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The Effect of Combined Aerobic and Resistance Exercise on Biochemical Factors in Patients with Type 2 Diabetes Mellitus

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Original Article

Abstract

Introduction: Diabetes mellitus is a common health problem worldwide, especially in Asia. Exercise training plays an important role in controlling diabetes variables. The aim of this research was to consider the effectiveness of exercise on biochemical parameters in patients with type 2 diabetes mellitus.

Materials and Methods: This randomized controlled clinical trial study was carried out with 40 patients with type 2 diabetes mellitus selected out of 702 volunteers. These individuals were randomly divided to two groups, combined (aerobic and resistance) exercise and control. Intervention protocol included 24 sessions (8 weeks) of aerobic exercise on the treadmill with zero slope, three days per week for 30 minutes per session. Intensity of training protocol was 50-70 percent of maximum heart rate, and that subjects wear a weighted vest. Measurements of parameters were done before and after 24 sessions.

Results: Basically, there were no significant differences in variable values. After eight weeks, fasting blood sugar (FBS) (P = 0.059), glycosylated hemoglobin (HbA1c) (P = 0.333) were significantly reduced in the combined group; but not low-density lipoprotein (LDL), very low-density of lipoprotein (VLDL), high-density lipoprotein (HDL), total cholesterol, triglyceride, and high-sensitivity C-reactive protein (HS-CRP) (P > 0.050 for all). Alternatively, the value remained unchanged in the combined group while it was increased in the control group (P = 0.001).

Conclusion: 24 sessions of aerobic exercise improved FBS and HbA1c in patients with type 2 diabetes mellitus. However, longer training duration is deemed to need to modify other variables.

Keywords: Exercise, Type 2 diabetes mellitus, Hb A1c, Blood glucose

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Introduction

Type 2 diabetes mellitus (DM) is one of the most common complications in modern societies and is estimated to be the seventh cause of death in 2030 (1). 1.6 million individuals are added to the population of people with DM annually, with the illness in one-third of these people remaining unidentified (2). The prevalence rate of type 2 DM in Asia and Iran is estimated to be 1.2-14.60% and 1.3-14.5%, respectively. Lifestyle changes and urbanization are the most common causes of the disease (2). Insulin resistance is one of the major problems in people with type 2 DM. Vascular endothelium is a valuable target for insulin function and plays a key role in improving insulin resistance (3). The high blood insulin level, combined with insulin resistance, causes sodium reabsorption, stimulation of the sympathetic nervous system, and vascular smooth muscle cell (VSMC) growth. An increase in plasma glucose along with insulin resistance in the vessel wall, results in organ damage and, ultimately, atherosclerosis. In addition, the binding of insulin to the receptor leads to the vasodilatation effects through the production of nitric oxide from the endothelium, which is destroyed in the insulin resistance (4).

The risk of cardiovascular diseases (CVDs) in patients with type 2 DM is 2 to 4 times higher than in individuals lacking these complications (1). Exercise intolerance is observed in these patients due to CVDs.

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Exercise intolerance negatively affects daily activities and restricts recreational, occupational, and educational activities. Type 2 DM is primarily caused by obesity and physical inactivity and is prevented by reducing body mass and regular exercise (5). Physical activity reduces hyperglycemia and body fat, thereby protecting advanced CVD complications (6). Exercise activities are a major contributor to type 2 DM care. The useful effects of aerobic exercise on the prevention of CVDs are clear (7). Aerobic exercise increases mitochondrial density, oxidative enzymes, insulin sensitivity, vascular response, and cardiac output, in addition to improving immune and pulmonary function (8). Decreased muscle strength is a risk factor for type 2 DM. Therefore, strength training with increasing muscle mass and strength, increasing muscle sensitivity, decreasing blood pressure, and decreasing body fat mass have favorable effects on glycemic control (8).

