was no LBP).

2.2. Medical Expert Information System Computer Kinesiology (MEIS CK). MEIS CK is primarily designed for the diagnostics and design of the treatment of functional disorders of the musculoskeletal system while respecting the fact that each person has its own individual norm.

The organism responds integrally to external and internal stimuli. MEIS CK depicts current disorders not only of the locomotor system itself but also reflective and segmental projection and associated distant reflex symptoms of visceral organ disorders and motor system response and metabolic response to endocrine disorders and psychosomatic effects [27, 42, 43].

MEIS CK consists of a diagnostic part and a therapeutic part. The diagnostic part was performed in all of the three groups by means of specialized tests (further on referred to as tests). The individualized therapeutic part was done only in Groups 1 and 2 according to CK principles.

2.2.1. Diagnostic Part. Numerical and graphical outputs of the diagnostic section served in designing the treatment process and checking its effectiveness. The decisive indicator of the effect of treatment is the dynamics of changes in the monitored parameters. CK diagnostics use 46 standard physiotherapy tests: ten tests of active movements (head rotation in the eye horizontal plane without head tilting or lateroflexion, trunk of body lateroflexion, and abduction and elevation of an extended upper limb—for each separately), 16 tests of passive movements (hip joint flexion with knee joint bend, hip joint flexion with extended knee joint, hip joint abduction, hip joint adduction, foot plantar flexion, foot dorsal flexion, knee joint flexion, and hip joint extension) [44], and 20 tests of palpation of reflexive changes—trigger points in selected muscles (flexor digitorum profundus, deltoid, pectoralis major, transverse part of trapezius, ascending part of trapezius, erector spinae, gluteus maximus, gracilis, iliotibial tract, and soleus) [27, 31, 32]. Each test was assessed by 3 grades: A, B, or C (such as the shortened muscle tests by Janda) [45]. Grade A is normal function, grade B is a slight dysfunction, and grade C is severe dysfunction. Evaluation of active and passive movements corresponds to Cyriax and Cyriax [46] and Kendall et al. [47]: A—range of movement is normal; B—range of movement is limited till 50%; and C—range of movement is limited by more than 50%. Similarly, we evaluated the findings of the trigger points (TP) in the muscles: A—no TP; B—muscle belly increased tension; C—presence of increased muscle belly tension and TP.

Table 1: Characteristics of participants in the study.

	Characteristics			
	Sex (M/F)	Age ± SD (years)	BMI ± SD (kg/m^2)	Follow-up ± SD (days)
Group 1	24/31	43.7 ± 9.7	26.4 ± 4.5	70.5 ± 51.7
Group 2	12/39	47.4 ± 13.5	25.6 ± 5.3	140.9 ± 90.3
Group 3	21/46	36.5 ± 15.7	25.0 ± 4.5	99.8 ± 65.4

Evaluation of TP palpation corresponds to examination rules by Travell, Simons, and Simons [48].

Each test is processed by a mathematical model included in the software program of Computer Kinesiology, version *Profi Complex Start 14.1*. Values were determined experimentally in correlation with spinal cord segment reflex projections and myofascial chains. The numerical outputs and graphs of the CK subroutines could thus provide information about the peaks of the faults of the locomotor system. The CK test section helps to find parts of the locomotor system that deviate the most from the physiological norm in their functions, and the diagnostic part helps to detect early functional disorders. Values of individual limits were determined experimentally. The diagnostic part of the MEIS CK system both provides the summary of numerical values of the motor system dysfunction as a whole, and predicates dysfunctions of body systems and organs. The MEIS CK system does not replace auxiliary medical examinations (laboratory tests, EMG, X-ray, CT, MRI, etc.) or classical medical differential diagnostics of organ pathology. The result of the software processing of numbers and graphs could help to consider potential causes of functional disorders of the motor system in the area of biomechanics, internal medicine, disorders of movement control, and psychosomatic causes [35].

2.2.2. Therapeutic Part. Therapy in Groups 1 and 2 always included two parts—a manual correction of reflexive changes of soft tissues according to MEIS CK on the day of diagnostics and an individual set of exercises with a special breathing regime according to MEIS CK performed by a participant twice a day (till the next check-up—selected breathing regime was *second's rhythm*, i.e., inspiration through the nose for 3 seconds, 2-second pause, expiration through the nose for 4 seconds, and 2-second pause. The breathing cycle was repeated 3-6 times in each position. The reason for the use of breathing exercises comes from the physiology of the brain stem reticular formation. Briefly, inspirium facilitates activity so that muscle tonus increases, while expirium facilitates an inhibitory effect on muscle tonus. This is a relatively safe method compared to other movements and could be performed even in the acute states.

Length of the therapy/follow-up was not the same for each group. In patients with acute back pain (Group 1), the time between two visits was usually shorter (according to clinical findings in the back or the leg) than in patients with chronic pain. Average therapy duration was 10 weeks. In Group 2, the interval between check-ups was usually longer than in Group 1 because the participants of this group had no clinical symptoms. Average therapy duration was 20 weeks. It was necessary to visit and treat patients with pain (from Group 1) manually and also to actualize individual exercises earlier than for participants from Group 2 (who were without pain). Time of follow-up in Group 3 was planned in between times for Groups 1 and 2. Follow-up was planned at 15 weeks (based on the MEIS system setup recommendations), but in reality, based on the discipline and circumstances of the patients, it was 14 weeks.

2.3. H Score. H Score parameter was the assessment tool of MEIS CK therapy efficacy. H Score was defined from the Total Dysfunction parameter (TD) and the presence/absence of the symptoms (lower back pain). TD is a useful marker for therapy effectiveness, and it expresses the overall sum of functional problems of the locomotor system (especially postural and biomechanical ones). Total Dysfunction is a single numerical value that shows the sum of the failures of the locomotor system, especially the posture, and the biomechanical ratios. The MEIS CK software evaluates the functional relationships of the right and left body parts in the frontal plane, the sagittal functional relations in the anterior-posterior plane, and the horizontal relations between the upper and lower body parts. The Total Dysfunction colored band graph was based on the results of the abovementioned tests and individual test results (degree of examination: A, B, or C). The TD parameter was divided into 4 different color zones (yellow, ≤59; green, 60-119; blue, 120-179; and red, ≥180-240). Three consecutive examinations were needed to evaluate the effectiveness of therapy over the course of days or weeks.

In the yellow zone (zone of ideal values), there can be persons who had almost all the test results within degree of examination A (normal function). Upon entering the study, there were no participants in the yellow zone. In the green zone, lighter functional disorders were present and tests were rated mostly A and sometimes B, and for exceptional cases, C. In the blue zone, which is represented by healthy people with functional deficits and minimal structural changes, there is a predominance of degree B and may contain degrees A and C. In the red zone, there are persons with most tests graded C (having more severe musculoskeletal disorders, e.g., acute problems and structural changes) (Figure 1).

H Score grades (0-3) were introduced because of the clinical significance of the study. The yellow zone is represented by H Score grade 0 (TD 0-59), the green zone is represented by H Score grade 1 (TD 60-119), the blue zone is represented by H Score grade 2 (TD 120-179), and the red zone is represented by H Score grade 3 (TD 180-240).

2.4. Statistical Analysis. An overview of demographic variables at baseline was presented using descriptive statistics and their 95% confidence intervals. For the baseline values of these criteria, the parametric test (Student's t-test or one-way ANOVA) was used for continuous variables and the Fisher's exact or chi-square tests were applied for dichotomous variables.

The improvement rate (IR), defined by at least a one-point decrease of the H Score (improvement in one color zone of TD (see paragraph above) that corresponds to a decrease by one H Score grade (one color zone), was adopted

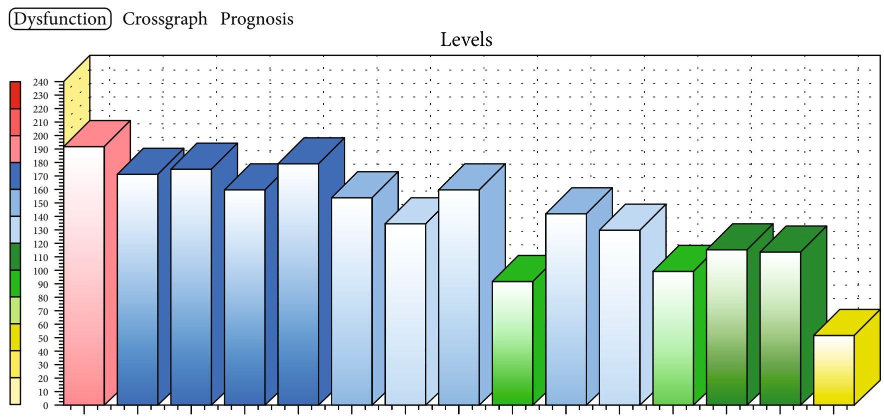

FIGURE 1: Illustrative graph of TD (an example of improving a person treated with MEIS CK therapy).

as the primary endpoint. This score was established for the purpose of this study, and it was composed of an objective parameter (TD, obtained from the MEIS CK) and a subjective parameter (absent or present back pain in subject).

The primary objective of the study was to confirm that the improvement rate (IR) of Group 1 (p) was not worse than Group 2 (h). The sample size was derived from the null hypothesis that the difference in the improvement rate between Group 1 (p) and healthy subjects was equal to or lower than -20%, i.e., $IR_p - IR_h \leq -20\%$, including the lower limit of the 95% confidence interval at the probability of a type 1 error of 0.05 at the statistical power of 80%. The number of subjects achieved at least 50 for each group to demonstrate the aim of the study.

Effect size was considered as an "effect of the time change" with p values of effect sizes between Groups 1, 2, and 3 included in the last row of Table 2.

The sample size of 173 subjects was justified for logistic regression using 5 covariates according to Peduzzi et al. [49]. McFadden's R-squared approach was higher than 0.4 indicating a good predictive ability of this model for the selected predictors. The continuous variables of predictors were assessed according to the median of the entire study population. The association was evaluated with the odds ratio mutually adjusted for all selected predictors, including a 95% confidence interval.

All tests were two-tailed, and the level of significance was set at 0.05. Statistical analyses and logistic regression were performed with Prism 8 (GraphPad Software, Inc., La Jolla, California, USA) and STATA version 15.1 software (StatCorp, Lakeway Drive, Texas, USA), respectively.

3. Results

The average TD in all three groups before and after the therapy/follow-up is shown in Table 2. We found significant improvement of dysfunction in Groups 1 and 2 after therapy/follow-up. The average TD remained different in all three groups before the therapy/follow-up ($p = 0.0003$), and after ($p < 0.0001$). Moreover, there was a statistically significant difference between Groups 1 and 2 before ($p = 0.0023$), and after the therapy ($p = 0.0096$).

The distribution of H Score in all three groups before and after the therapy/follow-up is shown in Figure 2. A significant improvement of H Score grade was generally observed in Groups 1 and 2. The distribution of H Score in Group 1 before the therapy was grades 2 and 3; after the therapy, there was a rearrangement to grades 1 ($p < 0.0001$), 2 ($p < 0.0001$), and 3 ($p < 0.0001$). Out of 40 patients in grade 3 before the therapy, only 2 remained within the same grade after the therapy; a significant improvement was even observed in 17 patients after therapy, so that they moved to grades 1 and 2, respectively. Group 2 had H Score grades of 1, 2, and 3 before the therapy, but after the therapy, it only had grades 1 ($p < 0.0001$) and 2 ($p = 0.4270$); out of 25 participants who were formerly in grade 3, none remained within grade 3 after the therapy ($p < 0.0001$). In Group 3, H Score grades before the follow-up were 1, 2, and 3; after the follow-up, the grades were still 1 ($p = 0.8161$), 2 ($p = 0.8571$), and 3 ($p = 0.6040$). Obviously, in Group 1, there was a rearrangement from a higher H Score grade to a lower one. Similarly, the same thing happened in Group 2. There was no change of distribution of H Score grade in Group 3 (Figure 2).

Table 3 documents that the improvement rate was 87.3% (95% Cl: 75.5 to 94.7%) for Group 1 and 78.4% (95% Cl: 64.7 to 88.7%) for Group 2. The primary objective of this study was achieved because the difference of improvement rates between Group 1 and Group 2 reached 8.8% (95% Cl: -5.5 to 23.2%), and therefore, the null hypothesis had to be rejected. The CK therapy in Group 1 was not worse than that in Group 2.

Furthermore, the 11.9% improvement rate in Group 3 confirmed the superiority of both groups with CK therapy; the difference of the IR was 75.3% (95% Cl: 63.6 to 87.1%) between Group 1 and Group 3 and 66.5% (95% Cl: 52.8 to 80.2%) between Group 2 and Group 3.

Results in Table 4 confirmed that the other factors (gender, age, and BMI) have not influenced the result of the CK therapy.

4. Discussion

Our pilot study offers verification of the efficiency of the MEIS CK method in acute and chronic low back pain. In

Table 2: Mean total dysfunction.

	Groups Group 1	Group 2	Group 3	ANOVA	Student's t-test (p)
TD before	190.8 ± 23.39	176.3 ± 24.29	167.8 ± 39.52	(p) 0.0003 (F) 8.417 (DF) 172	0.0023
TD after	134.6 ± 26.06	121.9 ± 23.03	173.4 ± 40.27	(p) < 0.0001 (F) 43.4 (DF) 172	0.0096
Effect size*	56.2	54.4	-5.6	n/a	n/a
p (Student's t-test)	<0.0001	<0.0001	0.0420	n/a	n/a

*The difference between TD before and TD after.

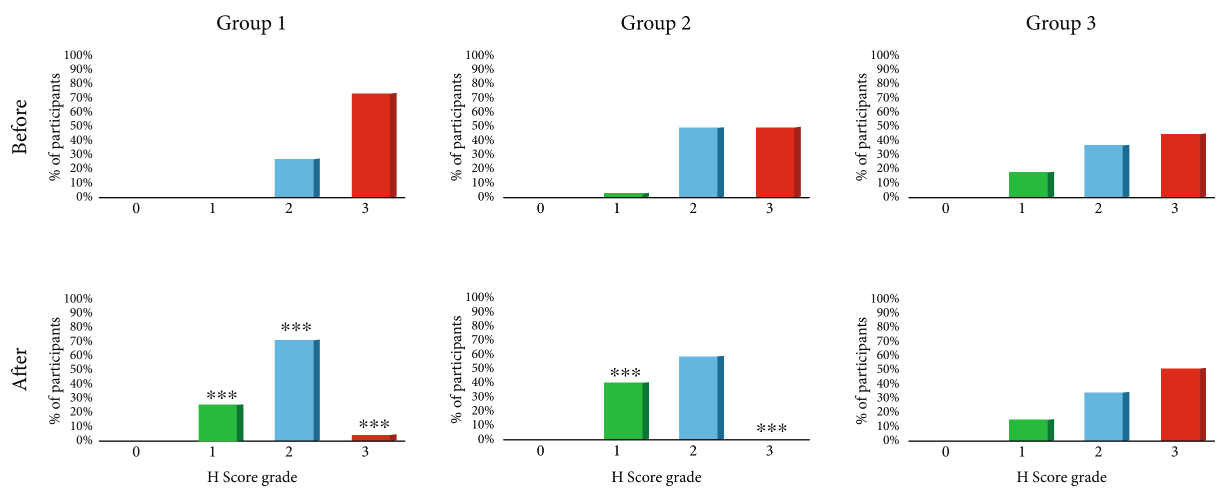

Figure 2: Proportion of H Score before and after CK therapy (Group 1, Group 2)/follow-up (Group 3), $^{***}p < 0.0001$.

Table 3: Proportions and the gross and adjusted ratios of chances of improvement depending on group.

Predictor		N	n	Proportions (%)	cOR (95% CI)	aOR (95% CI)	P (LR)
Group	2	51	40	78.4 (64.7-88.7)	1.0	1.0	
	1	55	48	87.3 (75.5-94.7)	1.89 (0.67-5.32)	2.05 (0.65-6.43)	0.318
	3	67	8	11.9 (5.3-22.2)	0.04 (0.01-0.10)	0.04 (0.01-0.11)	<0.0001

N: total number in the group; n: number of improvements in the group, proportion of improvements; cOR: rough ratio of chances; aOR: adjusted ratio of chances; P (LR): p value determined by logistic regression.

Table 4: Proportions and the gross and adjusted ratios of chances of improvement depending on other factors.

