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ORIGINAL ARTICLE

The Effects of Aerobic and Resistance Exercise Therapy with and without Weight Bearing on the Outcomes of Stem Cell Therapy for Knee Osteoarthritis: A Randomized Clinical Trial

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ABSTRACT

Background. The objective of this trial was to evaluate the effect of two exercise programs on patients undergoing the implantation of intraarticular stem cells. **Objectives.** We performed a randomized trial on sixteen patients under 65 years old with moderate knee OA after stem cell therapy. **Methods.** Patients were randomly divided into two groups of exercise therapy: weight-bearing (WB) and non-weight-bearing (non-WB). This program lasted 12 weeks, with follow-ups at 1 and 3 months. Primary outcomes were knee pain (visual analog scale (VAS)) and physical function (Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)). Secondary outcomes included: standing time, walking distance, pain-free walking distance, time to jelling, and a subscale of stiffness and pain of WOMAC. **Results.** Fifteen patients were retained. No adverse effect was reported. There was a significant improvement in pain and physical function in both groups compared to the baseline. VAS: from 55±7.6 to zero (effect size of 1.34), total WOMAC: from 93.75±1.39 to 30.87±5.22 at 1-month and 21.87±6.99 at 3-month (1.88 and 2.73, respectively). For secondary outcomes, walking distance (from 750.0±267.26 meter to 2000.0±0.0 meter and 2500.0±0.0 meter, respectively, and time to jelling (at 3 months, from 5.00±0.0 minute to 35.00±16.90 minute) improved significantly better in WB group. **Conclusion.** Both types of exercises were safe and improved primary and secondary outcomes. WB exercise has additional benefits of more pain reduction and functional improvement.

KEYWORDS: ***Knee, Non-Weight Bearing Exercise, Osteoarthritis, Sports Medicine, Stem Cells, Weight Bearing Exercise.***

INTRODUCTION

Knee osteoarthritis (OA) is the most common joint disorder and the leading cause of pain and disability. (1, 2) The prevalence of OA is constantly increasing, with a worldwide prevalence of about 10 percent. (3) Many factors, such as age, body mass index (BMI), previous knee injury, inflammation, gender, and family history, are involved in the development of OA. (4, 5).

Due to the progressive nature of this disorder, which leads to cartilage degeneration, unfortunately, many available treatments, such as analgesics, intra-articular injection of anti-inflammatory medications, or lubricants, are more symptom-relieving than curative, and in many cases the person will eventually have to undergo a joint replacement. (6-8) Therefore, efforts have been made to develop therapies to reverse OA process,

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and the results were emerging therapies such as stem cell therapy which is based on the regeneration of the lost cartilage tissue. (9) Mesenchymal stem cells (MSCs), which have self-renewal and directional differentiation capabilities, are derived from bone marrow or adipose tissue (autologous or allogeneic) and can be implanted into the joint. (10, 11) At the same time, they suppress synovial activation, which could help cartilage regeneration and reduce destruction. (12-14)

Although high-intensity, professional exercise may lead to OA, therapeutic exercises are the first line of treatment for OA. (1, 15, 16) It has been shown that these exercises are safe and effectively reduce pain and improve function. (1, 17, 18) Cohort studies have revealed that exercise can slow the destruction of articular cartilage. (19, 20) However, a general concern might be that weight-bearing exercise could damage cartilage and exacerbate OA. A 2015 study by Wondrasch found that weight-bearing shortly after knee surgery was safe for knee cartilage and had better results than delayed weight-bearing at clinical outcomes. (21) The results of another study have shown that therapeutic exercise in patients undergoing meniscectomy had increased glycosaminoglycan (GAG) levels. (22)

This study aimed to evaluate the effects of weight-bearing and non-weight-bearing exercises on clinical outcomes among patients who had undergone intra-articular implantation of mesenchymal cells (MSC) derived from autologous bone marrow.