According to the studies conducted by Bellavere et al. (9), Cuff et al. (10) and Walsh et al. (11), concurrent aerobic and resistance exercises play a greater role in preventing chronic complications of DM due to the combined effects of both types of exercise. The types of exercise performed in various studies include aerobic (12-16), resistance (17), and combined aerobic and resistance (14,18,19). The intensity of the exercises used in various studies included 60-65% heart rate reserve (HRR) for aerobic exercise and intensity required for resistance exercise starting from 30-50% one-repetition maximum (1RM) and reaching 70-80% 1RM at the end (20), 45-40% HRR (21), 65-85% HRR (22), 65% HRR (23), and 50-60% 1RM (first week) and increased intensity up to 75-85% 1RM (17), based on the activity or inactivity within six months (4), 35-80% of maximum heart rate (15), in terms of daily walking (24) and 65-85% of maximum heart rate (16). It should be noted that none of the above studies have used the intensity desired by the American Diabetes Association (ADA). Another point to note is that in studies reporting the effect of exercise of blood sugar control, the exercise was performed in a long term (six months or more) (12,17,25,26). Contrary to repeated recommendations for exercise and physical activity in patients with type 2 DM, it is still ignored, one of the reasons being the high number of exercise sessions in other exercise protocols (27). In this study, fewer sessions were used to facilitate exercise in patients with type 2 DM. Moreover, the intensity considered in the present study was determined based on the ADA (50-70% of maximum heart rate).

The present study was carried out with the aim to evaluate the effect of 24 sessions of aerobic and resistance training on biochemical parameters, with a vest with the external loading used in aerobic exercise. Since the vest can be simulated with a backpack, in case of reaching a positive result from this protocol, this method is a convenient and inexpensive way to be applied for all patients with type 2 DM.

Materials and Methods

This study was a randomized clinical trial registered with the code of ethics IR.SBMU.RETECH.REC approved in the ethics committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran, with the code IRCT2016121831443N1 on the Iranian Registry of Clinical Trials. The study population consisted of patients with type 2 DM referred to diabetes centers, clinics, and hospitals of Hamadan Province, Iran.

The study inclusion criteria included age range 40-60 years, body mass index (BMI) between 20-30 kg/m^2, at least two years history of type 2 DM, type 2 DM confirmed by an endocrinologist for entry into the study, glycosylated hemoglobin (HbA1c) ranged between 6% and 10%, avoiding any change in dietary pattern or drug use, not participating in exercise more than 30 minutes per week before the exercise intervention (28), lack of smoking, and use of drug and any alcoholic beverages (17,18,29), no hypertension (systolic blood pressure less than 160 mm Hg (14,18), no history of CVDs (28,29), no history of musculoskeletal disorders (MSDs) (29), no history of other metabolic diseases (29), lack of retinal vascular problems (19), lack of protein in urine or renal failure (14,18,19,28), no insulin use (17), no foot ulcer (30), history of DM not more than 10 years, and lack of severe peripheral neuropathy (31). Furthermore, the unwillingness to continue the study, feeling tired during exercise, shortness of breath during exercise, two consecutive absences, and stress and restlessness were regarded as the exclusion criteria (27).

Sampling was performed by the simple non-probability method, but the subjects were randomly assigned to the groups. The subjects were randomly grouped using the consecutive random method by the third person unaware of the study design using the random number table. Based on the results obtained from the study by Maiorana et al. (32) and determined common standard deviation (SD) of 1.8, mean variation of 1-, 1.3 and 1.3, and calculation of Delta = 1.88 with two study groups, and considering the type I and type II error values of the test as respectively 0.05 and 0.1 (test power of 90%), and $\lambda = 12.66$ from the corresponding table, the number of samples in each group was estimated to be 12 persons. Since the individuals might withdraw from the study for any reason, to reduce the adverse effect of this case, a sample size of 20 was considered in each group.

The intervention for the combined aerobic (with external load) and resistance exercise group was treadmill walking for eight weeks (24 sessions, 3 days per week), and the subjects completed the exercises wearing a vest with an external load. The vest was easily fastened around the patient's body, while allowing the upper and lower limbs to move freely. The weights used weighed 200-300 g and were easily put in and removed from the pockets. The weight inside the vest gradually increased during the 8 weeks, as in the first, second, third and fourth, and fifth to eighth weeks, 2%, 3%, 4%, and 5% body weight were applied, respectively (33). The activity intensity according to the ADA guidelines was determined to be 50-70% of maximum heart rate, moderate, and three days a week (31). The intensity range increased from 50% to 70% according to the patient's ability during the 8 weeks. The target heart rate was calculated using the Karvonen formula after obtaining the maximum heart rate from the exercise test. At each treatment session, the participants' fasting blood sugar (FBS) was measured using a glucose meter (Accu Check Performa, China) at the beginning and end of the exercise. If FBS was less than 100 mg/dl, the individual would receive 15 g of carbohydrates or dietary supplements. After re-measuring the blood glucose level after 20-30 minutes, and if increased to more than 100 mg/dl, the exercises began. Besides, if the patients' blood glucose in each treatment session was higher than 250 mg/dl, the exercise would not be performed. During the exercise, if symptoms of hypoglycemia appeared in any patient, their blood glucose levels were immediately monitored and exercise was discontinued if it was decreased (34).