Predictor		N	n	Proportions (%)	cOR (95% CI)	aOR (95% CI)	P (LR)
Sex	Male	57	35	61.4 (47.6-74.0)	1.0	1.0	
	Female	116	61	52.6 (43.1-61.9)	0.70 (0.37-1.33)	0.61 (0.22-1.67)	0.509
Age	<43.7 years	86	42	48.8 (37.9-59.9)	1.0	1.0	
	≥43.7 years	87	54	62.1 (51.0-72.3)	1.71 (0.94-3.14)	0.97 (0.38-2.47)	0.991
BMI	<24.3 kg/m^2	85	44	51.8 (40.7-62.7)	1.0	1.0	
	≥24.3 kg/m^2	88	52	59.1 (48.1-69.5)	1.35 (0.74-2.46)	0.90 (0.34-2.36)	0.716
Follow-up/therapy	<84 days	79	41	51.9 (40.4-63.3)	1.0	1.0	
	≥84 days	94	55	58.5 (47.9-68.6)	1.31 (0.72-2.39)	1.53 (0.61-3.85)	0.170

N: total number in the group; n: number of improvements in the group, proportion of improvements; cOR: rough ratio of chances; aOR: adjusted ratio of chances; P (LR): p value determined by logistic regression.

our study, 55 patients with acute and chronic back pain (secondary prevention) were treated, with an average treatment period of 71 days, and 51 healthy participants without LBP (primary prevention) were also treated, with an average treatment period of 141 days.

Treatment improvements in Groups 1 and 2 were due solely to the effect of the MEIS CK therapy. In Group 2, we treated 50% fewer men ($N = 12$) compared to Group 1 ($N = 24$) because women's interest in preventing back pain was higher.

We were successful in the improvement of conditions in 87% (48 of 55) of Group 1: 17 of 48 patients were completely deprived of back pain. In Group 1, redistribution of the H score from grade 3 to grades 1 and 2 seems to be a very important result—it means that participants were without symptoms (back pain) or functional disorders of the locomotor system were gone. Improvement in Group 2 was observed in 78.4% (i.e., 40 participants of the total number 51). Surprisingly, the H score of all 25 participants with grade 3 got better minimally by 1 grade. Participants from Group 2 with grades 1 and 2 were not patients with back pain, so MEIS CK could act as a primary means of prevention for back pain and a means of prevention for functional disorders of the locomotor system. Effect size analysis showed that treated Groups 1 and 2 had significant improvement in time.

MEIS CK is appropriate as a valid objectification tool in physiotherapy for early diagnostics and treatment of functional disorders of the motor system. Advantages of MEIS CK are as follows: standardization of tests, integral individual approach, and adequacy of the therapy considering the current condition of the patient.

Treatment of precisely selected muscles and soft tissues according to the MEIS CK algorithm helps to achieve fast reflexes and long-term therapeutic effects without adverse negative stress to the patient. Thanks to the visualization of actual findings in well-arranged charts, the patient is educated and motivated to performing everyday exercises selected individually by the MEIS CK software. Utilization of the diagnostic part of the MEIS CK system meets the WHO requirements for evidence by the EBM concept, and it can be used for the evaluation of the effectiveness of physiotherapeutic treatment procedures. MEIS CK is mostly used in outpatient practices of physiotherapists. It is also used in the frame of hospitalization in physiotherapeutic facilities and in the spa care [38–41].

Conservative treatment of back pain is subject to various physiotherapy methods worldwide. We failed to identify any single study that would deal with the treatment of low back pain similarly as the MEIS CK method, i.e., a combination of a manual correction of reflexive changes of soft tissues and physical exercise with a specific breathing regime in the second's rhythm. Next in Discussion, we present different methods that are more often used for the treatment of back pain. Unfortunately, we cannot compare our therapy results with the results of studies below.

Nonspecific low back pain is a large and costly problem. It has a lifetime prevalence in 80% of the workforce and is associated with high levels of fear avoidance and kinesiophobia. Although exercise is considered a modest effective treatment for chronic LBP, current evidence suggests that no single form of exercise is superior to another [25]. Nevertheless, stabilization exercises have been suggested to reduce symptoms of pain and disability and form an effective treatment. Meta-analysis showed the significant benefit of stabilization exercises versus any other treatment for control of long-term pain and disability with a mean difference of -6.39 (95% CI: -10.14 to -2.65) and -3.92 (95% CI: -7.25 to -0.59), respectively. There is strong evidence that stabilization exercises are not more effective than any other form of active exercise in the long term [25].

Among the other commonly used exercise interventions is motor control exercise (MCE). In 29 trials ($N = 2431$) with study samples ranging from 20 to 323 participants, pain intensity and disability were monitored as primary outcomes and function, quality of life, return to work, and recurrence were monitored as secondary outcomes. The overall results of the studies were that MCE is not superior to other forms of exercise and that the choice of exercise for chronic LBP should probably depend on patient or therapist preferences, therapist training, costs, and safety [50].

Motor control exercises to improve control and coordination of trunk muscles and graded activity under the principles of cognitive-behavioral therapy are examples of another 2 commonly used exercise therapies. The participants (172 patients) with chronic (>12 weeks) nonspecific LBP were randomly assigned to receive either motor control exercises or graded activity. Primary outcomes were average pain over the previous week (numeric rating scale) and function (Patient-Specific Functional Scale); secondary outcomes were disability (the 24-Item Roland-Morris Disability Questionnaire), global impression of change (Global Perceived Effect Scale), and quality of life (36-Item Short-Form Health Survey Questionnaire (SF-36)). Results of this study suggest that motor control exercises and graded activity have similar effects for patients with chronic nonspecific LBP [14].

The Back School consists of a therapeutic programme given to groups of people that includes both education and exercise. A study evaluating the effect of the Back School approach in patients with acute and subacute LBP came to the following conclusions: it is more effective than no treatment (MD: -6.10; 95% CI: -10.18 to -2.01); it has no difference at the intermediate term (MD: -4.34; 95% CI: -14.37 to 5.68) or long-term follow-up (MD: -12.16; 95% CI: -29.14 to 4.83); it reduces pain at a short-term follow-up compared to medical care (MD: -10.16; 95% CI: -19.11 to -1.22); and there are similarly many other instances showing that it has a questionable effect compared to other systems [51].

Concerning treatment effect, spinal manipulative therapy (SMT) is one of the many therapies for the treatment of LBP. There is a high-quality evidence that SMT has a small, significant, but not clinically relevant, short-term effect on pain relief (MD: -4.16; 95% CI: -6.97 to -1.36) and functional status (SMD: -0.22; 95% CI: -0.36 to -0.07) in comparison with other interventions. There is a very low-quality evidence that SMT has a significant short-term effect on pain relief and functional status when added to another intervention. Data were particularly sparse for recovery, return to work, quality of life, and costs of care. High-quality evidence suggests that there is no clinically relevant difference between SMT and other interventions for reducing pain and improving function in patients with chronic LBP [12].

McKenzie's method is the most widely supported physiotherapeutic method by numerous studies at present. Studies on McKenzie's method (e.g., [3, 52]) reported a greater decrease in pain and disability in the short-term follow-up, while was there was no documented difference between McKenzie's method and other standard treatments in the intermediate-term follow-up. This is a similar situation with that of a study focused on the results of the Back School mentioned above [51]. Unfortunately, data on the long-term effects of McKenzie's approach are not known yet. Also, it is mentioned in both studies that there is a lack of relevant data for McKenzie's method in patients with neck pain [3, 52].

Another review showed that for LBP patients, McKenzie's therapy does result in a greater decrease in pain and disability in the short term compared to other standard therapies. But making a firm conclusion on LBP treatment effectiveness is difficult because there are insufficient data on long-term effects on outcomes other than pain and disability, and no trial has yet compared McKenzie's method to placebo or no treatment. There are also insufficient data available on neck pain patients [3].

The first limitation of this study is the duration of treatment length: we were unable to perform three consecutive MEIS CK diagnostics and therapy at the same time intervals in all treated patients (Group 1) and participants (Group 2), because patients from Group 1 with LBP came for visits earlier than healthy participants from Group 2.

Subjective pain assessment using the Visual Analogue Scale (VAS) was not utilized because it was applicable in Group 1 only (Groups 2 and 3 were with no LBP). These patients had different lengths of pain duration, and chronic patients had different recurrence rates.

Finally, despite that smoking was not in the exclusion criteria, only four out of the total 173 persons admitted history of smoking in their anamnesis. For this reason, we could not evaluate the impact of smoking on the result of MEIS CK therapy, although its negative effect on the therapy is well recognized. Therefore, we have decided to neglect this factor in our study. In addition to physiotherapy, we also checked other factors (gender, age, and BMI) that could affect the outcome of therapy. It was shown that none of these factors influenced the outcome of MEIS CK therapy.

5. Conclusion

In our pilot study, we have focused on the therapy of acute and chronic back pain by Medical Expert Information System Computer Kinesiology. Patients with back pain did not respond to the conventional treatment prior to the onset of our therapy. Apart from the group of patients treated by physiotherapy, also a group without any pain underwent the CK therapy. To them, the therapy was a primary means of prevention for back pain. We also had a healthy control group. People in this group were only diagnosed and followed in time. The dissimilar length of the therapy in treated groups was caused by the presence or absence of symptoms (i.e., back pain or radicular pain in lower limb).

The effect of CK therapy was objectively assessed by the primary H Score parameter. H Score was derived from Total Dysfunction of the motor system and the presence or absence of symptoms at the beginning and end of therapy/follow-up. Subjective assessment of the efficacy of the treatment by VAS (Visual Analogue Scale) was not performed. Apart from physiotherapy, we focused also on checking other factors (gender, age, and BMI), but none of these factors have influenced the result of the therapy. The improvement in treated Groups 1 and 2 was caused exclusively by CK therapy.

On the basis of our study, we can postulate that Medical Expert Information System Computer Kinesiology may serve as the useful diagnostic tool for functional disorders that expands visualization methods alike X-ray, CT, MRI, and also other examinations.

Data Availability

The data (two figures and four tables) used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare that they have no conflicts of interest.

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Research Article

Improving Physical Fitness of Children with Intellectual and Developmental Disabilities through an Adapted Rhythmic Gymnastics Program in China

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Background. Health-related physical fitness is vital for children with intellectual and developmental disabilities (IDD) to gain healthier lives. The adapted rhythmic gymnastics (ARG) program was designed for children with IDD and is aimed at testing the effects of the exercise program on children's physical fitness. *Methods*. Participants were recruited from two special needs schools in Beijing of China. Twenty-two children with IDD were assigned to an ARG experimental group or a traditional control group. The experimental group took part in a 16-week ARG program consisting of three 50 min sessions each week. And children's body composition, aerobic capacity, and musculoskeletal functioning were measured by the Brockport Physical Fitness Test (BPFT) before and after the program. *Results*. The between-group analysis revealed great improvements for the experimental group in abdominal strength (curl-up test: $p = 0.025 < 0.05$) and upper limb strength (dumbbell press test: $p = 0.038 < 0.05$). Compared to the pretest, most of the physical fitness parameters improved significantly in the experimental group except BMI, and flexibility of the experimental group children showed a substantial increase. *Conclusions*. Most of the physical fitness parameters of children with IDD in the experimental group improved significantly, especially on abdominal strength and upper limb muscle strength when comparing to the control group.

1. Introduction

It is recognized that children with IDD are poorer at all kinds of physical activities than typical development children, which in turn renders them to be less active, to have poor motor abilities, and to attempt a sedentary lifestyle. Such conditions will lead them to many chronic diseases, such as obesity or cardiovascular disease. Low physical fitness also brings negative impacts on one's ability to integrate into society [1]. However, reasons for low levels of participation in physical activity among children with IDD are complicated including physical, social, cultural, and environmental elements [2]. IDD children are unable or unwilling to attend any physical training [3]. They prefer a passive lifestyle [4]; the psychological or physiological barriers also prevent them from exerting their bodies freely [5]. Due to the lack of awareness of the positive physical effects, they have low motivation in participating in exercise [6] [7]. Children with IDD are heterogeneous, which means different children may show different responses to a training program. Therefore, it is difficult to find the feasible exercise for them. Meanwhile, social supports for participation in exercise programs are not enough, which means children with IDD have little chance to acquire the adapted exercise programs [8].

Since poor fitness seems to be the threatening factor for exacerbating the disabilities associated with children with IDD [9], aerobic physical exercise can improve fitness through ameliorating motor performance that may positively affect participants' general health and life quality [10]. Research has demonstrated that [1] aerobic physical fitness can reduce the risk of gaining weight [11], reduce the chances of metabolic risk elements [12], and improve the cognitive function of individuals with intellectual disabilities [13, 14]. Nowadays, considerable work has been tried to promote these individuals' physical fitness through a variety of physical exercises. However, there is no standardized exercise program; the availability of recreational programs that aim at children with IDD is limited and not widely accessible [15], not to mention school-based physical exercise programs for IDD children. In China, the special needs school is the main compulsory education place for children with IDD. The special needs school enrolls various IDD forms, including children with autism spectrum disorders (ASD), intellectual disabilities (ID), Down's syndrome (DS), cerebral palsy (CP), and other multiple disabilities; the IQ scores of the school children with IDD are less than 40 points; and they are facing many cognitive problems, such as behavioral problems and health problems. Hence, school-based exercise programs are important for children with IDD to ameliorate their health-related problems in special needs schools. School-based exercise often includes the functional movements or postural tasks, such as quantities of squats, sit-ups, long-distance running, and repeated functional movements. However, these exercises are not attractive to children with IDD and may cause antipathy. Considering this point, the exercise program in this study was deliberately designed to adapt to the physical and psychological features of IDD children to inspire their motivation by doing interesting exercise.

The ARG program was designed based on the basic gymnastics exercise and dance elements with small apparatus, which was used to develop participants' self-control, motor skills, and physical fitness. Simple, single, and combined aerobic rhythmic movements are more suitable for children with different abilities to learn, because the sense of rhythm is children's innate ability, which makes each movement more natural. It is easy to master the ARG program for young-aged participants, which makes them become confident and initiative. The most valuable finding is that the rhythmic movements combined with music are more appealing to encourage the participants to engage in various kinds of movements than other activities. None of these programs have been designed or included children with IDD before.

The purpose of our study is to examine whether participation in an ARG program could have a positive impact on levels of physical fitness among children with IDD.

2. Methods

2.1. Participants. In this study, the participants included 22 children (13 boys and 9 girls) from two special needs schools in Beijing of China (School A: 12 participants; School B: 10 participants). Participants were identified as active and healthy. They did not have cardiac respiratory conditions that could be dangerous during aerobic rhythmic exercise, and they were able to understand basic visual and verbal instructions. The experimental group ($N = 12$; ASD = 4, ID = 5, and DS = 3; mean age = 7.2 years; and IDD level moderate) came from School A; through the fundamental motor skill test (FMS: stationary tests, locomotor skill tests, and objects controlled tests), 12 children out of 25 who performed higher scores got chosen. The FMS test indicates children's retardation of gross motor abilities and of a sufficient cognitive competence to adapt to the ARG program. In this study, the FMS test was only used to select participants, hence no FMS data analysis in this study. In School B, the FMS test was also executed to select 10 participants for the control group. The control group ($N = 10$; ASD = 4, ID = 3, and DS = 3; mean age = 7.5 years; and IDD level moderate) was matched for age, IDD level, and disability types with the experimental group (see Table 1).

Table 1: Descriptive characteristics of participants.

Characteristic		Experimental group ($N = 12$)	Control group ($N = 10$)
Age		7.2	7.5
Diagnosis	Autism	4	4
	Down's syndrome	3	3
	Intellectual disability	5	3
Weight (kg)		26.28	25.67
Height (cm)		122.53	122
BMI		17.37	15.69

2.2. Procedures

2.2.1. Adapted Rhythmic Gymnastics Program. The ARG movements were designed by professors who were gymnastics specialists from Beijing Normal University (BNU). Considering IDD children's low levels of moderate to vigorous physical activities (MVPA), this program was designed to be stimulating, interesting, and easy to manipulate and is based on children's motor skills and cognition. Because of the program is fun, understanding and mastering the exercise could overcome the children's participation barriers affecting their physical fitness [16]. The ARG program included music, rhythms, rhythmic movements, and dance elements with apparatus, which contributes to the development of children's motor abilities through crawling in different directions. For example, when children were passing and catching the ball, their brain started to work and their hands and eyes cooperated to determine the direction of the ball and to grasp the ball in a moment without long hesitation. In the process, children's upper limb strength, hand-eye coordination, and sense of direction were improved. Combined rhythmic movements could cultivate children's sense of balance; children acquired dynamic balance through dynamic displacements. The contents of the ARG program were separated into three categories: controlled movements, uncontrolled movements, and locomotor skills. Program details are shown in Table 2. Any gymnastics movements that would cause negative effects such as dizziness or injured were excluded.

The Delphi technique used to testify the appropriateness of the ARG movements was used to collect data from experts [17]. Experts included the special needs schools' physical education teachers ($N = 3$), rehabilitation teachers ($N = 2$), dance teachers ($N = 2$), and university professors ($N = 3$) whose research field was adapted physical education and who had ample knowledge about children with IDD. After

Table 2: The ARG program contents and functions.