MATERIALS AND METHODS

Trial design. The present study is a single-center randomized clinical trial designed to evaluate the effect of two different methods of exercise therapy (with and without weight bearing) on patients with knee OA who had undergone stem cell therapy. This study was designed and conducted at the Sports and Exercise department of Shahid Beheshti University. The trial protocol was registered with the National Ethics Committee (IRCT20180226038870N2), approved by the review board of Shahid Beheshti University of Medical Sciences, and implemented under the Helsinki Declaration.

Participants. Eligibility criteria for stem cell therapy and how to perform it are explained in an article related to the clinical trial. (11) Eligibility criteria for the current study include 1- Performing stem cell therapy within 1 week of starting the exercises 2- No complications of intra-articular stem cell implantation, including redness, tenderness, warmth, and swelling of the joint. 3- Non-involvement of the hip, ankle, and back joints, including pain or restriction of movement that prevents patients from performing sports. 4- Absence of neurological disorders such as stroke, peripheral neuropathy, Parkinson's disease, and multiple sclerosis 5- Ability to participate in regular exercise therapy sessions. 6- Satisfaction with participating in the study.

Randomization Procedures and Blinding and Sample Size. Based on the effect size equivalent to 0.5, which is recommended for OA clinical studies (23) for power 80% and according to the sample size considered in previous stem cell therapy studies (3, 11) and including 20% loss to follow-up, a sample size of 15 patients was considered. Patients who underwent stem cell therapy were divided into two groups of exercise therapy with WB and non-WB; using the block randomization method (size 4), a random 1: 1 was assigned. For this purpose, the statistical consultant used a random process to assign sequences. Due to the nature of the intervention and the need to be supervised, it was not possible to blind patients and the physician performing the project. The statistical consultant of the study was blind to the data he analyzed.

Intervention. The steps of the project were fully explained orally and in writing by the responsible physician for the patients. Then informed consent was obtained. Patients were called by phone the day before the assessment session and each exercise session to remind them to participate in the exercise therapy program. The time to assessment session was 1 week after stem cell therapy and after relieving the pain and inflammation caused by the intra-knee implantation. The same physician supervised the exercise of the patients, who was observing the patients in all the sessions of the exercise program. The exercise program performed for the patients was as follows: (Table 1 and Figure 1).

• Group A (WB group): Assessment session: exercise test was performed on a treadmill with heart rate control. Based on the results, a mild to a moderate exercise program of 40-60% heart rate reserve (HRR) was considered for each patient. (24) two days later, the exercise program consisted of an aerobic program (walking on a treadmill without grade) for 30 minutes. This program was performed 3 days a week on even days. From the second month, if the patients tolerated the exercise duration and according to the supervising physician's opinion, this time was increased to 35 minutes per session, and from the third month, to 40 minutes per session. The resistant training program is fully described in Table 1. In squat movement, the patient's knee flexion with the flat back was monitored by the supervising physician to reach maximum pain-free flexion, and then the knee flexion angle was measured. The Borg scale measured exercise intensity, and moderate intensity was considered for patients. (25).

• Group B (non-WB): assessment session: on a stationary bike to calculate the appropriate resistance for pedaling equal to 40-60 ٪ HRR. Two days after the exercise test, an aerobic exercise program was performed using a stationary bike 3 days a week, on odd days, and under the physician's supervision. The session duration was 30 minutes in the first month, 35 minutes in the second month, and 40 minutes in the third month for each session (Table 1). According to the Borg scale, these movements were also prescribed to patients with moderate intensity.

All resistant exercises in both groups were performed first with one knee and then with the opposite knee. These exercises were performed on the same days as aerobic exercises and under the physician's supervision. If the patient tolerated, 1 set would be added to all resistant exercises in each session in the second and third months.

Outcomes. The evaluation was performed before stem cell implantation and 4 and 12 weeks after the intervention. (26).

Preliminary outcomes: pain and physical function of the patients who reported themselves. (27, 28). The pain was assessed based on a visual analog scale (VAS) and function based on the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). (29).