Throughout the exercise period, the heart rate of all patients was monitored by the researcher using a digital heart rate monitor (Beurer Co., China). In addition, the patients' blood pressure was measured before the exercise and if it was less than or equal to 160.90 mmHg, the person was asked to sit for 10 minutes and the blood pressure was measured again. If there was no decrease in the blood pressure level, the exercises would not begin (34). All groups were asked not to change their physical activity and diet during the 8 weeks. The amount and type of medication varied among the patients, but they were not allowed to change their medication. Any medication (glucose lowering, anti-inflammatory, etc.), dosage, level of physical activity, each patient's diet, as well as any changes in these variables were recorded at the end of each week. These evaluations (with emphasis on not changing the diet, medication, and physical activity levels) were also performed for the control group without exercise at the beginning and at the end of eight weeks.

The biochemical parameters of all patients were measured using the standard technique before and after the intervention; FBS by glucose oxidase using a kit (Pars Azmoon kit, Tehran, Iran), HbA1c by chromatography using a kit (Nycocard, Norway), cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglyceride by enzymatic method using a kit (Pars Azmoon kit, Tehran, Iran), and high-sensitivity C-reactive protein (hs-CRP) quantitatively using a latex agglutination kit (Iran) were measured by an expert at the Mahdieh Hamadan Limited Surgical Laboratory. It should be noted that there was no blinding in any of the groups.

The normal distribution of the data was assessed by the Shapiro-Wilk test ($P > 0.050$). Furthermore, the Levene test for all variables was greater than 0.05. Additionally, the independent t-test was employed to compare the data between the two groups and paired t-test was used to assess differences between variables before and after 24 sessions of intervention. Finally, the data were analyzed in SPSS software (version 20, IBM Corporation, Armonk, NY, USA) and $P < 0.05$ was considered as the significance level.

Results

Following screening, 40 patients with type 2 DM participated in the study, 3 of whom were excluded from the intervention group (Figure 1). The demographic characteristics of the subjects before intervention are presented in table 1. There was no significant difference in the demographic characteristics between the two groups ($P > 0.050$).

The plasma serum levels before and after 8 weeks are presented in table 2. After the intervention, there was a significant difference in FBS between the two groups ($P = 0.050$) and the VLDL variable was almost significant ($P = 0.061$), however no significant difference was observed between the two groups in other indices ($P > 0.050$).

Discussion

In the present study, the effect of eight weeks of aerobic and resistance exercise (aerobic exercise with external load) on biochemical parameters of patients with type 2 DM was investigated.