Fundamental movement skills	Program categories	Contents	Functions
Uncontrolled movements	Rhythmic gymnastics exercises	Single rhythmic movements; combined rhythmic movements; complete rhythmic movements	To develop big muscle groups, promote neural and muscular coordination, enhance the body control and displacement ability through low-impact rhythmic movements of the limbs in multiple dimensions and movements. To evoke the automatic postural control by vertical and horizontal jumps. To achieve the visual and kinesthetic stimuli and to improve the balance via combining with the auditory, tactile, visual, and vestibular stimuli
Controlled movements	Rhythmic movement with small apparatus	Ball, hoop, elastic band exercises	Through the completion of different forms of apparatus control movements: throwing, catching, racking, and rolling the ball and the tension of elastic band, to develop control of small muscles, to improve the orientation and neural sensitivity and to train the sensory ability
Locomotor skills	Rhythmic exercises on mats	Crawl, roll, rotate, tumble without passing through the cervical vertebra	Through crawling, rolling, and turning in different forms and directions, to promote the development of neural organs, to enhance the perception, to improve the ability of coordination and exertion of the whole body, and to increase the trunk muscle strength
Uncontrolled movements	Functional training exercises	Strength, aerobic, flexibility, agility; body coordination exercise	Enhance the physical fitness and acquire various technical motors skillfully through repeated muscle strength exercises, stretch exercise, and core power training exercise

three rounds of questionnaire, the adapted motors identified by experts got chosen. To further confirm the feasibility of the ARG program, the preexperiment was conducted before the program. The teachers taught the experimental group children with expert-identified ARG movements for about seven 20 min classes and judged their acceptance of the contents from children's learning states. Finally, 96% expert-identified contents got chosen for the final program. Music acted as an important element in the ARG program. Music offered children both amusement and comfort. Researchers suggested that music was the signal to guide children's movements [18] and also attracted children's attention to complete tasks [19]. All movements were coordinated with the rhythm. Fast-tempo music such as *Zunea-Zunea* was chosen to stimulate children's enthusiasm and cue them to step on the tempo. Children could shake their heads and bend their knees consistently within the rhythm. Slow-paced music was played while stretching and relaxing.

After the preexperiment, the ARG program was finalized. Teachers ($N = 4$) of the ARG program, majoring in gymnastics from Beijing Normal University, were supervised by an instructor with expertise in working with disabilities. Children in the experimental group participated three times a week in a 50 min class for 16 weeks, each class (Table 3) included the following stages: *stage one*, class routines (3 minutes) to promote the interaction between children and teachers; *stage two*, warm-up (5 minutes) to reduce the possibility of injury and keep up to speed at the exercise; *stage three*, core activities (35 min) including basic rhythmic gymnastics skills such as imitating animals and several exercise games such as crawling to compete with other peers; *stage four*, cool-down (5 min) to explore the children's satisfaction level; and *last stage*, feedback (3 min) to end up the class.

The ARG program was delivered from September 2019 to January 2020. All activities were performed in the children's familiar classroom to lessen their anxiety and reduce their distractions. Participants should be involved in at least 90% of the program to ensure the results of the program were convincing. The control group children adhered to their regular school schedule, which means traditional physical education classes at a frequency of three times per week, for 50 minutes in each class. No instruction in rhythmic gymnastics was given to the control group children during the period of the intervention program.

Teachers provided both visual and verbal clues when taught the ARG contents to motivate children's participation. Children were able to increase the intensity of rhythmic activities when the teacher gave the cues and made the exaggerated demonstrations to attract children's attention. Participants could imitate the teacher's actions most of the time. The ratio of teachers and students was no more than 1 : 3 for the whole program, ensuring each child can receive personalized guidance and have the opportunity to interact socially with teachers and peers. During the class, teachers created a direct and interesting learning atmosphere.

The parents or guardians of the children in the experimental group have signed an informed consent form, agreeing to the child's participation in the activity, and all procedures are in line with Helsinki's statement.

2.2.2. Measurements. The BPFT was a criterion-referenced test of the health-related physical fitness test, appropriate for children of all abilities [20]. This research tested the physical fitness levels of children with IDD using seven parameters in BPFT: body mass index (BMI), 10 m PACER run, curl-ups, dumbbell press, trunk lift, standing long jump,

Table 3: Model of the ARG training program.

Stages	Activities	Time (minutes)
(1) Routine	Greeted to teachers and peers and conducted regular routines (assemble, attention, and straddle) to promote the relationship between teacher and children	3
(2) Warm-up	Children followed the rhythm of medium-speed music for warm-up (running, marking time, and joint mobility) to increase muscle temperature, prevent injury, and gradually enter the learning state	5
(3) Core exercise	Basic rhythmic exercise (12 minutes) Children followed the fast-tempo music to imitate the rhythmic movements of animals (frog, rabbit, goose, and monkey) and to practice the rhythmic combination exercises Mat rhythmic exercise and games (15 minutes) Children learned crawling, rolling, and other mat exercises and competed in drilling circle and jumping circle Children passed the ball with the teachers to promote hand-eye coordination and to enhance interaction between teachers and children Functional training exercise (8 minutes) Children performed 10 times∗2 groups sit-ups and 8 times∗2 groups supine leg lifts to promote the strength of the waist and abdomen Children performed dynamic and static stretching to promote flexibility of the back and limbs Children performed push-ups for 8 times∗2 groups to improve the strength of limbs	35
(4) Cool-down	Children performed breathing exercises to rest and calm the body back	5
(5) Summary	Teacher summarized children's performance and said farewell	2

and sit-and-reach test. Verbal instruction and demonstration were showed to participants before each test item until they understood the tasks. Continuous motivation was given to all participants [21]. Tests were all performed in a large classroom with nonslip mats to keep from disturbances. Given that the subjects in this research were under the age of 10, it was reasonable to modify the tests (BPFT were usually used for 10-17 children) and to use each participant as their own comparison by examining the change between pre- and postprogram assessments.

Body composition was reflected by BMI. BMI was calculated as the weight (kg) divided by the square of height (m^2). Participants' weights and heights were measured using a standard protocol. Body composition would unlikely be changed in a short period of time; there were no disability-specific standards for body composition [18].

Aerobic functioning was reflected by the achieved level on the 10 m PACER run test. Considering that children in this research were under 10 years old, the distance was modified from the original 20 meters to 10 meters as a recommended distance. The test required children to run between two cones 10 meters apart at a steady pace; the test ended when the child failed to reach the end destination when time is up; the final distance the children ran was recorded.

The musculoskeletal function included muscular strength, endurance, and flexibility. The abdominal endurance was assessed using a curl-up test. The test was to perform as many curl-ups as one can in 30 s; the number of complete curl-ups performed in the prescriptive time was recorded.

The upper limb's strength and endurance were measured by the dumbbell press. Participants used one hand to lift a 1 kg dumbbell as many times as possible in 30 s; the exercise continued at a steady pace until the participants were no longer able to lift the weight up. The sum numbers of the two hands were recorded.

The back strength was tested by trunk lift. Participants used the muscles of the back to lift the upper body up and to hold the position for at least 1 s; after three trials, the best score was recorded.

The standing long jump tested the children's lower limbs' explosive strength, which requires speed, coordination, and explosive movement. Children were asked to jump as far as possible with two feet from a standing position. The performance was tested and measured as the distance jumped in centimeters. After 3 trials, the best score was recorded.

Flexibility was assessed by the modified sit-and-reach test (flexibility of the hamstring and lower back); participants sat down at the test apparatus. One leg was fully extended with the foot flat against the testing instruments; the other knee was bent. The participants reached directly forward with both hands and held the position for at least 1 s. After 3 trials, the maximum value was used to reflect flexibility. Each leg's flexibility was tested separately.

The pretest was performed one week prior to the initiation of the study, and the posttest was completed within one week of its conclusion. All tests were undertaken by the students of the Department of Physical Education from BNU, who were trained in the administration of the BPFT and supervised by an instructor expert in adapted physical education.

2.3. Data Analysis. Data were analyzed using the SPSS 20.0 statistical software. The statistical significance level was set at 0.05. Descriptive statistics were conducted to describe the participants in this study and to calculate the mean and standard deviation. Paired-samples t-tests were used to test the pre- and postperformances of the two groups, which are aimed at finding if there were some progress made by children in the two groups after physical exercise. Independent-samples t-tests were used to test whether there were significant differences in pre- and postperformances

Table 4: Comparison of pre- and postphysical fitness tests of the two groups.

Variable	Pre- and posttests of the experimental group				Pre- and posttests of the control group			
	Mean	Std. dev.	t	p value	Mean	Std. dev.	t	p value
BMI	0.051	0.369	0.477	0.642	-0.033	0.070	-1.492	0.17
CU	-1.25	1.765	-2.454	0.032*	0.3	1.494	0.635	0.541
TL (cm)	-6.167	5.686	-3.757	0.003 *	-1.2	4.826	-0.786	0.452
DP	-7.917	7.621	-3.598	0.004 *	-0.1	4.458	-0.071	0.945
$S\&R_{(L)}$ (cm)	-1.5	4.89	-1.063	0.311	3.2	4.566	2.216	0.054
$S\&R_{(R)}$ (cm)	-1.083	4.379	-0.857	0.41	2.9	5.705	1.608	0.142
SLJ	-8.25	4.351	-6.568	≤0.001 *	-8.2	7.036	-3.685	0.005 *
10 m R (cm)	-27.42	30.077	-3.158	0.009 *	-17.4	53.217	-1.034	0.328

*Significant difference between pre- and posttest of the two groups, $p < 0.05$. CU: curl-up; TL: trunk lift; DP: dumbbell press; $S\&R_{(R)}$: sit&reach (right); $S\&R_{(L)}$: sit&reach (left); SLJ: standing long jump; 10 m R: 10 m PACER run; Std. dev.: standard deviation.

between the two groups. The assumption of homogeneity of variances (Levene's test) was violated for the 10 m PACER run test; the assumption of normality (Wilcoxon) was violated for the standing long jump test and the 10 m PACER run test; hence, the standing long jump test and the 10 m PACER run test were assessed by the Mann Whitney *U* test. There were no significant differences between groups before the intervention.

3. Results

The attendance rate of the two groups of children in the program was 97% (experimental group) and 95.5% (control group) separately, which made the results convincing.

3.1. Paired-Samples t-Test Results. From Table 4, it can be figured out that the experimental group children had greater improvements in five dependent variables of physical fitness ($p < 0.05$). The curl-up test ($t = -2.454$, $p = 0.032 < 0.05$), trunk lift test ($t = -3.757$, $p = 0.003 < 0.05$), dumbbell press test ($t = -3.598$, $p = 0.004 < 0.05$), standing long jump test ($t = -6.568$, $p \leq 0.001$), and 10 m PACER run test ($t = -3.158$, $p = 0.009 < 0.05$) had significant differences compared to pretest, except the BMI test and sit-and-reach test ($p > 0.05$). Only the standing long jump test ($t = -3.685$, $p = 0.005 < 0.05$) was significantly improved in the control group, while other parameters were not significantly different from the pretest. The curl-up test ($t = 0.635$, $p = 0.541 > 0.05$) and sit-and-reach test ($t_{(L)} = 2.216$, $p_{(L)} = 0.054 > 0.05$; $t_{(R)} = 1.608$, $p_{(R)} = 0.142 > 0.05$) even decreased slightly from the pretest.

3.2. Independent-Samples t-Test Results. In order to eliminate the interference of other factors on the experimental results, the physical fitness between the two groups was compared. At pretest, there was no significant difference in all parameters of physical fitness between the two groups. ($p > 0.05$). Hence, it could be concluded that participants in both groups were similar in relevant variables before the intervention began (Table 5). At posttest, there were significant differences between the two groups on the curl-up test ($p = 0.025 < 0.05$), dumbbell press test ($p = 0.038 < 0.05$), and sit-and-reach test ($p_{(L)} = 0.043 < 0.05$, $p_{(R)} = 0.047 < 0.05$). However, the BMI test ($p = 0.109 > 0.05$), trunk lift test ($p = 0.957 > 0.05$), standing long jump test ($p = 0.346 > 0.05$), and 10 m PACER run test ($p = 0.674 > 0.05$) showed no significant differences between the two groups.

From Tables 4 and 5, it can be found that muscle strength, especially abdominal strength, upper limb strength, and flexibility of the experimental group participants, improved significantly, compared with the control group.

4. Discussion

The aim of this study was to determine whether a well-designed ARG program had positive effects on IDD children's physical fitness. The program should be feasible and adaptable for children with IDD. Rhythmic gymnastics contained the elements of music, dance, and physical exercise. First, children could control their bodies freely in different directions through basic gymnastics movements. In addition, when manipulating with the apparatus, children could acquire dynamic balance and practice their hand-eye coordination. Furthermore, music plays an important role in rhythmic gymnastics. It can ease children's anxiety, promote the completion of sports tasks, and play a guiding role in the entire process of sports learning. For IDD children, more feasible artistic gymnastics programs are needed to promote their physical and mental health.

4.1. Promoting Children's Participation. All children love games. Children in the experimental group participated in multiple games, such as racing games and various animal-imitating actions, which made the ARG program more attractive and could induce children to participate in sports activities according to their own wishes. Music is used to satisfy children's attention needs. Previous research has shown that music or rhythm can help increase the attention of IDD children [22] and also make them more interested in what they are doing [23]. Lasma and Rachman's research found that due to the rhythm and fun that accompanies music, the daily training of artistic gymnastics can improve mood [24]. When the music starts playing, the children focus on the teacher and shake their body spontaneously following

Table 5: Comparison of pre- and postphysical fitness tests between the two groups.

Variable	Groups	Pre Mean	Pre Std. dev.	p value	Post Mean	Post Std. dev.	p value
BMI	Experimental	17.37	2.128	0.107	17.32	1.958	0.109
	Control	15.79	2.249		15.83	2.228	
CU	Experimental	7.42	2.275	0.818	8.67	1.67	0.025 *
	Control	7.2	2.044		6.9	1.729	
TL	Experimental	18.833	7.998	0.957	25	6.12	0.058
	Control	19	5.85		20.2	4.803	
DP	Experimental	15.08	7.192	0.85	23	11.552	0.038 *
	Control	14.5	6.964		14.6	5.232	
$S\&R_{(L)}$ (cm)	Experimental	1.892	6.457	0.39	3.433	8.426	0.043 *
	Control	-0.63	7.913		-3.85	7.502	
$S\&R_{(R)}$ (cm)	Experimental	-0.275	7.376	0.415	0.8	7.56	0.047 *
	Control	-3.01	7.549		-6.03	6.97	
SLJ	Experimental	32	13.778	0.381	40.25	17.5	0.346
	Control	30.1	23.106		38.3	29.522	
10 m R (cm)	Experimental	121.75	33.987	0.628	149.17	40.43	0.674
	Control	127.8	51.592		145.2	66.661	

*Significant difference between pre- and posttest of the two groups, $p < 0.05$. CU: curl-up; TL: trunk lift; DP: dumbbell press; $S\&R_{(R)}$: sit&reach (right); $S\&R_{(L)}$: sit&reach (left); SLJ: standing long jump; 10 m R: 10 m PACER run; Std. dev.: standard deviation.

the music. During competitions, each child was actively encouraged by the teacher and showed enthusiasm in the company of his companion. In an interesting learning atmosphere, children's emotions have gradually stabilized, and learning efficiency has also improved.

4.2. Positive Impacts of the Two Different Courses. The results showed that after 16 weeks of physical training, the physical health parameters of most children in both groups showed an upward trend. It can be concluded that different forms of exercise can have a positive effect on physical health. These results also indicate that exercise may result in increased physical activities to make people with intellectual disabilities healthier, which is consistent with Heller's research [25]. Research studies of Wu et al., Hayakawa and Kobayashi, and Halle et al. also show that physical exercise and sports have a positive effect on the physical health of participants in special needs groups [26–28]. In our study, IDD children from the experimental group had significantly improved upper limb strength and endurance compared with the pretest. Part of the reason may be that ARG courses are more interesting than traditional functional exercises. Therefore, the motivations of children were stimulated and they were willing to exercise for a long time. IDD children's motivations are hard to inspire, but it is important to complete a large amount of exercise tasks. In the ARG program, the core strength training of children was arranged to promote the growth of core muscles and deep small muscle groups of the bodies, which they usually cannot exercise. In order to improve children's upper limb strength, abdominal strength, and back muscle strength, various types of crawling competitions are set up. Therefore, after the experiment, the curl-ups and dumbbell press results of the children in the experimental group improved more than the control group.