Secondary consequences: Walking distance, pain-free walking distance, standing time, time to jelling (time lasts for stiffing the joint), WOMAC subscale include: pain, stiffness, Total WOMAC score, Knee flexion range.

Table 1. Exercises for Weight Bearing and Non-Weight Bearing Groups

		Group A (WB exercises)	Group B (non-WB exercises)
Aerobic			
	Frequency	3 d/w	3 d/w
	Intensity	Moderate, Borg: 5/10	Moderate, Borg: 5/10
	Time	30 min. during the first month, 35 min. During the second month, finally, 40 min. The last month.	30 min. during the first month, 35 min. During the second month, finally, 40 min. The last month.
	Type	Walking	Stationary cycling
Resistance For quadriceps muscles group			
	Frequency	3 d/w	3 d/w
	Intensity	Moderate, Borg: 5/10 or until being tired	Moderate, Borg: 5/10 or until being tired
	Time	3 sets (for the first month)	3 sets (for the first month)
	Type	Squat	Isometric contraction of quadriceps in the supine position
Resistance For hamstring and posterior cuff muscles group			
	Frequency	3 d/w	3 d/w
	Intensity	Moderate, Borg: 5/10 or until being tired	Moderate, Borg: 5/10 or until being tired
	Time	3 sets (for the first month)	3 sets (for the first month)
	Type	Double leg Cuff raise	Flexion of the knee 30 degrees in the prone position, and when the patient can bear the weight of one leg in this position without pain, the weight of the opposite leg is dropped on the first leg.
Resistance For hamstring and posterior cuff muscles group			
	Frequency	3 d/w	3 d/w
	Intensity	Moderate, Borg: 5/10 or until being tired	Moderate, Borg: 5/10 or until being tired
	Time	3 sets (for the first month)	3 sets (for the first month)
	Type	Single leg Balance	Plantar flexion with the non-elastic band in the sitting position

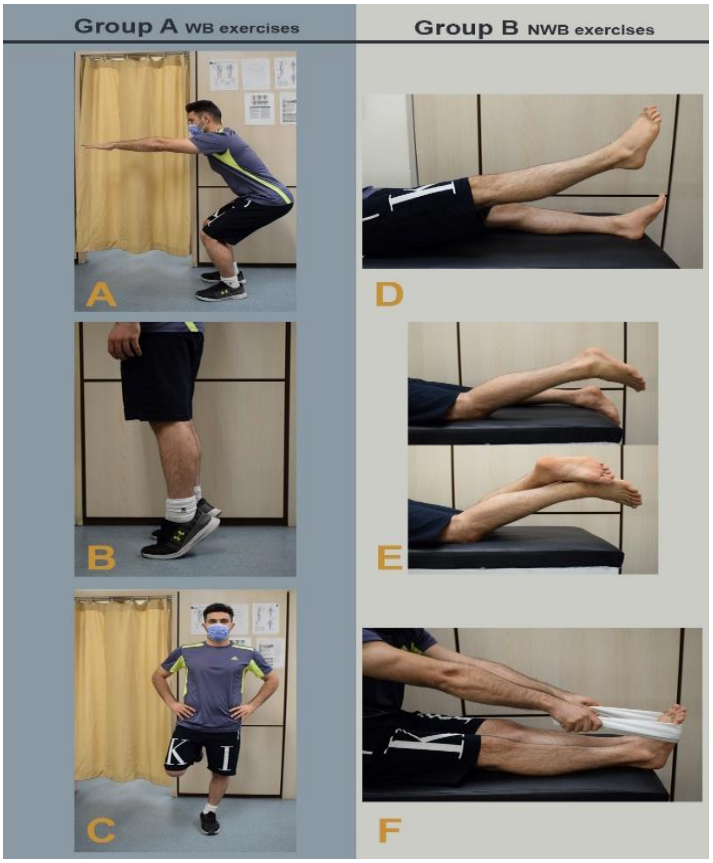

Figure 1. Weight-bearing exercises vs. non-weight-bearing exercises. A. Squat, **B.** Double leg Cuff raise, **C.** Single leg Balance, **D.** Isometric contraction of quadriceps in the supine position, **E.** Flexion of the knee 30 degrees in the prone position and when the patient can bear the weight of one leg in this position without pain, the weight of the opposite leg is dropped on the first leg in the order shown in the figure. **F.** Plantar foot flexion with the non-elastic band in a sitting position.