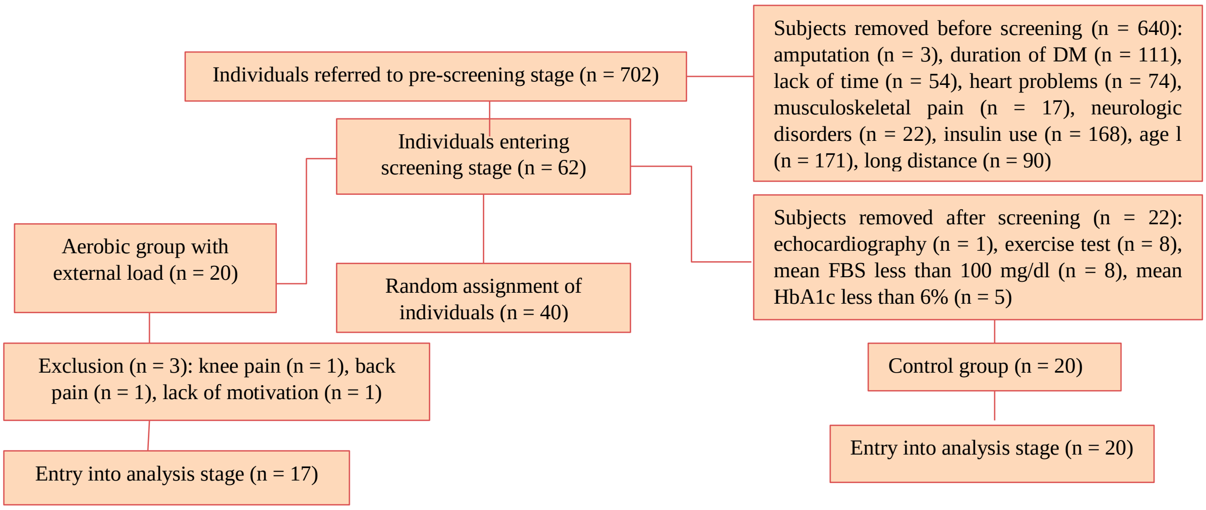

Figure 1. Stages of selection of participants
FBS: Fasting blood sugar; HbA1c: Glycosylated Hemoglobin

The results suggested that the combined aerobic and resistance training (aerobic exercise with external load) for eight weeks (24 sessions) can significantly decrease FBS and HbA1c levels compared to before the exercise. In the control group, there was also a significant difference in FBS but no change in HbA1c between the two groups.

Although no similar studies were found, the literature review was indicative of the use of similar variables in interventions on patients with type 2 DM, however differences were observed in the duration of exercise. Investigations on exercise time are divided into three groups of short-term exercise as a single session or limited sessions (23,35,36), mid-term exercise as one month, two months, three months, and four months (16), and long-term exercise as six months or more (12,17). Type 1 (short term) exercise is easier in terms of execution and research, but there is no time needed for physiological adaptation (1); whereas there is a physiological adaptation in the third type (long term) exercise and no study was found to report any doubt on the physiological adaptation and effects of these exercises on glycemic control. In a study, Gordon et al. reported the lack of decrease in HbA1c and a significant decrease in this index after 3 and 6 months of exercise, respectively (12). Performing long-term exercise is very difficult, and discontinuation of exercise programs, exacerbation of DM, and lack of complete success of rehabilitation programs can be seen in practice. Therefore, the second type of exercise was used in the present study to control the blood glucose levels among the individuals.

Different protocols have been developed in studies on the effects of the second type exercise on the biochemical parameters of individuals with type 2 DM. Accordingly, Horii et al. (37), Ribeiro et al. (38), and Tibana et al. (39) used eight weeks of resistance exercise in their studies, which will be described in detail in the following.

Horii et al. investigated the effect of eight weeks of resistance exercise with and without a 5-alpha-dihydrotestosterone inhibitor injection in rats aged 20 weeks. Resistance training was performed three times a week on a 1.1 m ladder and an 80° slope. The results revealed an increase in insulin sensitivity and glycemic control compared to the control group and the inhibitor injection group (37).

Table 1. Demographic characteristics of the combined (aerobic and resistance) and control groups

Variable	Combined aerobic and resistance group (n = 20)	Control group (n = 20)	P value
Age (year)	48.33 ± 5.74	48.90 ± 4.69	0.896
Height (cm)	167.70 ± 33.18	169.60 ± 67.96	0.809
Weight (kg)	74.73 ± 8.36	74.03 ± 9.91	0.935
BMI (kg/m^2)	26.66 ± 2.30	26.93 ± 2.42	0.766
History of illness (year)	5.58 ± 2.84	5.43 ± 1.99	0.790

BMI: Body mass index
Data were reported as mean ± SD.

Table 2. Plasma serum levels before and after 8 weeks

Variable	Combined aerobic and resistance group (n = 17)			Control group (n = 20)			P value
	Before intervention	After intervention	P value	Before intervention	After intervention	P value	
FBS (mg/dl)	156.67 ± 39.16	105.08 ± 16.28*	0.001	146.00 ± 30.19	129.93 ± 40.53¥	0.059	0.050
HbA1c (%)	7.74 ± 1.57	6.53 ± 1.10*	0.002	7.54 ± 1.43	7.21 ± 1.60	0.333	0.221
HDL (mg/dl)	42.66 ± 10.98	42.33 ± 8.60	0.894	52.13 ± 13.27	42.06 ± 8.86*	0.001	0.938
LDL (mg/dl)	79.91 ± 47.83	79.33 ± 27.34	0.945	79.00 ± 33.79	87.26 ± 41.15	0.394	0.572
VLDL (mg/dl)	27.91 ± 9.71	24.00 ± 5.00	0.097	31.66 ± 14.80	19.53 ± 6.49*¥	0.005	0.061
Cholesterol (mg/dl)	149.16 ± 52.60	144.66 ± 31.56	0.646	165.06 ± 35.70	145.40 ± 30.17	0.075	0.952
Triglyceride (mg/dl)	156.25 ± 78.76	114.33 ± 27.93*	0.050	154.46 ± 80.32	114.26 ± 54.39	0.027	0.997
HS-CRP (mg/dl)	2.66 ± 0.71	2.77 ± 0.63	0.683	2.87 ± 0.49	2.90 ± 0.07	0.398	0.489