4.3. Effects of the ARG on Improving the Physical Fitness Seemed Better. The results showed that the muscle strength, explosive power, and aerobic exercise capacity of the children in the experimental group were greatly improved, compared with the pretest. This may be promoted by aerobic gymnastics, because basic gymnastics has a positive effect on the children's muscular strength and endurance and the explosive power of the upper and lower limbs. Previous studies have shown that aerobic gymnastics has a positive effect on balance ability [29–31], body coordination [32–35], muscle strength, muscle endurance, and flexibility [30, 36, 37] of the practitioner. Strength, balance, and body coordination contribute to the development of participants' motor skills and physical fitness, which is essential for building a healthier life. Mehrtash et al. explain that special aerobic gymnastics training can affect young boys' explosiveness, dynamic and static muscle endurance, flexibility, and exercise frequency [38]. Akyol and Pektas's research shows that the combination of gymnastics training and music can effectively improve the balance ability, coordination, and flexibility of DS and ASD children [39]. At present, the topic of how gymnastics improves the fitness of special children is relatively new, and research in this area is not much.

4.3.1. Aerobic Capacity. Aerobic capacity is one of the qualities to be developed in rhythmic gymnastics which requires a long time of technical and physical exercises. The muscular endurance and aerobic capacity of children in the experimental group were improved. Through continuous vertical and horizontal jumping in different directions in the ARG program, children's lower limb strength and dynamic balance have been improved, and standing long-distance jumping has also been improved. In addition, long-term aerobic exercise can promote children's aerobic function. Compared with routine tests, children can run longer distances at a stable speed. Studies have shown that moderate to intense aerobic exercise can improve the cardiovascular system and respiratory system [40]. In the ARG courses, children with IDD carried out the aerobic exercise in rhythm continuously to improve their aerobic capacity. The data in our experiment is consistent with the result of Silva et al.'s research. In her study, gymnastics participants achieved better results than nonparticipants on the six-minute walk test, indicating that participants in gymnastics events had better aerobic endurance [41]. Research studies of Dowdy et al., Lestari et al., and Montosa et al. have shown that the aerobic capacity and maximal oxygen uptake (VO_2Max) of participants can be improved through aerobic activities such as aerobic dance [42–44]. The above studies have demonstrated the improvement effect of aerobic exercise on cardiorespiratory fitness for different populations. Their research supports to a certain extent the conclusion in this paper that gymnastics may enhance the cardiorespiratory fitness of special children.

4.3.2. Muscle Strength. Muscle strength is related to intelligence. Usually, children with IDD shows weak muscle strength, but muscle strength is important for health, for keeping good body shape, and for gaining independence in activities of daily living [45]. In our study, muscle strength and endurance of the experimental group improved significantly compared to pretest. The data is consistent with studies of Zaharia et al. and Batista et al. that aerobics is a great help for strength [46, 47]. *Upper limb motor function* is an essential component to complete the fundamental motors required in daily life, such as moving, lifting, and holding stuffs. In our study, the upper limb strength (dumbbell press test) of children in the experimental group may be improved by crawling using the upper limbs to control the body. The muscles of the extremities continuously overcome resistance and contract continuously through repeated exercise. Through rhythmic exercise and manipulation of equipment, the muscles can be contracted to increase the strength of the upper limbs. *Abdominal strength* can be enhanced by imitating animal movements, such as frog balance, monkey jumping, and various core strength training exercises. Stimulating abdominal strength will also make the child's motor skills more proficient. *Lower limb explosive strength* can be measured by the standing long jump test. Both groups of children improved significantly in this test, which reflected the increased control, coordination, and explosive movement of the children. It can be inferred that various functional motor skills in the control group, such as squats, standing vertical jumps, and other simple body movements, can enhance children's lower limbs. Skopal et al.'s and Douda's research studies show that gymnastics has a positive effect on participants' lower limb strength [48, 49]. Abalo et al.'s research shows that aerobic gymnastics participants perform better in vertical jumping strength, which means that their lower extremity explosion intensity has been significantly improved through gymnastics exercises [50]. Piazza et al.'s also concluded that practicing rhythmic gymnastics can improve athletes' lower limb strength [51]. Douda and Tokmakidis believe that the reason why gymnastics improves the strength of lower limbs is that gymnastics could strengthen participants' musculoskeletal and nervous systems through systematic, repetitive, and progressive exercises [52]. Although the research object is not children with special needs, the above research provides theoretical support for our research.

4.3.3. Flexibility. The sit-and-reach test was used to determine the flexibility. The results showed that the children in the experimental group performed better than those in the control group, and there were significant differences between the two groups. Although the progress of the children in the experimental group was small, the control group children were less flexible than before. This means that according to ARG practice, the experimental group children kept their flexibility stable and had a substantial increase. Gymnastics plays an important role in promoting the flexibility of the participants' body [53, 54]. Various forms of limb stretching and basic gymnastics movements in gymnastics can increase the flexibility of the muscles and spine. In Batista et al.'s study, gymnasts' lower limbs exhibited higher active and passive flexibility [53]. Hence, in the 1960s, Ohyama's research showed that participants' flexibility (trunk flexion, extension, and lateral bending) developed after two weeks of gymnastics training, which is similar to our research findings [55].

4.3.4. BMI. At present, most of the studies on BMI and aerobic fitness mainly target nondisabled groups. In the study of Montosa et al., girls and adolescents had low BMI, waist circumference, and body fat percentage after aerobic exercises [56]. Gerstl et al.'s research also shows that rhythmic gymnastics has a positive effect on girls' BMI [57]. Miteva et al.'s research shows that gymnasts have a low percentage of body fat and a high percentage of muscle mass [58]. For IDD children, Bo et al. believe that aerobic exercise could reduce their BMI index [59], while Pitetti et al. and Hinckson et al. believe that aerobic exercise has little effect on the BMI of IDD children [60, 61]. The conclusion in this study is consistent with the research of Pitetti et al. and Hinckson et al., which is different from the other abovementioned research studies. One possible reason lies in the particularity of the research object in this study. IDD children are inferior to nondisabled groups in physical strength, motor skills, and intelligence, which prevents IDD children from reaching maximum exercise intensity in each class. Furthermore, the intervention duration of the ARG program in this study was relatively short (4 months) to evaluate the changes of body composition in IDD children.

Results of our ARG program support the idea that properly selected exercise can improve the development of physical fitness in children with IDD. Our study has limitations. First, the sample size is small. In order to distinguish between different forms of disability that may exist between accurate diagnoses, a larger sample size is required, and the popularization of the results requires further examination through a large sample size. Second, there are not many schools with special needs participating in the program. It is necessary to verify the promotion of the ARG program in more schools, and when all schools have obtained the same effect, this can reflect more stable and reliable conclusions.

5. Conclusion

This research demonstrated that after participating in a 16-week ARG program which targeted the development of rhythmic movement skills and basic gymnastics exercise, the levels of health-related physical fitness of children with IDD improved. Moreover, significant improvements were reported for most of the physical fitness parameters, such as muscle strength, aerobic capacity, and explosive strength when compared to the pretest. The ARG program provided rhythmic movements that were safe and feasible for children with IDD as evidenced by the progress participants made. Long-term and feasible exercise participation needs to be emphasized to promote physical fitness. However, future research could be needed to examine how well these physical fitness improvements are maintained.

Data Availability

The data was collected from the pretest and the posttest of the experiment.

Conflicts of Interest

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' Contributions

Chenchen XU was in charge of the literature review and conducted the experiment, data collection, and writing of the manuscript; Mengxue KANG was responsible for data analysis and interpretation and for editing the draft of the manuscript; Mingyan YAO was in charge of the research concept and teaching instruction. Guanting DUAN was responsible for teaching courses.

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Research Article

Which Neighborhood Destinations Matter in the Asian Context? The Role of Destinations in Older Adults' Physical Activity and Sedentary Behaviors

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Background. Neighborhood destinations play important roles in daily activity levels of older adults. However, little is known about how specific destinations are associated with these activities and/or sedentary behaviors, especially in Asia. This study investigated how neighborhood destinations were associated with physical activity recommendations and excessive sedentary time among older adults. *Methods*. A telephone-based survey was conducted to collect cross-sectional data on the sociodemographic variables, residential neighborhoods, physical activities, and sedentary behaviors of 1,040 adults aged 65 years and above. Using data derived from Geographic Information Systems (GIS), an adjusted logistic regression was performed to examine the relationships between five neighborhood destination types (i.e., recreational facilities, utilitarian destinations, transit stops, temples, and schools) and both overall physical activity level and sedentary behavior. *Results*. Significant interactions related to physical activity and sedentary behavior were observed based on both gender and neighborhood destinations. After adjusting for potential confounders, older men living in neighborhoods containing higher numbers of temples were more likely to achieve physical activity recommendations (OR = 1.85; 95% CI: 1.16–2.96). On the other hand, older women living in neighborhoods containing higher numbers of utilitarian destinations were more likely to engage in excessive sedentary time (OR = 1.70; 95% CI: 1.12–2.56). *Conclusions*. In Asia, the presence of favorable local neighborhood temples may support physical activity levels for older men, while utilitarian destinations (which have previously been found to support activeness) may be related to excessive sedentary behaviors in older women.

1. Background

The older adult population is now increasing on a global scale. A United Nations report indicates that Taiwan is expected to be among the top 10 most-aged countries by 2050 (with more than 40% of the population aged 60 or over) [1]. A key aspect of promoting healthy and active aging in these societies is to ensure that older adults maintain the functional abilities necessary to facilitate health and well-being [2]. Research has shown that physical inactivity and sedentary behavior are the two modifiable behavioral risk factors related to daily physical function in older adults [3, 4]. In addition to the adverse impacts on physical independence, physical inactivity and prolonged sedentary time are related to higher risks of mortality and noncommunicable diseases in older adults [5, 6]. In order to make long-term changes in larger populations, it is critical to develop effective strategies for older adults through urban design and environmental initiatives.

Ecological models provide theoretical bases for understanding the role of environmental walkable attributes on physical activity [7] and sedentary behavior [8]. These models can thus inform initiatives designed to promote healthy and active ageing. In particular, neighborhoods with good access to destinations within walkable distances may support daily resident activity [9]. Previous studies have emphasized that physical activity among older adults can positively be influenced by the presence of neighborhood destinations, including utilitarian facilities (i.e., local stores and services), recreational areas (i.e., parks and sports facilities), and transit stops [9–11]. However, few studies have examined how a variety of neighborhood destination options relates to sedentary behaviors in older adults. In addition to utilitarian, recreational, and public transit destinations, neighborhood schools can also serve as public open spaces to provide opportunities for older adults to engage in daily physical activity. Based on local cultural and environmental contexts, temples can be considered distinct neighborhood destinations in a number of Asian countries, as well. Most of the Taiwanese population (around 70%) practices Buddhism, Dao, or a folk religion (i.e., superstitious beliefs) [12]. There is also a considerable density of temples in Taiwan (i.e., more than 12,000 total; one for every 2,000 people in 2018) [13, 14]. Neighborhood temples thus play a central role in everyday religious and social activity for Taiwanese seniors. We therefore hypothesized that neighborhoods containing a variety of destinations (e.g., recreational facilities, utilitarian destinations, transit stops, temples, and schools) were positively associated with physical activity levels in older adults (i.e., more physical activity resulting from trips between the home and destination), but negatively related to sedentary behavior (i.e., less sedentary time spent in the home). This study strengthened the evidence base and examined age-friendly environments in Asian contexts to investigate how a broad range of neighborhood destinations were related to physical activity levels and sedentary behaviors in older adults.

2. Methods

2.1. Participants and Procedures. A cross-sectional telephone survey using a computer-assisted telephone interviewing (CATI) technique was conducted among older Taiwanese adults in 2017. We acquired a representative sample that closely matched the characteristics of the older adult population in Taiwan using a two-phase sampling procedure. The first phase involved dividing Taiwan into four geographic areas (i.e., northern, southern, western, and eastern). The second phase involved randomly selecting respondents of the desired sex and age attributes. Well-trained interviewers (at least 8 hours of training for research ethics, questionnaire, and interviewing skills) then conducted a standardized questionnaire during each telephone survey. A total of 3,282 older adults were reached. Of these, 1,068 completed the survey (a response rate of 32.5%). No incentives were provided. Verbal informed consent was obtained at the beginning of each phone survey. All procedures used in this study were reviewed and confirmed by the Research Ethics Committee of National Taiwan Normal University (REC number: 201706HM020).

2.2. Self-Reported Physical Activity and Sedentary Behavior

2.2.1. Physical Activity. The total amount of physical activity among older adults was assessed using the International Physical Activity Questionnaire-short version (IPAQ-SV). The test-retest reliability and criterion validity of the Taiwanese IPAQ-SV was both high ($r = 0.78$) and acceptable ($r = 0.31 - 0.41$) [15]. The Taiwanese IPAQ-SV is available for use via telephone survey and is thus widely utilized in phone surveys among older adult populations in Taiwan [16, 17]. Three physical activity types were determined as follows: (1) vigorous-intensity physical activity, (2) moderate-intensity physical activity (excluding walking), and (3) walking. The time spent in each of these three physical activities was calculated by multiplying frequency (i.e., how many times per week) by duration (i.e., how many hours and minutes per day). The sum indicated total physical activity. According to the recommended levels of physical activity for older adults [5], we categorized physical activity into two levels (i.e., "not achieving the physical activity recommendation (less than 150 min/week)" and "achieving the physical activity recommendation (equal to or greater than 150 min/week)".

2.2.2. Sedentary Behavior. The total time spent in sedentary behavior was measured using the validated Sedentary Behavior Questionnaire for the Elderly in Taiwan [18]. Total sedentary time was calculated for a seven-day period prior to taking the survey by adding the time spent on the following activities: screen-based sedentary time, reading, chatting with others, eating, sitting for hobbies, sitting while working or volunteering, and other sedentary activities. We categorized overall sedentary time into "less than eight hours/day" and "more than eight hours/day" using the cut-off point for heightened risk for all-cause mortality in older adults [19].

2.3. Objective Neighborhood Destinations. This study examined five types of neighborhood destinations (i.e., recreational facilities, utilitarian destinations, temples, schools, and public transportation). The data used for these destinations were obtained from the National Land Surveying and Mapping Center and Ministry of the Interior in Taiwan [20, 21]. Neighborhood destinations were assessed using geographic information systems (GIS) software (ArcGIS Pro; ESRI, Redlands, CA). The sum of each destination was computed for each participant's geocoded residential neighborhood. Each destination was categorized into "high" and "low" categories according to median value. The following five neighborhood destination types were revealed:

(i) Recreational facilities. The total number of parks and sports facilities. The sum of recreational facilities was categorized into "high ($N \geq 1$)" and "low ($N = 0$)."

(ii) Utilitarian destinations. The total number of shops, convenience stores, supermarkets, post offices, libraries, book stores, restaurants, banks, and pharmacies. The sum of utilitarian destinations was categorized into "high ($N \geq 4$)" and "low ($N < 4$)."

(iii) Temples. The total numbers of temples related to Buddhist, Daoist, and folk religions (churches and chapels were not included). The sum of temples was categorized into "high ($N \geq 2$)" and "low ($N < 2$)."

(iv) Schools. The total numbers of elementary schools, junior high schools, high schools, colleges, and universities. The sum of schools was categorized into "high ($N \geq 2$)" and "low ($N < 2$)."

(v) Public transportation. The total number of stations and bus stops. The sum of public transportation was categorized into "high ($N \geq 12$)" and "low ($N < 12$)."

2.4. Sociodemographic Variables. Participants were asked to report their age, gender, current marital status, living status, educational level, employment status, health behaviors (i.e., smoking status, alcohol consumption, and diet), height, weight (i.e., body mass index (BMI)), and self-rated health.

2.5. Statistical Analyses. Data were analyzed from 1,040 respondents who had no missing data. Binary logistic regression models were used to analyze the relationships between the five types of destinations and both physical activity levels and sedentary behaviors for the total sample (adjusted for potential confounders). Likelihood ratio tests were then conducted to examine the interaction terms for the outcome variables (i.e., physical activity and sedentary behavior) between objective neighborhood destinations and gender. The sample was divided according to gender when significant interactions were found. Finally, subgroup analyses were conducted based on gender. Odds ratios and 95% confidence intervals (CIs) were computed for each variable using IBM SPSS 25.0 (significance was set at $P < 0.05$).

3. Results

3.1. Participant Characteristics. Table 1 shows the basic characteristics for the total sample and according to gender. Mean respondent age (SD) was 73.04 (± 6.13) years (50.5% were men, 64.3% were aged 65–74 years, 30.6% had tertiary degrees, 10.3% had full-time jobs, 75.9% were married, 85.7% were living with others, 7.0% were current smokers, 9.7% consumed alcohol, 82.3% had healthy diets, 12.3% reported poor health status, and 52.8% were of normal-weight). A total of 79.3% respondents completed at least 150 minutes of weekly physical activity, while 30.9% engaged in daily sedentary behavior for more than eight hours. Chi-square tests revealed that older men were more likely to be married, have full-time jobs, tertiary educations, smoke, and consume alcohol.