Statistical Analysis. Findings were presented as mean (standard deviation (SD)) and frequency (percentage), depending on the covariates to be continuous, respectively. The chi-squared test was used to compare the categorical variables between WB and non-WB groups. Moreover, the independent samples t-test was used to compare VAS, WOMAC subscales, walking distance, and standing time between the two intervention groups. The Cohen's d effect size was calculated to assess the strength of the intervention's impact on the outcomes. Repeated measures ANOVA was applied to compare the 1- and 3- month follow-ups with the baseline measurements. The analyses were performed using the statistical software Stata (ver. 13). The significance level was chosen to be 0.05.

RESULTS

From Sep 2020 to Feb 2021, Twenty-six patients who were candidates for stem cell therapy were visited by the attending physician. (Figure 2).

Based on the eligibility criteria for stem cell therapy, the patients were similar in baseline characteristics (published in the article by Emadedin et al. (11)). There was no significant difference in the severity of joint involvement based on the degree of Kellgren Lawrence grading (30) and the duration of the disease. Most participants (93.3%) were female (group A: 7 and group B: 7) with a mean age of 50 years and an average overweight. (Table 2).

According to the criteria for stem cell therapy, patients were allowed to take NSAIDs in case of joint pain. However, none of the patients were taking NSAIDs at enrollment. Sixteen patients were randomly divided into 9 in group A and 7 in group B, and 15 (93.7%) completed the study. (Figure 2).

The total exercise therapy sessions for each person in each group were 36 sessions. None of the patients experienced any side effects of stem cell therapy (according to the CONSORT criteria) (31) or exercise therapy, including pain, tenderness, redness at the implantation site, pain in other joints, or non-intervention complications, including fever or other systemic symptoms.

Table 2. Demographics and baseline characteristics of the patients with and without weight-bearing exercises

Characteristics	With Weight Bearing	Without Weight Bearing
Gender		
Male, n (%)	1 (12.5%)	0%
Female, n (%)	7 (87.5%)	7 (100%)
Age (year)	53.50 ± 2.77	53.85 ± 4.14
BMI (kg/ m^2)	29.76 ± 0.43	29.45 ± 1.13
Symptom duration (Month)	27.00± 5.55	27.43 ± 5.85
KLRC		
Grade 1, n (%)	0	0
Grade 2, n (%)	1 (11.1%)	0
Grade 3, n (%)	8 (88.8%)	7(100%)
Total Heart Rate 40%	107.25±1.49	107.43±1.72
Total Heart Rate 60%	129.12±1.55	129.28±0.95