FBS: Fasting blood sugar; HbA1c: Glycosylated Hemoglobin; HDL: High density lipoprotein; LDL: low density lipoprotein; VLDL: Very-low density lipoprotein; HS-CRP: High sensitivity C-Reactive protein;
* Intra-group comparison of indices (P < 0.050); ¥ Inter-group comparison of indices (P < 0.050)
Data were reported as mean ± SD.

They used laboratory mice in their study and argued that animal samples were nutritionally and environmentally controllable (37), which was not similar to the present study in this view. The results of the study by Ribeiro et al. indicated that eight weeks of resistance exercise had a positive effect on FBS and lipid profile of the samples. The resistance exercise was performed in two common and pyramidal types (ascending) and the sample consisted of 29 women over 60 years of age. In both groups, positive results were obtained in biomarkers and there was no difference between the two groups. In this study, there was no control group for comparison (38), which is one of the major drawbacks. Given the results of the study by Ribeiro et al (38), one of the reasons for the lack of effect of resistance exercise in comparison to the control group in the present study may be attributed to the entry of the individuals aged 40-60 years. In this age range, the muscle strength and mass do not decrease as much as those of the individuals over 60 years of age so that the muscle strength can increase by resistance exercise and positive changes be observed in biomarkers. Although there was a significant decrease in HbA1c and FBS after the intervention in the combined aerobic and resistance group, there was no difference compared to the control group. Tibana et al. examined the effect of eight weeks of resistance exercise (8-12 RM) on FBS, HbA1c, HDL, and triglyceride indices in obese young women. After 24 sessions of resistance exercise, no change was found in any of the indices (39). The difference between the above study and the present study is in the BMI inclusion criterion. 1% decrease in HbA1c was observed in the participants under intervention of the present study. Given that 1% increase in this variable results in an 18% increase in coronary artery diseases (CADs) (40) and its 0.2% decrease is followed by a 10% decrease in mortality (41), a positive result was observed for HbA1c. Additionally, reducing HbA1c and controlling its level below 7% is the gold standard for reducing CVDs (42) and this was observed after the intervention.

There are various mechanisms to control blood sugar through exercise. The decrease in the insulin resistance through exercise is directly related to the increased concentration of glucose transporter type 4 (GLUT-4) in the plasma membrane or sarcoplasm. Aerobic exercise indirectly increases the number of insulin receptors and increases glucose transmission by converting Type IIb fiber to Type IIa. Moreover, exercise increases muscle fiber hypertrophy and increases muscle mass, resulting in increased muscle glycogen and glucose and ultimately lower blood sugar (6).

Another biochemical marker is HDL, which is common to be of low level in type 2 DM and may be the leading cause of CVDs in these patients (43). HDL has the antioxidant, anti-inflammatory, antithrombotic, endothelial function enhancing, and endothelial repair roles. The amount and function of HDL deceases in DM and both of these factors decrease the protective effect in the patients (44). Thus, physical activity is recommended to increase HDL to control blood sugar in people with type 2 DM (45). In their study, Zaer Ghodsi et al. examined the effect of eight weeks of exercise on HDL levels. The eccentric and concentric exercises used in their study increased HDL levels (30). In another study, eight weeks of high intensity exercise increased the HDL level (46); however, the type of exercise performed in the two studies (30,45) was different from the present study. After six weeks of aerobic and aerobic exercise with loaded external vests in postmenopausal women with osteoporosis, Roghani et al. reported no increase in the HDL level (47), which is consistent with the findings of the present study. Although the combined exercise in the present study did not change HDL in the intervention group, the lack of exercise significantly reduced HDL in the control group. The most common cause of HDL decrease is inactivity (48). Therefore, a decrease in HDL in the control group is an alarm signal for CVDs. Perhaps if the intensity and duration of exercise increased, a significant increase in HDL would be observed.