3.2. Objective Neighborhood Destinations Associated with Physical Activity and Sedentary Behavior (Total Sample). For the total sample, older adults living in neighborhoods with higher numbers of temples were more likely to engage in physical activity adding up to at least 150 minutes/week (OR = 1.71 ; 95% CI: 1.21–2.41). Older adults living in neighborhoods with greater numbers of utilitarian destinations were more likely to engage in sedentary time lasting more than eight hours/day (OR = 1.48; 95% CI: 1.12–1.95) (Table 2).

3.3. Interactions between Gender and Objective Neighborhood Environment. Significant interactions relating to physical activity were observed between gender and temples ($P = 0.03$). Significant interactions relating to sedentary behavior were found between gender and utilitarian destinations ($P = 0.04$) (Table 3).

3.4. Objective Neighborhood Destinations Associated with Physical Activity and Sedentary Behavior in Older Men and Women. A gender stratification revealed that neighborhoods with higher numbers of temples were positively associated with the achievement of physical activity recommendations in older men (OR = 1.85; 95% CI: 1.16–2.96). On the other hand, neighborhoods with higher numbers of utilitarian destinations were related to excessive sedentary time in older women (OR = 1.70; 95% CI: 1.12–2.56) (Tables 4 and 5).

4. Discussion

This is the first study to examine a range of objective neighborhood destinations and their relationships with both physical activity levels and sedentary behaviors among older populations in an Asian context. Results revealed that different neighborhood destinations had specific behavioral effects according to gender. This is consistent with previous findings [17]. Our results showed that a higher number of neighborhood temples aided older men in meeting their daily physical activity recommendations, while a greater number of utilitarian destinations was associated with excessive sedentary time in older women. These findings may provide two critical implications for urban policy and planning initiatives designed to promote "Active Aging" in Asian countries. First, neighborhood temples should be considered prominent local destinations for promoting daily physical activity levels for older men. Second, although previous studies have found that utilitarian destinations were related to increased walking time [9, 22] (in the Asian context, see [23, 24], walking-supportive environmental attributes may increase sedentary behavior for older adults in Asian countries.

This study uniquely found that higher numbers of neighborhood temples were positively associated with older men meeting the recommended 150 minutes of total weekly physical activity. It is traditionally assumed that men and women have distinct gender roles in a number of Asian cultures (e.g., Japanese, Korean, and Chinese). Here, women are more likely to be responsible for housework [25, 26]. On the other hand, older men may have more free time. Here, temples may provide a "Third Place (social surroundings separate from the usual social environments)" [27] in which older men can engage in social events and religious activities in the Taiwanese cultural context. Easy access to neighborhood temples can thus motivate older men to engage in increased physical activity while traveling to these locations from home. Previous studies have found that environmental

Table 1: Characteristics of the study participants ($N = 1{,}040$).

	Total sample ($N = 1040$)		Older men ($N = 525$)		Older women ($N = 515$)		
	N	%	N	%	N	%	P value[a]
Age group (years)							0.26
65-74	669	64.3%	329	62.7%	340	66.0%	
75+	371	35.7%	196	37.3%	175	34.0%	
Marital status							<0.001*
Married	789	75.9%	428	81.5%	361	70.1%	
Unmarried	251	24.1%	97	18.5%	154	29.9%	
Employment status							0.001*
Full-time job	107	10.3%	71	13.5%	36	7.0%	
No full-time job	933	89.7%	454	86.5%	479	93.0%	
Educational level (years)							<0.001*
<13	722	69.4%	336	64.0%	386	75.0%	
≥13	318	30.6%	189	36.0%	129	25.0%	
Living status							0.83
Alone	149	14.3%	74	14.1%	75	14.6%	
With others	891	85.7%	451	85.9%	440	85.4%	
Current smoking status							<0.001*
Yes	73	7.0%	66	12.6%	7	1.4%	
No	967	93.0%	459	87.4%	508	98.6%	
Alcohol consumption							<0.001*
Yes	101	9.7%	89	17.0%	12	2.3%	
No	939	90.3%	436	83.0%	503	97.7%	
Healthy diet							0.04*
Yes	856	82.3%	420	80.0%	436	84.7%	
No	184	17.7%	105	20.0%	79	15.3%	
BMI (kg/m^2)							0.52
Normal weight	549	52.8%	272	51.8%	277	53.8%	
Not normal weight	491	47.2%	253	48.2%	238	46.2%	
Self-rated health							0.07
Good	493	47.4%	266	50.7%	227	44.1%	
Fair	419	40.3%	194	37.0%	225	43.7%	
Poor	128	12.3%	65	12.4%	63	12.2%	
Physical activity							0.49
150+ min/week	825	79.3%	412	78.5%	413	80.2%	
<150 min/week	215	20.7%	113	21.5%	102	19.8%	
Sedentary behavior							0.35
8+ hours/day	321	30.9%	169	32.2%	152	29.5%	
<8 hours/day	719	69.1%	356	67.8%	363	70.5%	

[a]Chi-square tests.
*$P < .05$.

settings (e.g., shopping malls [28] and parks [29]) can be used for community-level physical activity programs or interventions. Our results also suggest that neighborhood temples can serve as important environmental settings for effective community-based physical activity interventions among older men. In this regard, urban planners in Taiwan may consider how religious spaces can be used to support aging populations.

Contrary to our hypothesis, we also found that neighborhoods with more utilitarian destinations were associated with excessive sedentary time among older women. This is consistent with previous findings in the Asian context asserting that walkable neighborhood attributes were positively associated with sedentary behaviors [23, 24]. Here, it is possible that neighborhoods with higher numbers of utilitarian destinations

Table 2: Associations of objectively measured neighborhood destinations with physical activity and sedentary behavior in the total sample.

	Odds of meeting physical activity recommendation			Odds of excessive sedentary time		
	OR	95% CI	P	OR	95% CI	P
Recreational facilities						
Low		1.00 (ref.)			1.00 (ref.)	
High	1.06	0.77-1.47	0.72	1.32	0.98-1.77	0.07
Utilitarian destinations						
Low		1.00 (ref.)			1.00 (ref.)	
High	1.01	0.74-1.39	0.92	1.48	1.12-1.95	0.006*
Temple						
Low		1.00 (ref.)			1.00 (ref.)	
High	1.71	1.21-2.41	0.002*	1.10	0.76-1.34	0.96
Schools						
Low		1.00 (ref.)			1.00 (ref.)	
High	1.23	0.90-1.68	0.19	1.17	0.89-1.53	0.27
Public transportation						
Low		1.00 (ref.)			1.00 (ref.)	
High	0.91	0.66-1.24	0.54	1.21	0.92-1.59	0.18

Adjusted for gender, age, current marital status, living status, educational level, employment status, smoking status, alcohol consumption, healthy diet, BMI, and self-rated health. *Statistically significant ($P < .05$).

Table 3: Statistical significance of the interactions between gender and variables related to destinations using binary logistic regression models.

Objective neighborhood destinations	P value for interaction term with gender	
	Physical activity P value	Sedentary behavior P value
Recreational facilities	0.82	0.15
Utilitarian destinations	0.81	0.04*
Temple	0.03*	0.92
Schools	0.35	0.38
Public transportation	0.72	0.20

Adjusted for age, current marital status, living status, educational level, employment status, smoking status, alcohol consumption, healthy diet, BMI, and self-rated health.
*Statistically significant ($P < .05$).

reduce the time it takes older women to complete daily errands. Such individuals would thus have increased time to engage in sedentary behaviors. First, these results suggest that the possible negative impacts of favorable neighborhood destinations on sedentary behavior should be considered when planning intervention programs. Second, an increasing number of studies are finding different environmental/behavioral associations between Western and Asian countries. Our results thus suggest the importance of further examining these relationships in the Asian context.

This study had several limitations. First, it employed a cross-sectional design that may have limited the causal inferences between neighborhood destinations and active/sedentary behaviors among older adults. Second, respondents self-reported their physical activities and sedentary behaviors. Responses were thus subject to recall bias. Further studies should thus attempt to objectively measure these factors among older adults. Finally, older adults in Taiwan may be reluctant to report their exact residential addresses [23]. The neighborhood destinations used in this study were thus obtained according to participant residential neighborhood rather than exact residential addresses. Nevertheless, residential neighborhood units have widely been used as validated geographic areas when measuring walkability attributes [30].

Table 4: Associations of the objectively measured neighborhood destinations with physical activity by gender.

	Odds of meeting physical activity recommendation					
	Older men			Older women		
	OR	95% CI	P	OR	95% CI	P
Temple						
Low		1.00 (ref.)			1.00 (ref.)	
High	1.85	1.16-2.96	0.01*	1.52	0.91-2.54	0.11

Adjusted for age, current marital status, living status, educational level, employment status, smoking status, alcohol consumption, healthy diet, BMI, and self-rated health.
*Statistically significant ($P < .05$).

Table 5: Associations of the objectively measured neighborhood destinations with sedentary behavior by gender.

	Odds of excessive sedentary behavior					
	Older men			Older women		
	OR	95% CI	P	OR	95% CI	P
Utilitarian destinations						
Low		1.00 (ref.)			1.00 (ref.)	
High	1.33	0.91-1.97	0.14	1.70	1.12-2.56	0.01*

Adjusted for age, current marital status, living status, educational level, employment status, smoking status, alcohol consumption, healthy diet, BMI, and self-rated health.
*Statistically significant ($P < .05$).

5. Conclusions

Gender is a potential moderator between neighborhood destinations and physical activity/sedentary behavior among older adults. In Asia, conveniently located neighborhood temples may support older men in reaching their daily physical activity requirements, while utilitarian destinations (which have previously been found as activity-supportive attributes) may be related to excessive sedentary behavior among older women.

Data Availability

The dataset supporting the conclusions of this article is available in the laboratory of Dr. Yung Liao (corresponding author).

Disclosure

The Ministry of Science and Technology of Taiwan was not involved in the study design, data collection process, analysis, interpretation, or writing of this manuscript.

Conflicts of Interest

The author declares no conflicts of interest.

Authors' Contributions

Jong-Hwan Park and Jung-Hoon Park contributed equally to this work.

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Research Article

Impact of Acute Eccentric versus Concentric Running on Exercise-Induced Fat Oxidation and Postexercise Physical Activity in Untrained Men

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Introduction. This study aimed at comparing the rate of exercise-induced fat oxidation and postexercise free-living physical activity after constant-load flat running (FR) and downhill running (DHR) bouts at an intensity that elicited maximal fat oxidation. *Methods*. Participants were 11 healthy untrained men (mean age 25.6 ± 3.3 years; VO_{2max} 39.11 ± 8.05 ml/kg/min). The study included four visits. The first two visits determined the intensity of maximal fat oxidation during incremental FR and DHR tests. The second two visits involved constant-load FR or DHR at the intensity that elicited maximal fat oxidation in a counterbalanced order separated by two weeks. Gas exchange analysis was used to measure substrate oxidation during all exercise sessions. Sedentary time and physical activity were measured using ActiGraph triaxial accelerometers for three days including the day of exercise tests (the second day). *Results*. During the incremental exercise tests, fat oxidation was significantly greater during the first stage of FR ($P < 0.05$) but started to increase during the fourth stage of DHR, although this did not reach significance. Of the 11 participants, 7 had greater fat oxidation during DHR. During continuous constant-load running, fat oxidation was higher during DHR than FR but at only two stages was either significant or borderline significant, and the time/group interaction was not significant. There was no significant effect on sedentary time of time/group interaction ($P = 0.769$), but there was a significant effect of time ($P = 0.005$), and there was no significant effect on total physical activity of time/group interaction ($P = 0.283$) or time ($P = 0.602$). *Conclusion*. Acute aerobic eccentric exercise at an intensity eliciting maximal fat oxidation enhanced exercise-induced fat oxidation without worsening postexercise free-living physical activity, indicating it could be a useful training modality in weight management programs.

1. Introduction

Eccentric exercise such as downhill running requires less metabolic effort than traditional running (i.e., flat running). This type of exercise is therefore a promising training strategy for a nonactive population such as obese and sedentary individuals. For example, in a study involving obese women, 12 weeks of descending stair walking improved functional fitness and blood profile to a greater extent than did ascending stair walking [1]. Likewise, Julian et al. [2] found that 12-week eccentric cycling significantly improved insulin resistance while concentric cycling did not, although both types of training improved maximal oxygen consumption, body composition, and leg strength. Eccentric exercise can improve metabolic and physical characteristics with fewer training sessions; for example, one session a week of eccentric isokinetic contraction for eight weeks in untrained individuals increased resting energy expenditure and fat oxidation [3].

However, there are methodological issues surrounding studies measuring internal physiological effort using energy expenditure and substrate oxidation and external work load using speed and resistance during eccentric exercise, which require further experimental research. For example, Penailillo et al. [4] found that fat oxidation during acute eccentric cycling was 72% greater than concentric cycling, and energy expenditure was 36% lower than concentric cycling. However, this experimental study used similar relative oxygen consumption, meaning different absolute power output. In another study, when the relative exercise intensity was kept constant at 60% VO_{2peak}, there was no significant difference in fat oxidation between continuous 40-minute flat and downhill running bouts [5]. As fat oxidation is minimal at high-intensity exercise, the high intensity used in this study could explain the lack of difference between the conditions. Isacco et al. [6] compared concentric and eccentric cycling at 35% Vo_{2peak} for 45 min and found no significant differences in fat or carbohydrate (CHO) oxidation between the two conditions. However, it was not clear whether this intensity induced the greatest capacity for fat oxidation in both conditions. To examine this, a comparison study at the intensity that elicits maximal fat oxidation is required.

It is well established that moderate exercise intensity causes greater use of fat sources than higher intensity levels [7], and an optimal intensity that elicits maximal fat oxidation has been determined [8]. The level of fat oxidation in response to this optimal intensity differs according to several factors including mode, modality, gender, and fitness levels [9, 10] and has not been examined during eccentric exercise. Thus, the main aim of the present study was to compare the response of substrate oxidation at an intensity that elicits maximal fat oxidation during acute eccentric running compared to concentric flat running in healthy untrained men.

Many studies of traditional concentric exercise have found no effect of structured concentric exercise training on nonexercise energy expenditure and/or physical activity. For example, habitual physical activity and energy expenditure were monitored for 16 days in male and female participants, with four exercise bouts that expended 500 kcal performed in the second half of the intervention, and this study concluded that the exercise program did not change energy expenditure due to spontaneous activity [11]. A 2014 review concluded that there was limited evidence to support the hypothesis that prescribed exercise decreases nonexercise physical activity and energy expenditure, although proper techniques such as indirect calorimetry and doubly labeled water are required [12]. Unlike concentric traditional exercise, unaccustomed eccentric contractions produce muscle damage, soreness, and force impairment [13] that can last several days [14]. Such muscle soreness and damage decreases performance in strength and power tests in posteccentric cycling exercise [15]. The magnitude of muscle damage is affected by several factors including the intensity and slope of eccentric exercise [16]. We hypothesized that the intensity currently proposed to induce maximal fat oxidation causes low to mild muscle damage, such that it can increase exercise-induced fat oxidation with no impairment of postexercise free-living physical activity.

2. Methods

2.1. Participant Characteristics. The included participants were 11 healthy young men (mean age 25.6 ± 3.3 years; body mass index (BMI) $24.70 \pm 2.14\,kg/m^2$; VO_{2max} 39.11 ± 8.05 ml/kg/min; and maximal heart rate 191 ± 9 beats/min), who upon recruitment engaged in aerobic exercise for 30 to 150 minutes per week. This included recreational walking activities and job type (e.g., students of College of Sport Sciences and Physical Activity at King Saud University). Exclusion criteria included engagement in regular resistance training, BMI > $30\,kg/m^2$, sedentary behavior (i.e., did not perform any training in a typical week), or engagement in regular aerobic training for more than 150 minutes per week.

2.2. Study Procedure. The experiment had a crossover counterbalanced design separated by two weeks and took place at the Exercise Physiology Laboratories at the Exercise Physiology Department, College of Sport Sciences and Physical Activity, King Saud University (KSU). The laboratory is air-conditioned, with the temperature held constant at 21°C. The study included four visits: two to determine the intensity at which maximal fat oxidation was induced during concentric exercise (flat running) and eccentric exercise (downhill running). The second two visits involved continuous flat and downhill running at the intensity that elicited maximal fat oxidation. Gas exchange analysis was used to measure the substrate oxidation during all exercise sessions, as described below.