KLRC: Kellgeren- Lawrence radiographic criteria

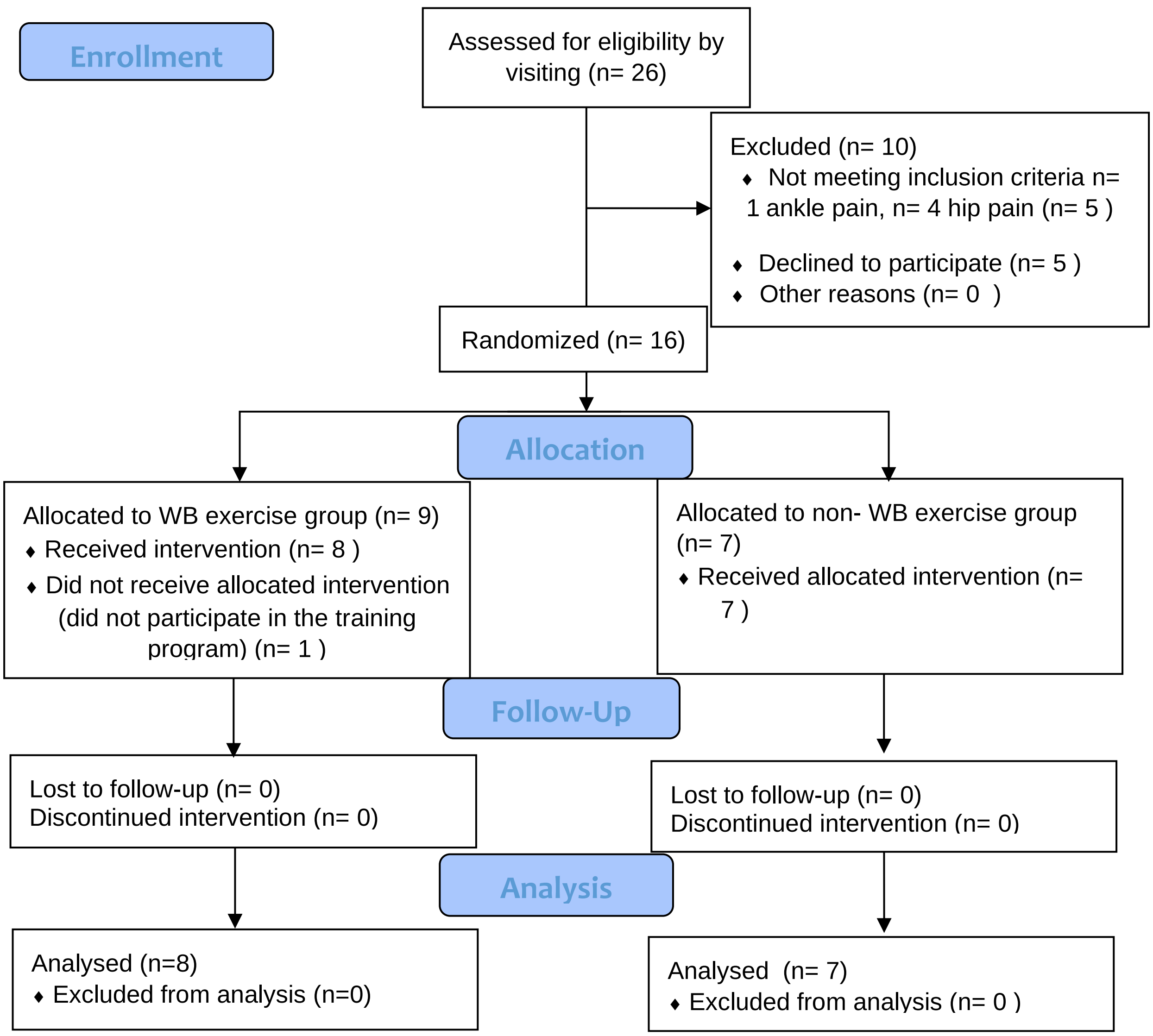

Figure 2. Participant Flow Through the Randomized Clinical Trial

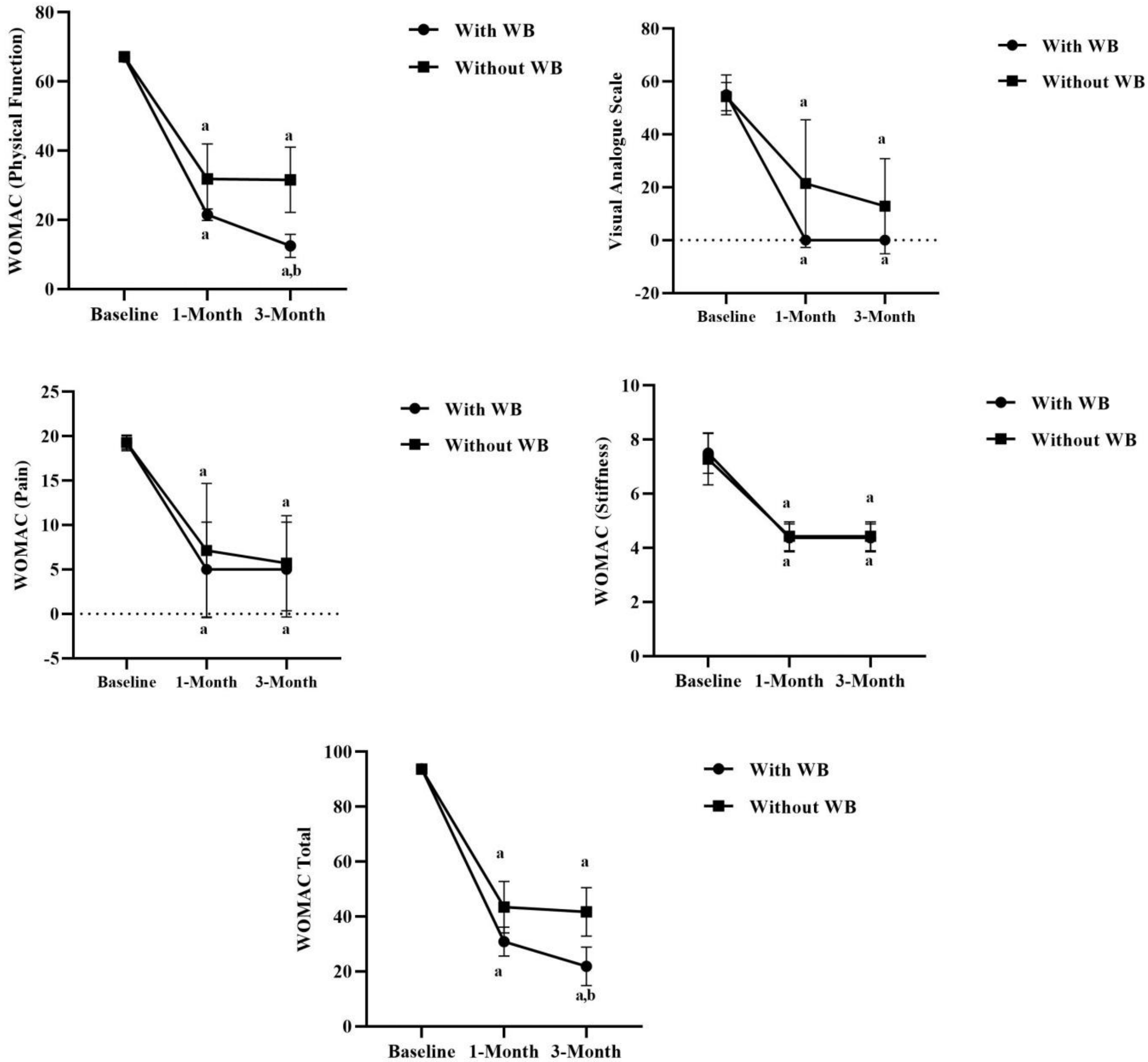

Figure 3. Comparison of VAS and the WOMAC subscales between the baseline and the intervention follow-up time. (a: is significant with baseline; **b:** is significant with 1-month). **VAS.** Visual analog scale, **WOMAC.** Western Ontario and McMaster Universities Osteoarthritis Index.

Preliminary Outcomes. Response variables measured at three-time points of baseline, 1 and 3-month follow-ups are reported in Table 3, for WB and non-WB groups. To examine the impact of the intervention on responses, the mean change of each post-intervention time 1- and 3-month with the baseline time was compared across groups with and without WB. Table 3 displayed the effect size for the measured outcomes. The positive effect size demonstrated an increased mean difference for patients in the non-WB group compared to the WB group, whereas the negative effect size demonstrated a decrease.

The effect size of 1.34 revealed that VAS measures in the WB group decreased more than the non-WB group 1 month after baseline, and the difference was statistically significant. While the difference in change from baseline was not statistically significant between the two study groups 3 months after baseline.