Researchers believe that changing HDL levels is difficult. If the intensity and duration of exercise are insufficient, no change will occur in this index. The mechanism of HDL change after exercise is very complicated. Enzymes such as hepatic lipase, lipoprotein lipase, and cholesteryl ester transfer protein (CETP) play a major role in changing the HDL concentration. The main reason for the HDL increase immediately after exercise refers to a decrease in the activity of the CETP. Decreased activity of this protein slows down the HDL catabolism (prolonging the half-life), hence increasing the HDL level (49).

Liver insulin resistance and elevated FBS levels increase VLDL in the liver and decrease LDL consumption in the bloodstream (50). The results of investigations indicate that the effects of aerobic exercise on LDL and cholesterol are beneficial when it is accompanied by diet and weight loss (49). Based on the studies reviewed on the effect of exercise on the aforementioned indices, if exercise is not associated with diet, it has no significant effect on reducing these indices. After 12 weeks of resistance training and diet, Ruby et al. reported no change in VLDL levels, whereas the LDL levels decreased in the subjects (51). In the studies conducted by Aggarwala et al. (four weeks of aerobic exercise) (6) and Roghani et al. (six weeks of aerobic exercise and aerobic exercise with external load) (47), no change was observed in the LDL levels before the intervention. Researchers believe that the LDL level is rarely changed by exercise. Post-exercise lipid profile levels are strongly dependent on high triglyceride, LDL, and low HDL levels (52). The participants in the current study had normal lipid profiles, and it was difficult to change these variables and compare them with the intensity and timing of other studies (52).

HS-CRP is a sensitive inflammatory marker that increases the risk of CVDs (53). Increased HS-CRP results in increased insulin resistance (54), increased risk of DM (55), increased triglyceride, and decreased HDL (46). There are many inconsistencies in the studies regarding this index due to the increase in HS-CRP because of the production of stress hormones after intense exercise (46). In the studies by Ribeiro et al. (eight weeks of resistance exercise) (38), Zaer Ghodsi et al. (eight weeks of high intensity exercise) (46), and Hammonds et al. (eight weeks of aerobic exercise) (56), a reduction was observed in HS-CRP among the subjects, while four weeks of aerobic, resistance, and combined exercise in the study by Alberga et al. showed no change in this index (57), which was in line with the results of the present study.

Limitations

Only the individuals with DM in the age range of 40-60 years participated in this study. Therefore, it is not possible to extend the results to the individuals in other age groups. Furthermore, there was no complete control on the subjects over the diet, amount and time of DM medication, and other effective environmental factors during the entire period of the study. Finally, the most important limitation of the present study was fatigue caused by a long period of evaluation (elementary assessment, endocrinologist visit, cardiologist visit, laboratory tests, echocardiography, and exercise test) and intervention (24 sessions).

Recommendations

It is recommended that interventions be conducted at higher intensities and more sessions with careful monitoring of the diet of the individuals with DM. It is also advisable to perform an intervention in people with type 1 and type 2 DM.

Conclusion

After 24 sessions of combined aerobic and resistance exercise, significant changes were observed only in FBS compared to the control group and the VLDL variable was close to significant. However, a significant decrease in FBS and HbA1c indices was also observed in the combined aerobic and resistance group. The decrease in the HDL index in the control group and its lack of change in the combined group is an alarm signal for the inactive individuals.

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Authors' Contribution

Soulmaz Rahbar: Study design and ideation, attract funding for study, support, executional, and scientific services of the study, providing study equipment and samples, data collection, analysis and interpretation of results, expert statistics services, manuscript arrangement, manuscript expert assessment in scientific terms, responsibility for maintaining the integrity of the study process from the beginning to the publication, and responding to the opinions of the reviewers; Sedigheh Sadat Naimi: Study design and ideation, support, executional, and scientific services of the study, providing study equipment and samples, analysis and interpretation of results, expert statistics services, manuscript arrangement, manuscript expert assessment in scientific terms, confirmation of the final manuscript for submission to the journal office, responsibility for maintaining the integrity of the study process from the beginning to the publication, and responding to the opinions of the reviewers.

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Conflict of Interests

The authors declare no conflict of interest. Dr. Sedigheh Sadat Naimi has been working as a faculty member of the department of physiotherapy at Shahid Beheshti University of Medical Sciences since 1994. Soulmaz Rahbar has been a Ph.D. student at School of Rehabilitation, Shahid Beheshti University of Medical Sciences from 2012 to 2016.

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