All participants were asked to maintain their normal dietary intake between tests and to replicate their average food intake as closely as possible on the day before the exercise tests. Participants were asked to abstain from strenuous exercise and excessive consumption of caffeine in the 24 h before the test. All participants were instructed to arrive at the laboratory between 8 am and 11 am, following an overnight fasting. The experiment was conducted with the human subjects' understanding and consent of the experimental process The Institutional Review Board (IRB) at KSU approved the study procedure (reference number KSU-SE-17-6).

2.3. Incremental and Constant-Load Exercise Tests. A graded exercise test was performed on a treadmill beginning at 4 km/h with a 0% gradient for 3 minutes per stage, with the speed increasing by 1 km/h per stage until the respiratory exchange ratio (RER) reached 1.0, in order to determine the intensity that elicited maximal fat oxidation. Maximal aerobic capacity was measured during the flat running (FR) test only, where participants rested for 10 minutes after the first stage and resumed running at a gradient of 3.5%, which increased by 2.5% every three minutes until volitional exhaustion was reached.

To determine the intensity that elicits maximal fat oxidation during downhill running (DHR), a graded exercise test was performed on a treadmill beginning at 4 km/h with a –

12% gradient for 3 minutes per stage, with the speed increasing by 1 km/h per stage until the RER reached 1.0.

Two running constant-load exercise tests were performed on separate days at gradients of 0% (FR) and –12% (DHR) for 40 minutes, consisting of 8 minutes of running at the intensity that elicited maximal fat oxidation during incremental FR and DHR interspersed by low-intensity walking for 2 minutes.

2.4. Measurement of Substrate Oxidation. Gas exchange was collected and analyzed during all exercise tests using the Parvo Medics Analyser Module (TrueOne® 2400, Metabolic Measurement System, Parvo Medics Inc., USA), which was calibrated for gas and flow meter before all tests following the manufacturer's guidelines. Participants also wore a Polar heart rate (HR) chest strap to monitor exercise-induced HR (Polar H10, Polar Electro 2020, NY, USA).

Expired air measurements were averaged every 30 seconds, and consumption of oxygen (VO_2) and carbon dioxide (VCO_2) in liters per minute and RER were exported to an Excel file. Fat and CHO oxidation were calculated using the following formulae:

$$\begin{aligned}\text{Total fat oxidation} &= 1.67\,VO_2 - 1.67\,VCO_2,\\ \text{Total CHO oxidation} &= 4.55\,VCO_2 - 3.21\,VO_2.\end{aligned} \quad (1)$$

2.5. Measurement of Sedentary Time and Physical Activity. The participants' sedentary time and physical activity were measured using ActiGraph triaxial accelerometers (wGT3X-BT, ActiGraph LLC, Pensacola, FL). Accelerometers were initialized, and then, data were downloaded and analyzed using ActiLife v6013.3 (ActiGraph LLC, Pensacola, FL). The participants were instructed to wear their accelerometer for three days, including the day of the exercise test (the second day). Participants were instructed to wear the accelerometers on their right hip at all times except when they were bathing or sleeping.

The raw data from the accelerometers were downloaded, and counts per minute (CPM) were calculated from the vertical axis movement. The wear time of the accelerometers was validated using the algorithm published by Troiano et al. [17]. Nonwear time was classified as a zero reading sustained for a period of 60 minutes with a tolerance of 1–2 minutes of counts between 0 and 100. Participants with valid data of a minimum of 600 minutes of wear time on all three days were included in the final analysis.

Cut-points developed by Freedson et al. [18] were used to categorize physical activity intensities as sedentary (<99 CPM), light activity (100–1951 CPM), moderate activity (1952–5724 CPM), vigorous activity (5725–9498 CPM), and very vigorous activity (≥9499 CPM).

2.6. Statistical Analysis. Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 25 for Windows (SPSS Statistics 25.0, IBM, NY, USA). Two-way repeated-measures tests were performed to analyze the exercise stages (five stages in each session) and exercise conditions (FR and DHR) for oxygen consumption and substrate oxidation. Two-way repeated-measures tests were also performed to analyze the exercise conditions (FR and DHR) and time of measurements (pre- and postexercise) for sedentary and total physical activity. Independent sample t-tests were conducted to evaluate significant differences between FR and DHR at each comparable time point of all tests. An α-level of 0.05 was used to determine statistical significance.

3. Results

The incremental running test showed significantly higher levels of oxygen consumption during FR than DHR at all stages from 4 to 8 km/h ($P < 0.001$), as shown in Table 1.

Fat oxidation was significantly greater during FR in the first stage ($P < 0.05$), while it started to increase from the fourth stage during DHR but did not reach significance. In the last two stages, RER was significantly higher during FR than during DHR ($P < 0.05$). Figure 1 shows the individual variation in the maximal fat oxidation during the incremental test of FR and DHR; 4 out of 11 participants had greater fat oxidation during FR.

During continuous constant-load running, there were no significant differences in VO_2 between FR and DHR, although the mean value of VO_2 was greater at all stages during DHR, leading to a significant time effect and time∗group effect, as shown in Table 2.

CHO oxidation was higher during FR than during DHR in four stages, but the differences were not significant. The fat oxidation was higher during DHR than during FR but at only two stages was this difference either significant or borderline significant, and time∗group was not significant. The average contribution of fat and CHO sources to energy expenditure was 38.3 ± 2.8% and 61.7 ± 2.8%, respectively, for FR and 52.0 ± 1.2% and 48.0 ± 1.2%, respectively, for DHR.

In terms of sedentary activity, there was no significant effect of time∗group ($P = 0.769$), and there was a significant effect of time ($P = 0.005$). Time spent in sedentary activity was higher before DHR than before FR by 74.2 min (95% confidence interval (CI) 4.6, 143.9; $t[10] = 2.376$; and $P = 0.039$) and after DHR than after FR by 90.4 min (95% CI 3.5, 177.3; $t[10] = 2.319$; and $P = 0.043$, Table 3).

For total physical activity, there was no significant effect of time∗group ($P = 0.283$), and there was no significant effect of time ($P = 0.602$). Time spent in total physical activity was higher after FR than after DHR by 72.7 min (95% CI 3.90, 141.5; $t[10] = 2.355$; and $P = 0.040$, Table 3).

4. Discussion

This study aimed at comparing the maximal fat oxidation during incremental FR and DHR tests and the rate of exercise-induced fat oxidation and postexercise free-living physical activity of constant-load FR and DHR exercise at the point of maximal fat oxidation. During the incremental exercise test, the response of fat oxidation at a matched running speed was higher during FR than during DHR at the first two stages but was higher during the later stages of DHR, although this difference was not significant. The maximal fat oxidation was greater during DHR in 7 out of 11

Table 1: Comparison between physiological responses during incremental flat running (FR) and downhill running (DHR) tests.

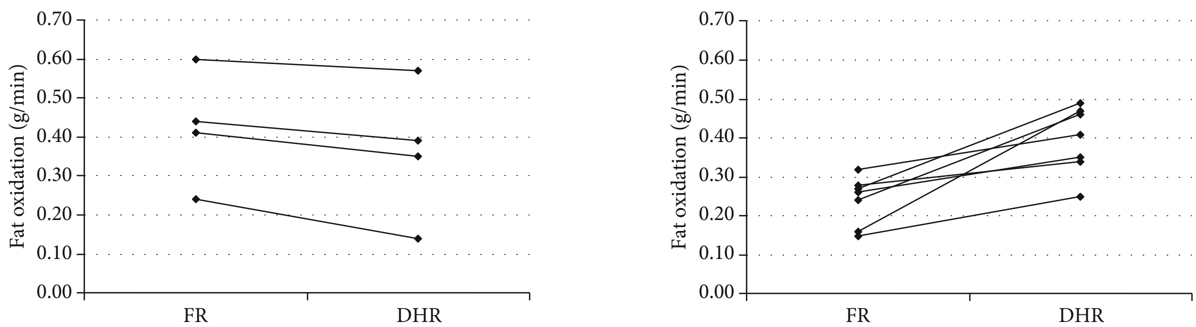
Speed	FR	DHR	Mean change (95% CI)	Percentage change (%)	P value
			VO_2 (ml/min/kg)		
4 km/h	9.35 ± 0.6	7.34 ± 0.7	2.01 (1.6-2.4)	21.45	<0.001
5 km/h	11.20 ± 0.7	8.18 ± 0.8	2.97 (2.3-3.7)	26.52	<0.001
6 km/h	14.84 ± 2.4	9.87 ± 0.9	4.98 (3.5-6.5)	33.56	<0.001
7 km/h	20.80 ± 2.2	15.84 ± 1.7	4.92 (3.7-6.2)	23.65	<0.001
8 km/h	25.34 ± 2.2	19.82 ± 1.5	5.51 (3.5-7.5)	21.74	<0.001
Time effect			<0.001		
Time∗group			<0.001		
			Fat oxidation (g/min)		
4 km/h	0.20 ± 0.08	0.10 ± 0.11	0.10 (0.04-0.17)	50	0.033
5 km/h	0.25 ± 0.11	0.16 ± 0.10	0.09 (0.009-0.18)	36	0.051
6 km/h	0.27 ± 0.15	0.20 ± 0.10	0.07 (-0.02-0.16)	25.9	0.231
7 km/h	0.22 ± 0.92	0.34 ± 0.13	-0.12 (-0.06-0.25)	54.4	0.186
8 km/h	0.16 ± 0.17	0.34 ± 0.14	-0.17 (-0.38-0.03)	106.3	0.071
Time effect			0.535		
Time∗group			0.060		
			CHO oxidation (g/min)		
4 km/h	0.46 ± 0.20	0.46 ± 0.31	0.003 (-0.21-0.21)	0.65	0.978
5 km/h	0.52 ± 0.24	0.38 ± 0.21	0.14 (-0.10-0.38)	26.92	0.180
6 km/h	0.89 ± 0.33	0.41 ± 0.22	0.47 (0.20-0.75)	52.81	0.001
7 km/h	1.71 ± 0.78	0.65 ± 0.31	1.06 (0.43-1.69)	61.99	0.034
8 km/h	2.05 ± 0.92	0.99 ± 0.42	1.06 (0.32-1.79)	51.71	0.012
Time effect			<0.001		
Time∗group			0.020		
			RER		
4 km/h	0.84 ± 0.05	0.89 ± 0.12	-0.05 (-0.12-0.03)	5.95	0.294
5 km/h	0.84 ± 0.06	0.84 ± 0.07	-0.01 (-0.07-0.06)	1.19	0.820
6 km/h	0.87 ± 0.05	0.83 ± 0.07	0.04 (-0.01-0.10)	4.59	0.192
7 km/h	0.92 ± 0.07	0.83 ± 0.06	0.09 (0.03-0.15)	9.78	0.007
8 km/h	0.94 ± 0.07	0.86 ± 0.06	0.08 (0.01-0.15)	8.51	0.034
Time effect			<0.001		
Time∗group			0.004		

Data are presented as mean ± SD. FR: flat running; DHR: downhill running; CI: confidence interval; CHO: carbohydrate; RER: respiratory exchange ratio. P value significant at $P < 0.05$, 0.01 level.

participants. The fat oxidation rate during exercise sustained at an intensity that elicited maximal fat oxidation was greater during DHR than during FR. Moreover, this intensity level of DHR did not affect postexercise free-living physical activity, which may suggest that it induced no or mild muscle damage.

The study participants were untrained young Saudi men, and their maximal fat oxidation was low, comparable with previously published sedentary, type 2 diabetes, and obese groups. For example, the maximal fat oxidation during FR and DHR in this study was close to or comparable with women with type 2 diabetes (0.38 g/min), and fat oxidation during FR and DHR was lower than untrained healthy women (0.54 g/min) [19]. The same outcomes were found in obese young men (0.38 ± 0.13 g/min) while fat oxidation in the active was 0.58 ± 0.07 g/min [20]. The low level of fat oxidation in the present healthy young male participants raises the question of whether ethnicity may [21] or may not [22, 23] partially explain variations of fat oxidation; further studies on Saudi and Arab populations are required to answer this.

In the constant-load exercise bouts, the increase in VO_2 was greater during DHR than during FR, which could be attributed to the increase of the VO_2 slow component due to greater fatigue on motor units during eccentric contraction forcing recruitment of additional motor units to achieve the same work rate [24]. This increase in mechanical



(a) Participants ($n = 4$) who had greater maximal fat oxidation during FR (b) Participants ($n = 7$) who had greater maximal fat oxidation during DHR

Figure 1: Individual variation in the maximal fat oxidation (a, b) during incremental exercise tests of flat running (FR) and downhill running (DHR).

demands during DHR was accompanied by an increase in HR. These mechanical demands of eccentric muscle contraction did not decelerate the response of fat oxidation with the constant-load exercise, but the muscles filled energy demands using CHO sources rather than using fat sources. We previously found that the alteration in exercise-induced energy demands during concentric moderate-intensity interval exercise is largely filled by CHO sources with no effect on the gradually constant increase in fat oxidation [25]. The rate of fat oxidation increased with exercise time (significant time effect), independent of exercise modality (insignificant time∗group effect), which is in line with the concept that fat is oxidized during constant-load exercise [26, 27].

The contribution of the fat source to energy expenditure during both conditions was not affected by time, remaining constant during both FR and DHR. Isacco et al. [6] found that the contribution of CHO and fat source in energy expenditure was 53.1% CHO and 46.9% fat during concentric exercise vs. 46.2% CHO and 53.8% fat during eccentric exercise. In our study, the contributions of CHO and fat sources to energy expenditure were 61.7% and 38.3%, respectively, during FR vs. 48.0% and 52.0%, respectively, during DHR. It should be noted that Isacco et al. [6] used a bicycle at 30 revolutions per minute, with the same relative intensity during concentric and eccentric exercises, but this does not explain the differences to our study in the concentric modality results but comparable eccentric modality results. Penailillo et al. [4] conducted exercise bouts at 60% of maximal concentric power output (relative intensity: 76% for concentric and 38% for eccentric) and found that both energy expenditure and CHO expenditure were lower during eccentric than concentric exercise by 36% and 42%, respectively, and fat utilization was greater during eccentric than concentric by 72%. This difference between concentric and eccentric exercises is greater than in the present study or in Isacco et al.'s study.

Several confounders should be considered when comparing the present concentric and eccentric outcomes with other available studies. For example, the −12% gradient used in the present study could increase cardiovascular and metabolic demands and muscle damage to a greater extent than gentler inclinations, such as between −5% and −10% [28]. Moreover, several factors such as insulin level [19], mode of exercise [29], and the recruitment of muscle mass during the test [30] influence the rate of exercise-induced fat oxidation. For example, when individuals performed cycling and rowing exercises at the same intensity, fat oxidation was greater during the rowing session, and this was likely due to the larger muscle mass recruited during rowing [30]. Lastly, Penailillo et al. [4] reported that all participants showed greater fat oxidation during eccentric exercise, while four of our study participants had a greater rate of fat oxidation during the concentric FR exercise (Figure 1). Large individual variations in the rate of maximal fat oxidation have been previously reported [31].

Considering the pre- and postexercise activity levels, our data showed that there were no significant interactions between exercise duration and modality and no statistically significant differences between pre- and postexercise in time spent in sedentary and physical activity in both exercise conditions. The small reduction in total physical activity after DHR (−4.7%) could be attributed to mild muscle damage, while physical activity after FR tended to increase (6.9%). This finding is in line with some previous studies in supporting the importance of low-intensity eccentric exercise in general population exercise programs. For example, downhill walking at 6 km/h and an inclination of −5% for 30 min caused mild muscle damage and delayed-onset muscle soreness the day after exercise compared with uphill walking at an inclination of 5%, but this did not cause significant impairment in glucose metabolism [32]. Likewise, low to mild muscle damage after eccentric exercise did not alter postexercise metabolic responses (i.e., glucose tolerance) [33]. Our results prove that performing eccentric exercise at an intensity that elicits maximal fat oxidation (i.e., speed at 7 to 8 km/h with an inclination of −12%) did not affect postexercise free-living physical activity.

It is known that an initial bout of acute eccentric exercise can cause increased postexercise muscle damage, which can be gradually relieved with subsequent repeated exercise bouts. However, the magnitude of impact during acute eccentric exercise and the local muscle adaptation during chronic eccentric training among heterogeneous individuals is not conclusively known. For example, in a study of active young men conducted in our laboratory, half of the participants showed no differences in voluntary muscle contraction capability between pre-, post-, and 24 h postacute eccentric

TABLE 2: Comparison between physiological responses during constant-load flat running (FR) and downhill running (DHR) tests.