Figure 3 shows how the VAS score decreased during the follow-up period in both groups with and without WB. The VAS average was reduced to zero after one and three months (mean=55±7.6), which was statistically significant. There was no significant difference in time follow-up between 1 month and 3 months.

Similar changes were observed in WOMAC total score, which revealed that physical function improved in both groups compared to baseline, and in the WB group, this improvement was significantly better than the non-WB group. The changes in the WB group were significant in both 1-month and 3-month follow-ups compared to the non-WB. (from 93.75±1.39 to 30.87±5.22 at 1-month and 21.87±6.99 at 3-month and effect size of: 1.88 and 2.73, respectively, effect Size: 1.88 and 2.37, respectively) (Figure 3).

Secondary Outcomes. Walking distance and time to jelling in the WB group were better than in the non-WB group: walking distance was significantly better at both 1-month and 3-month measurements: from 750.0±267.26 meter to 2000.0±0.0 meter and 2500.0±0.0 meter, respectively, with an effect size of -1.13 and -1.54 respectively. This difference was significantly bigger for time to jelling at 3 months (from 5.00±0.0 minutes to 35.00±16.90 minutes, with an effect size of -1.59). Both groups significantly improved in baseline in terms of pain-free walking distance and standing time, but there was no clear difference between the two groups. (Table 3).

Results for Two Groups. The results of both groups' exercise volume are listed separately in the supplementary tables. All patients were able to perform a resistant program of 3 sets per session in the first month, 4 sets per session in the second month, and 5 sets per session in the third month. Both groups were the same in terms of the volume of exercise performed.

Table 3. Response variables measured at baseline, 1-, and 3-month follow-ups (mean (SD))

	Baseline	1-Month	Cohen's d Effect Size	3-Month	Cohen's d Effect Size
VAS					
With WB	55±7.60	0		0	
Without WB	54.28±5.34	21.42±24.10	1.34*	12.85±17.99	0.94
WOMAC Total					
With WB	93.75±1.39	30.87±5.22		21.87±6.99	
Without WB	93.71±1.11	43.43±9.39	1.88*	41.71±8.86	2.73*
WOMAC Pain					
With WB	19.25±0.88	5.00±5.34		5.00±5.34	
Without WB	19.28±0.75	7.14±7.56	0.33	5.71±5.34	0.13
WOMAC Function					
With WB	67.00±1.07	21.50±1.69		12.50±3.33	
Without WB	67.14±0.89	31.85±10.09	1.57*	31.57±9.43	2.96*
WOMAC Stiffness					
With WB	7.50±0.75	4.37±0.52		4.37±0.52	
Without WB	7.28±0.95	4.43±0.53	0.26	4.43±0.53	0.26
Time To Jelling					
With WB	5.00±0.0	17.50±10.35		35.00±16.90	
Without WB	5.71±1.89	12.85±11.85	-0.51	12.86±11.85	-1.59*
Pain free Walking Distance					
With WB	312.50±258.77	1375±694.36		2000±1069.04	
Without WB	357.14±243.97	1214.28±566.94	-0.35	1214.28±566.94	-1.01
Standing Time					
With WB	22.50±13.88	30.0±0.0		30.0±0.0	
Without WB	12.85±16.03	12.85±16.03	-0.73	12.86±16.03	-0.74
Walking Distance					
With WB	750.0±267.26	2000.0±0.0		2500.0±534.52	
Without WB	714.28±267.26	1428.57±534.52	-1.13*	1571.43±534.52	-1.54*

VAS: Visual Analogue Scale; **WB:** Weight Bearing; **WOMAC:** Western Ontario and McMaster Universities Osteoarthritis Index, *****Significant effect size of the mean difference between with and without WB.

DISCUSSION

It is the first randomized clinical trial to evaluate the effect of WB and non-WB aerobic and resistant exercise therapy in patients with mild to moderate knee OA who have undergone intra-knee stem cell implantation. Our findings suggest that exercise therapy improves the clinical outcomes of these patients.