Time	FR	DHR	Mean change (95% CI)	Percentage change (%)	P value
			VO_2 (ml/min/kg)		
8 minutes	15.48 ± 5.6	17.91 ± 4.8	-2.43 (-7.7-2.8)	15.69	0.413
18 minutes	15.21 ± 5.9	17.91 ± 4.8	-2.70 (-7.8-2.4)	17.75	0.273
28 minutes	15.32 ± 5.5	18.73 ± 5.5	-3.4 (-8.5-1.7)	22.19	0.184
38 minutes	15.42 ± 5.34	19.27 ± 5.8	-3.86 (-9.0-1.3)	25.03	0.139
48 minutes	15.89 ± 5.6	19.42 ± 5.8	-3.52 (-8.6-1.6)	22.15	0.186
Time effect			<0.001		
Time∗group			0.006		
			Fat oxidation (g/min)		
8 minutes	0.26 ± 0.15	0.38 ± 0.19	-0.13 (-0.25–-0.004)	50.0	0.120
18 minutes	0.22 ± 0.12	0.37 ± 0.21	-0.15 (-0.26–-0.04)	68.18	0.056
28 minutes	0.23 ± 0.13	0.41 ± 0.24	-0.18 (-0.32–-0.05)	78.26	0.046
38 minutes	0.25 ± 0.15	0.41 ± 0.24	-0.16 (-0.30–-0.02)	64.0	0.089
48 minutes	0.28 ± 0.14	0.42 ± 0.25	-0.14 (-0.28-0.01)	50	0.146
Time effect			0.016		
Time∗group			0.319		
			CHO oxidation (g/min)		
8 minutes	0.91 ± 0.43	0.76 ± 0.28	0.14 (-0.24-0.52)	15.38	0.384
18 minutes	0.97 ± 0.45	0.85 ± 0.36	0.12 (-0.33-0.57)	12.37	0.532
28 minutes	0.97 ± 0.49	0.83 ± 0.36	0.14 (-0.31-0.58)	14.43	0.487
38 minutes	0.91 ± 0.45	0.87 ± 0.36	0.04 (-0.40-0.48)	4.39	0.833
48 minutes	0.88 ± 0.43	0.88 ± 0.40	-0.01 (-0.43-0.42)	1.13	0.971
Time effect			0.420		
Time∗group			0.300		
			RER		
8 minutes	0.87 ± 0.06	0.83 ± 0.04	0.04 (-0.003-0.08)	4.59	0.113
18 minutes	0.89 ± 0.05	0.84 ± 0.05	0.05 (0.01-0.09)	5.62	0.041
28 minutes	0.89 ± 0.06	0.83 ± 0.04	0.05 (0.01-0.10)	5.62	0.036
38 minutes	0.88 ± 0.06	0.84 ± 0.04	0.04 (-0.01-0.08)	4.54	0.150
48 minutes	0.86 ± 0.06	0.84 ± 0.05	0.03 (-0.02-0.08)	3.49	0.274
Time effect			0.212		
Time∗group			0.323		
			HR (beat/min)		
8 minutes	112.3 ± 21.56	126.8 ± 22.50	-14.5 (-34.9-5.9)	12.91	0.158
18 minutes	112.80 ± 17.45	131.60 ± 21.87	-18.8 (-37.8-0.22)	16.67	0.048
28 minutes	117.40 ± 16.83	136.80 ± 25.34	-19.40 (-38.9-0.15)	16.52	0.059
38 minutes	115.3 ± 15.73	138.70 ± 28.14	-23.4 (-46.6–-0.22)	20.29	0.034
48 minutes	115.7 ± 22.25	141.80 ± 27.61	-26.1 (-52.9-0.68)	22.56	0.032
Time effect			<0.001		
Time∗group			0.053		

Data are presented as mean ± SD. FR: flat running; DHR: downhill running; CI: confidence interval; CHO: carbohydrate; RER: respiratory exchange ratio; HR: heart rate. P value significant at $P < 0.05$, 0.01 level.

Table 3: Time spent in sedentary and physical activity pre- and postexercise.

Variables	FR (mean ± SD)	DHR (mean ± SD)
Sedentary (minutes per day)		
Preexercise	702.5 ± 116.6	776.8 ± 76.3*
Postexercise	693.8 ± 70.9	784.2 ± 120.5*
Total physical activity (minutes per day)		
Preexercise	260.4 ± 86.3	235.6 ± 95.9
Postexercise	279.7 ± 96.8	225.0 ± 131.7*

Data are presented as mean ± SD. FR: flat running; DHR: downhill running. *Significantly different ($P \leq 0.05$) compared to FR.

exercise, demonstrating that the impact of acute eccentric exercise on muscle damage was minimal in this population [5]. Melanson et al. [34] stated that there are wide variations among individuals in their nonexercise physical activity response to structured exercise training.

5. Conclusion

With the qualification that not all participants had a greater rate of fat oxidation during incremental eccentric than concentric exercise bout, this study showed that acute aerobic eccentric exercise at an intensity eliciting maximal fat oxidation enhanced exercise-induced fat oxidation without worsening postexercise free-living physical activity, indicating it could be a useful training modality in weight management programs.

Future studies should investigate whether any expected improvement in body weight during DHR is due to the greater utilization of fat or due to the higher amount of work load compared to FR. Moreover, as the responses of VO_2 and HR during DHR were different from FR, and due to the fact that monitoring fat oxidation is not feasible during filed exercise training, understanding the adaptation of physiological parameters at the level of maximal fat oxidation should be examined in laboratory and field chronic experimental studies.

Data Availability

The data used to support the findings of this study are included within the article. For further information, please contact the corresponding author.

Conflicts of Interest

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

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Research Article

Evidence-Based Optimal Cutoff Values with the Validation of Criterion-Referenced Standards for Sarcopenic Elderly Fitness Improvement

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This study provides a newly updated perspective of information on severely screened 21 previous studies of the various measurement methods for improving physical fitness and providing determined cutoff values from our reserved elderly human database. We aimed to provide scientific evidence-based information regarding physical fitness standards for developing useful prognostics, promoting and maintaining health programs for sarcopenic elderly. 21 previous studies emphasizing criterion referenced standards and receiver operator characteristic (ROC) curve analyses for improving physical fitness were screened. For predicting the prevalence of sarcopenia, the *t*-test, logistic regression, linear regression, ROC curve analyses, and voluntary categorizations such as the twentieth or sixtieth percentile classification were used. Based on these scientific evidences, we determined cutoff values from our reserved DB and realized that 75 years for men and 70 years for women are the transitional period during which there are large declines in muscle and fat mass ($p < 0.01$), which reflects physical function tests ($p < 0.01$) in both genders. Using the six factors with ideal cutoff thresholds, an individual exercise program can be designed for alleviating symptoms of frailty caused by sarcopenia for the elderly.

1. Introduction

Sarcopenia is a progressive deterioration of the loss of muscular mass and strength during aging [1, 2]. Sarcopenia is significantly associated with declining physical activities, which induces a lower level of quality of life that eventually contributes to death. According to the European Working Group on Sarcopenia in Older People (EWGSOP), prognostic criteria for considering the treatment of sarcopenia include muscle mass (quantitative aspect), muscle strength (qualitative aspect), and physical performance [3, 4]. Effective interventions for ameliorating this syndrome have been considered, from pharmaceutical to nutritional and physical training aspects, to decelerate the gradual onset of the sarcopenic state. Jung et al. reported that a recommended diet may be associated with higher muscle mass function in Korean elderly people [5], and a traditional British dietary pattern is associated with a 2.1-fold increase in the risk of prevalent sarcopenia, even with adequate protein intake [6]. About 10% of community-dwelling older adults and 35% of them under institutional care fail to eat enough recommended daily protein intake (0.7 g/kg body weight/day) [7]. Especially, this study is focused on physical activities, which appear to be less adverse-effective than other methods and even lead to positively broad-ranging effects, not only on physical but also on psychological aspects of our bodies. Physical fitness is an important and prerequisite condition for the suitable exercise treatment as an intervention for decelerating the progression of sarcopenia, at the very least.

An inappropriate physical fitness level by way of physical inactivity can result in metabolic chronic diseases such as high blood pressure and diabetes. Declining physical fitness-related factors according to aging are raised, such as physiological function (muscle strength, balance, weight, grip strength, and BMI), fatigue, depression, and cognitive recognition, and improving these factors should be primarily

Table 1: The characteristics of elderly subjects.

	Men ($n = 585$)			Women ($n = 910$)		
	High muscle ($n = 397$)	Low muscle ($n = 188$)	p value	High muscle ($n = 618$)	Low muscle ($n = 292$)	p value
Age (yr)	70.92 ± 4.36	73.12 ± 5.13	<0.001	70.89 ± 4.91	73.94 ± 5.54	<0.001
High (cm)	167.67 ± 4.95	161.45 ± 4.78	<0.001	154.14 ± 4.29	148.19 ± 4.22	<0.001
Weight (kg)	68.74 ± 6.64	57.80 ± 7.19	<0.001	60.24 ± 7.06	50.74 ± 5.57	<0.001
BMI (kg/m^2)	24.48 ± 2.21	22.19 ± 2.45	<0.001	25.36 ± 3.13	23.16 ± 2.58	<0.001
Lean mass (kg)	28.60 ± 2.40	23.31 ± 1.88	<0.001	20.47 ± 1.62	16.80 ± 1.19	<0.001
Per BF (%)	24.53 ± 5.03	24.44 ± 6.30	0.855	35.64 ± 6.49	35.91 ± 5.74	0.524
Waist (cm)	88.30 ± 6.45	82.17 ± 7.40	<0.001	89.53 ± 8.77	84.10 ± 8.34	<0.001
TC (mg/dl)	184.78 ± 35.59	180.61 ± 36.63	0.209	195.88 ± 37.52	196.70 ± 36.00	0.762
TG (mg/dl)	109.29 ± 49.16	98.99 ± 40.98	0.012	118.51 ± 49.67	123.53 ± 55.50	0.187
HDL-C (mg/dl)	54.85 ± 12.90	56.68 ± 13.73	0.133	57.80 ± 14.05	58.28 ± 14.07	0.635
LDL-C (mg/dl)	117.40 ± 32.67	112.13 ± 31.78	0.077	123.32 ± 34.23	122.81 ± 32.61	0.835
Glucose (mg/dl)	101.08 ± 16.50	98.73 ± 17.02	0.128	99.43 ± 17.32	98.76 ± 19.13	0.614
SBP (mmHg)	129.39 ± 14.78	129.54 ± 15.57	0.910	130.78 ± 16.48	131.25 ± 17.44	0.692
DBP (mmHg)	74.58 ± 9.07	74.09 ± 9.43	0.554	74.61 ± 9.36	73.27 ± 9.24	0.045
Arm curl (rep)	20.06 ± 5.13	17.03 ± 4.78	<0.001	17.03 ± 4.45	15.13 ± 4.18	<0.001
Grip (kg)	36.11 ± 5.27	30.47 ± 4.71	<0.001	22.79 ± 3.90	19.58 ± 3.29	<0.001
Low limb extension (nm)	141.95 ± 36.75	108.99 ± 26.26	<0.001	83.15 ± 21.93	68.28 ± 18.43	<0.001
Low limb flexion (nm)	81.15 ± 21.75	60.61 ± 17.01	<0.001	45.50 ± 13.73	34.80 ± 10.40	<0.001

considered the main standard for developing effective intervention to promote physical fitness in the elderly [8, 9]. A series of studies on considering the supportive concepts of "exercise as medicine" demonstrated that regular physical exercise can protect against metabolic disease, cancer, retinal degeneration, and even memory loss [10].

In elderly participants with nonphysical activity, their health state can be easily aggravated via various vulnerabilities caused by the lack of physical fitness, including derived chronic diseases, which can turn into long-lasting frailty. Aging muscle mass decreases by about 2–3% every year after 60 years of age, which causes frailty (expressed as sarcopenia or declining physiological reservoir) as one of the geriatric syndromes due to decreased functional abilities (e.g., muscle strength, walking speed, and balance) [11, 12]. Fried et al. define frailty as characterized by the presence of more than three among five specific items: decreased vitality, slower gait speed, weakness, decreased physical activities, and decreased weight [13]. Prognostic categorization defining by pre- and postpathogenesis should be emphasized. Furthermore, the standard defined by the above clear categorization should be included in the notion of frailty in order to develop and provide an optimized frailty prevention program, to help delay the effects of the aging process.

Developing health-related standards for promoting physical fitness in elderly people have not only socioeconomic but also individual-centered benefits for relieving related chronic disease derived from poor lifestyle choices, which provides scientific evidence-based information for pursuing improvements in the quality of life for each individual.

The main aims of the study are detailed as follows: by searching case studies worldwide regarding validated criterion and reference standards for physical fitness and using an elderly cohort physical fitness-related database (DB) established with patients all across Korea, this study traces prevalence patterns of declines in recognition and physical fitness in the elderly population. We thus aimed to provide scientific evidence-based information regarding physical fitness standards for developing useful prognostics and promoting and maintaining a health program through this field study.

2. Materials and Methods

2.1. The Characteristics of Elderly Subjects. One thousand four hundred and ninety-five elderly subjects were randomly selected for recruiting from the representative countrywide physical fitness DB of elderly population during 2014 to 2015. Eighteen variables were applied to the gender-specific subject subgroups to analyze the characteristics of the population (Table 1). The variables are as follows: age (yrs), height (cm), weight (kg), body mass index (BMI, kg/m^2), lean body mass (kg), % body fat (%), waist (cm), total cholesterol (TC, mg/dl), triglycerides (TG, mg/dl), HDL-C (mg/dl), LDL-C (mg/dl), serum glucose (mg/dl), systolic blood pressure (SBP, mmHg), diastolic blood pressure (DBP, mmHg), arm curl (repetition), grip (kg), low limb extension (LLE, Nm), and low limb flexion (LLF, Nm). This study was approved by the institutional review board at the Korea Institute of Sport Science (KISS-201504-EFS-002-01).

2.2. Identification and Selection of Studies. Twenty-one previous studies emphasizing criterion referenced standards (CRS) and receiver operator characteristic (ROC) curve analyses for improving physical fitness are shown in Table 2. The severe screening process to identify the final studies selected involved a literature search in two databases, PubMed and the Research Information Service System (RISS, https://www.riss.kr/index.do; $n = 112$). Relevant articles were reviewed; until finally, 21 studies were selected in accordance with our chosen criteria for subjects, including criteria, title, abstract, and treatment (Figure 1). Optimized variables such as physiological and physical function-related variables and statistical methods were examined to apply to further our field study.

This study describes the study elimination process. Reasonable thresholds for physical fitness are pursued by various methods. Potentially related previous studies were identified through PubMed and the Research Information Service System (RISS, https://www.riss.kr/index.do). Three severe screening stages, excluding such unrelated with the scope, allow subtracting to obtain the highly qualified 21 studies.

2.3. ROC-Related Outcomes from Elderly Subjects as a Field Study. The main outcome predicting sarcopenia prevalence is measured in both genders in over 70 years of age population. We incorporated the definition of sarcopenia according to the indication from the recommendation of the European Working Group on Sarcopenia in Older People (EWGSOP) [3]. The measured profiles for indicating ideal thresholds are as follows: arm curl (30-second arm curl, number of biceps curls that can be completed in 30 seconds holding a hand weight of five pounds, which was 2.3 kg, for women, and eight pounds, which is 3.6 kg, for men) and low limb strength extension (Nm, lower limb extension force was measured (AP3150, Hur, Kokkola, Finland)). The maximal force output from two trials was measured at 0.01 kg units; sit-to-stand (repetition, maximal sit-to-stand number counted within 30 seconds), timed up and go test (TUG, in seconds, the time to stand from a chair, walk three meters, and walk back and sit down in the chair), and six-minute walk (m, walking distance for six minutes).

2.4. Statistics. Whole data were described as the mean ± standard deviation (S.D.). According to the previous study describing the skeletal muscle mass index (SMI, kg/m^2), we expressed lower than two standard deviations below the mean value as compared with the SMI value as low muscle and the opposite defined as high muscle [1]. A t-test was used to examine the differences between the high and low muscles of each variable in the elderly population (Table 1). For cutoff values, logistic regression involving data from sarcopenic elderly individuals was performed, and each of the significant variables showed a difference in cutoff threshold with respect to gender (Table 3). SAS version 9.4 (SAS Institute, Cary, NC, USA) and SPSS version 18.0 (IBM, Armonk, NY, USA) were used for all statistical analyses. A value of $p < 0.05$ was considered to indicate statistically significant difference in all analyses.

3. Results

3.1. The Characteristics of Elderly Subjects. In our DB, 75 years for men and 70 years for women were determined to be the transitional age dividing high and low muscle compositions in both genders ($p < 0.01$) (Figure 2). An abrupt decrease in muscle mass with rapidly increasing fat mass is shown in this age period; BMI, lean mass, per BF ($p < 0.01$); however, physiological variables such as total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), serum glucose, and blood pressure (BP) do not significantly change in this age period. Physical function tests show all significant differences that were present in the high muscle mass group in both genders have significantly higher values as compared with those in the lower muscle mass group ($p < 0.01$) (Table 1).

Three aging groups such as 65-69, 70-74, and more than 75 years are sex-differently divided according to the value (kg) of the lean body mass. Orange and blue indicate the men and women groups, respectively. ∗ indicates significant difference ($p < 0.05$) to 65-69 year group of corresponding sex; # indicates significant difference ($p < 0.05$) to each sex group of 70-74 years.

3.2. 21 Selected Studies. In selecting highly qualified articles relevant to ROC for physical fitness, 21 articles were finally selected and are shown in Table 2. In the articles, measuring methods are mainly focused on various ranges of age as a means to move forward for the next analysis as this field study. Target variables for CRS are categorized as physiological (e.g., BP, TG, HDL, glucose, insulin, BMI, VO_2 max, and cholesterol) and physical function (e.g., muscle strength, physical compositions, and walking and running tests) factors. Logistic regression, ROC curve analysis, linear regressions, validation methods, and voluntary categorization such as the 20th or 60th percentile classification were examined. Other factors such as ethnical differences and specific ranges of age are overlooked for the further study.

3.3. Physical Fitness-Related ROC Curve Outcomes for Preventing Prognostic Sarcopenia. In gender-different elderly populations, ROC curve analysis for setting optimal cutoff thresholds with ideal sensitivity and specificity values provides priceless information for developing interventions for ameliorating sarcopenia symptoms (Table 3). When predicting prevalence of sarcopenia in elderly people, six physical functions (arm curl, limb strength extension and flexion, sit-to-stand, TUG, and six-minute walk test) in both genders all have significant p values ($p < 0.05$). The cutoff values of sit-to-stand and six-minute walk tests in elderly women have better thresholds than those in elderly men. Sensitivity of low limb strength extension and flexion is 83% and 80% in men and 86% and 86% in women, respectively. Specificity of the six-minute walk test in men and women is 93% and 82%, respectively. Comparatively high values in sensitivity and specificity (both with more than 70%) are shown in low limb strength extension (83% and 75%), low limb strength flexion (80% and 76%), and TUG (71% and 70%) only in men.

TABLE 2: Screened studies using various methods for measuring physical fitness.

Authors	Subjects	Target for criterion referenced standards (CRS)	Methods of criterion-referenced standards	Miscellaneous
Amini et al. [11]	American football players ($n = 62$)	Waist circumference, quadriceps leak torque, systolic & diastolic BP	ROC curve analysis followed by logistic regression for prediction	Lessening cardiometabolic risk-like type 2 diabetes and cardiovascular disease
Jang [12]	Pre & post 50 yrs men ($n = 7226$)	Muscle strength and metabolic syndrome (triglyceride, HDL cholesterol, glucose, systolic diastolic BP)	ROC and 20% below –> low level and logistic regression (low muscle strength vs. metabolic syndrome)	Low muscle strength: lowest age-specific 20th percentile (2.56 kg/kg body weight in pre 50 vs. 2.50 kg/kg body weight in post 50) High muscle strength: highest age-specific 20th percentile
Ruiz et al. [15]	69 pain treatment patients	Lower pressure pain threshold (PPT, dependent), knee mechanics (independent)	Univariable linear regression for lower PPT and multiple variable linear regression	Knee mechanics are associated with PPT
Sénéchal et al. [17]	Systematic review ($n = 59$)	Moderate to vigorous physical activity, 6MWT	Logistic regression for cutoff (accelerometry measured moderate to vigorous physical activity compared to sedentary in elderly) and Bland-Altman method used; however, the results are obscure	Sedentary ratio, activity difference, and exercise time reflect the results assessed by accelerometry
Hooten et al. [20]	Review			Changed evaluation trends shown from performance centered to health-related test and norm referenced to CR evaluation. Criterion-referenced standards vs. norm-referenced evaluation ROC introduced
Hanifah et al. [21]	Review			Criterion-referenced evaluation developed history. Advantages of CRS (absolute, diagnostic supportive), drawbacks of CRS (misclassification such as false mastery and false nonmastery, nonsufficient incentives etc.)
Authors	Subjects	Target for criterion-referenced standards (CRS)	Methods of criterion-referenced standards	Miscellaneous
Gorman et al. [22]	65~84 yrs both gender elderly ($n = 3074$)	Chair stands in 30 s, arm curls in 30 s, 6 min walk, 8 foot up and go (1)	ROC for predicting independent physical function in later life and logistic regression	For later life (~90 yrs), internet-based program recommended (https://www.fmh.ulisboa.pt/ehlab/calculator/)
Duncan et al. [23]	Review (setting CRS transition history)	Make participants get into HFZ	ROC analysis, LMS (L = skewness, M = median, S = coefficient of variation), centile	Single cutoff score ≥ health fitness zone (HFZ), needs improvement zone (NIZ) set for warning potential risk
Kawakami et al. [24]	Systematic review			Selected article had different methods, analyses, and results that prevented comparison between studies ≥ junk article
Zhu et al. [25]	55 yrs and older both gender elderly ($n = 3392$)	BMI, hand grip strength	ROC for hand grip strength cut-points and impaired hand grip cut-points vs. mobility limitation by logistic regression	Optimal hand grip strength cut-points for mobility limitation and the cut-points discriminate BMI
Cureton and Warren [26]	Systematic review		False-positive/false-negative analysis, regression model, visual inspection	

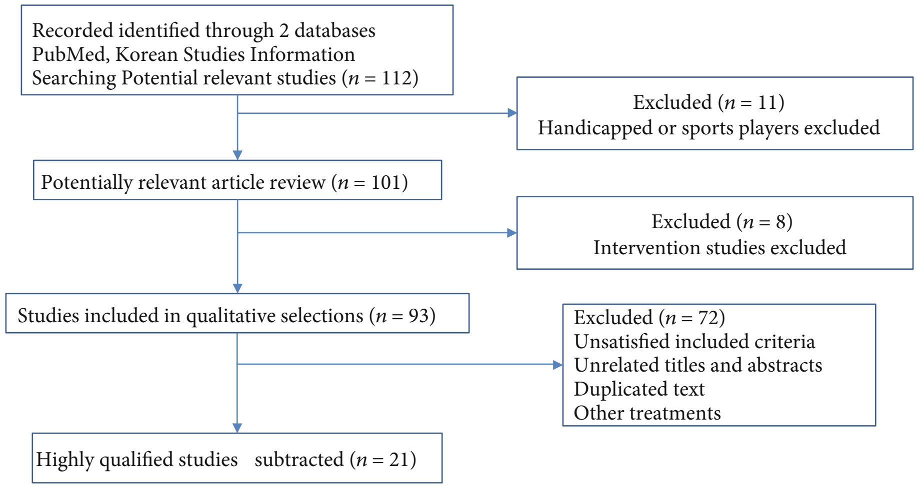

FIGURE 1: The screening process of physical fitness-relevant appropriate threshold values to identify studies.

TABLE 3: Results of ROC curve analysis predicting prevalence sarcopenia in elderly.

Senior fitness variables	Prevalence (%)	AUC (95% CI)	Cutoff value	Sensitivity	Specificity	p value
Men						
Arm curl (rep.)	8.45	0.718 (0.679~0.754)	≤16	68.75	71.54	<0.001
Low limb strength_ extension (nm)	7.90	0.849 (0.815~0.879)	≤109.22	82.93	75.31	<0.001
Low limb strength_ flexion (nm)	7.90	0.829 (0.794~0.861)	≤61.72	80.49	75.94	<0.001
Sit-to-stand (rep.)	7.50	0.714 (0.674~0.753)	≤12	48.72	83.58	<0.001
TUG (sec.)	7.61	0.763 (0.725~0.798)	>6.367	71.43	70.00	<0.001
6 min walk (m)	6.51	0.707 (0.655~0.755)	≤388.3	40.91	93.35	0.019
Women						
Arm curl (rep.)	12.47	0.715 (0.684~0.744)	≤14	60.36	71.50	<0.001
Low limb strength extension (nm)	9.97	0.728 (0.695~0.760)	≤76.04	86.49	56.74	<0.001
Low limb strength flexion (nm)	9.97	0.793 (0.762~0.821)	≤37.74	86.49	64.67	<0.001
Sit-to-stand (rep.)	12.0	0.676 (0.641~0.710)	≤14	69.66	61.81	<0.001
TUG (sec.)	11.9	0.702 (0.669~0.733)	>6.687	68.37	61.29	<0.001
6 min walk (m)	7.46	0.793 (0.746~0.835)	≤402.8	68.00	82.90	0.019

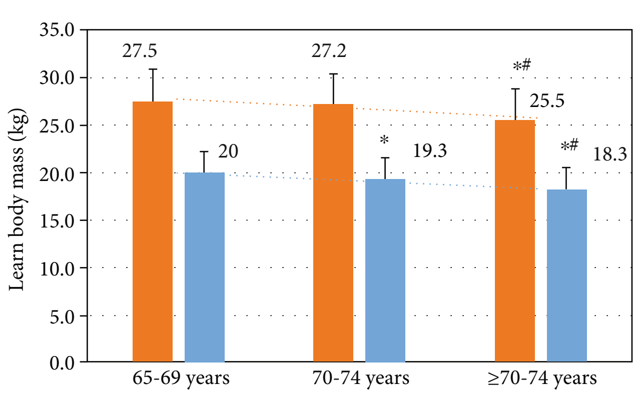

FIGURE 2: Lean body mass according to different aging groups.

4. Discussion

In this study, we searched 21 severely screened previous studies to identify the measurement methods regarding improving physical fitness without consideration of specific age periods. Logistic regression, ROC curve analysis, linear regression, and voluntary categorizations such as the twentieth or sixtieth percentile classifications were used to provide cutoff points of physical fitness profiles. Based on this scientific evidence, we determined cutoff threshold values from our reserved elderly human DB and realized that 75 years for men and 70 years for women are the transitional age period for muscle and fat mass ($p < 0.01$), which reflects physical function tests ($p < 0.01$) that indicate physical fitness levels in both genders.

4.1. Why This Study Focuses on Elderly People and Provides Information That Allows to Develop Useful Prognostics, Maintaining and Promoting Health Programs. Our study for setting health-related CRS focuses on elderly individuals who especially have limitations in their physical abilities. Factors directly related to metabolic disorder are remarkably relevant to physical fitness factors. Comparative hand grip strength, seated hip adductor stretching, and six-minute walk test in men and comparative hand grip strength in women significantly affect as physical factors on classifying physical fitness in elderly peoples as the prefrailty and frailty. The most important factor affecting frailty in the aged is comparative hand grip strength. Individuals with lower comparative grip strength (i.e., the lower 33.3% group) present with three times more chronic prevalence diseases as compared with those with higher comparative grip strength (i.e., the higher 33.3% group). Elderly individuals with comparative higher grip strength are also typically confident in recognition and balance capacity (https://nfa.kspo.or.kr). In light of these results, it should be noted that the elderly population in Korea represented around 12.2% of the total population in 2013 and will be more than 24% in 2030 (https://kostat.go.kr/portal/eng/index.action). Thus, it is important to provide beneficial information to elongate the healthy lifespan as much as possible.

4.2. ROC and Non-ROC-Used Methods or Analysis of Criterion-Referenced Standards (CRS) by Selected Articles. Research efforts for establishing CRS and ROC regarding physical fitness for ameliorating and at least maintaining a healthy state have been made, and some studies were thus selected through a severe screening process in this study to identify the chosen variables in various age groups, with an aim at providing evidence-based information to design a preventive and prognostic sarcopenic management program for elderly people by incorporating appropriate ROC values from our DB, as we clarified the aim of this study in Introduction for this field study. One study used height, BMI, waist, and fat ratio as dependent variables with a 20 m shuttle run as an independent variable for oxidative capacity for comparing overweight kids with normal kids to decide the minimal cutoff point for oxidative capacity in children [14]. A prognostic study for preventing the risk of cardiovascular diseases in kids according to cutoff points of metabolic risk provided each of suitable thresholds by using quartile [15]. Another study used the ROC curve to determine the cutoff threshold of each physical composition regarding the risky relationship between type II diabetes and cardiovascular diseases in American football players [16].

A nine-year follow-up study provided cutoff points by using the ROC curve for a threshold between muscular strength and metabolic syndrome in aging men (5,685 under 50 years vs. 1,541 over 50 years of age) [17]. In this study, three study groups were divided as model 1 (no exercise during the last three months), model 2 (middle level of exercise during the last three months), and model 3 (vigorous level of exercise during the last three months).

Another study provided a risk threshold of physiological factors (VO2 max, HDL, glucose, and triglyceride) in oxidative capacity via using the ROC curve for age and gender-differentiated adolescents between 12~18 yrs ($n = 1240$), in order to show the reasonable area of the risk threshold at each one-year point to prevent metabolic disease [18].

Other studies used cross-validation for a more accurate cutoff point, rather than ROC curve analysis [19]. Hooten et al. used multiple variable linear regression for the relation between knee joint kinetics and pressure pain threshold [20]. Multiple regression was used for predictive factors such as physical composition to physical fitness standards [21]. Gorman et al. used logistic regression [22], while Duncan et al. randomly divided groups into the following quantile ranks according to cardiorespiratory fitness: lower, middle, and high groups, representing the lower twentieth, twentieth to fifty-ninth, and over sixtieth, respectively [23]. A fourteen-year follow-up longitudinal study for 266 type 2 diabetic patients shows that the symptoms of type 2 diabetes in 33% declined due to the promotion of a physical fitness program [24]. The criterion reference standard for physical activity used in this study was baseline VO2 max at an AUC of 0.70 (95% CI, 0.66-0.73, with sensitivity and specificity being 0.64, respectively) and the optimal cutoff threshold was decided as 10.8 METs for cardiorespiratory fitness.

4.3. Providing Cutoff Threshold for Diagnostic and Preventive Sarcopenia. Based on the screened previous studies, we decided to provide the cutoff points of meaningful values from our own elderly human DB. Six physically functional profiles are disclosed to have significant intereffects with sarcopenia in both genders ($p < 0.05$), and are as follows: arm curl, low limb strength extension, low limb strength flexion, sit-to-stand, TUG, and six-minute walk test. Absolute muscle output force from the upper and lower limbs is likely higher in men; however, such results should be considered together with the ratio with their burdening load, such as weight. It cannot then possibly determine that necessary muscle force is sufficient for their physical functionality. The sit-to-stand and six-minute walk tests indicate all physical functions necessary for resistant and oxidative capacities, and elderly women have higher values in these tests. For longevity, muscular oxidative capacity is possibly required more so than other capacities (of note, the longevity of Korean women ranked third in the world in 2015). In relation with muscular mass comparison between high and low muscles, the average age difference is also shown to be 70 and 73 years, respectively (Table 1). This suggests that this is a decisive turning point of age on the abrupt muscular declines in both qualitative and quantitative ways. Using the six factors with ideal cutoff thresholds can be used to effectively design a tailor-made individual exercise program for alleviating the worsen symptom of frailty caused by sarcopenia for the decisive period of elderly.

5. Conclusions

To provide evidence-based scientific information for useful prognostics and for promoting and maintaining a health program, our study identified beneficial outcomes, like those in the following:

(1) We pinpointed 21 relevant severely selected articles that include logistic regression, ROC curve analysis, linear regression, and voluntary categorizations to

produce optimized cutoff points of physical fitness profiles

(2) We continuously traced ideal cutoff threshold values from our reserved elderly human DB and found that individuals aged from 75 years for men and 70 years for women are within the specifically transitional age period for muscle mass ($p < 0.01$), which reflects the need for physical function tests in both genders ($p < 0.01$)

Worsened symptom of sarcopenia usually induces fall in aged persons because of decreased quality and quantity of muscle, which is directly related to the low quality of life in elderly peoples. As the prognostic cutoff values of each physical fitness-related variable for the aged person were provided, ideal physical fitness promoting program can be designed and applied to promote muscle function or at least deaccelerate the worsening of muscle function which possibly contributes to the independent life of aged peoples. This evidence-based field study can contribute to strengthen the standardization of physical fitness-related variables, and the benefit of lifelong health promotion in senescent elderly peoples and the results in this study can be used for a health policy to prevent the symptom of sarcopenia by publicizing as a subject of national-wide recommendation.

Regular exercise elderly-doers decrease possibility to be hospitalized, which induces successful aging such as better quality of life and independent life. An optimal socioeconomic model can be suggested through which each aged person lives a healthy life by reducing medical expenses via doing exercise with a reasonably designed exercise program.

Data Availability

The data used to support the findings of this study have been deposited in the Korea Institute of Sport Science.

Conflicts of Interest

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

Acknowledgments

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