There was significant improvement in knee pain and function based on the VAS and WOMAC questionnaire and walking distance after 36 supervised training sessions in WB exercises compared to the non-WB. Pain-free walking distance, standing time, and total score on the WOMAC questionnaire in both groups significantly improved compared to before implantation.

Numerous studies have evaluated the effects of WB and non-WB exercises on symptoms and physical function in patients with knee OA (32-35).

Almost all of these studies indicate an improvement in clinical outcomes after a regular exercise program. The results of the present study are consistent with them.

Exercises that include a combination of aerobic and resistance exercises are very effective in controlling the symptoms of patients with knee OA (15, 36, 37). Hughes et al. showed that it improves pain and 6-minute walking test (6MWT) results (38).

Evidence has shown that various exercises (strengthening quadriceps muscles, then a combination of strengthening and aerobic exercises such as walking programs, etc.) can reduce pain and improve the physical function of patients with knee OA (39, 40). However, the type of exercise did not have a different effect on the pain and activity of patients (41, 42). However, the present study showed that WB exercises based on the WOMAC questionnaire and walking distance and pain based on the VAS scale significantly improved patients' performance.

These findings are consistent with the Multan et al. study, which showed that WB exercise improves knee joint cartilage (43). In addition, a 2018 BJS review showed that WB exercise in patients at risk for knee OA or patients with knee OA is not harmful to the knee cartilage and is, in some cases, more beneficial than non-WB exercise. (1).

The main purpose of this study was to evaluate the effect of exercise therapy with WB and without WB and to compare these two exercise therapy methods on patients' outcomes with knee OA who have undergone intra-knee implantation of MSC. At the same time, the answer to the question of whether putting weight on the knee with OA will lead to worsening its condition or not? This study sought to find safe and effective exercises for prescribing knee stem cell therapy for OA.

Stem Cell Therapy. Because analgesics have many side effects, and many patients are reluctant to undergo knee replacement surgery (11, 44, 45), supportive therapies based on the regeneration of lost cartilage have been developed (12, 46). MSC grafting to the joint can relieve synovial inflammation (12) and regenerate articular cartilage. (10, 47) Emadedin et al. at 2018 showed that this treatment could reduce pain and improve patients' function (11). However, due to the novelty of this treatment, there is a need for complementary therapies to improve the results of this treatment.

Strengths of this Study. This study is the first to evaluate exercise therapy's effect with and without weight bearing in patients with knee OA who have undergone stem cell implantation. Both groups were similar in terms of type and volume of exercise. The difference is that in one group, the desired muscle was strengthened by WB, and in the other group without WB. Because stem cell implantation for knee OA is a new treatment, to eliminate this intervention's disruptive effect, the authors of this study similarly divided patients into two groups WB and non-WB. (Table 2) Therefore, the differences observed in the intervention results are only related to the type of exercise program and not cell therapy.

Limitations of this Study. The present study consisted of a relatively small and homogeneous group of people with knee OA. In this regard, it should be examined whether the results of this study can be generalized to the community with knee OA who have undergone stem cell therapy or not. The results were recorded at intervals of 1 and 3 months after the start of the exercise program, so it is impossible to comment on the effectiveness of this treatment for a long time after the intervention. For this purpose, it is necessary to have follow-up studies for further evaluations of these patients.

CONCLUSION

These findings suggest that exercise therapy, especially in combination with weight bearing, can be performed as a normal and safe routine in managing patients with knee OA who have undergone stem cell therapy.

APPLICABLE REMARKS

- After stem cell therapy for knee OA, patients should be encouraged to exercise programs, including WB and non-WB. It will improve the outcomes of stem cell therapy.

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AUTHORS' CONTRIBUTIONS

MH, AAY, MPE, and SS conceived the idea for the study; MH and AAY obtained funding for the study; MH, AAY, MPE, SS, and NL designed the trial protocol; NL recruited participants and coordinated the trial; NL responsible for statistical analyses; MH and NL drafted the manuscript, and all authors read and approved the final version for submission.

CONFLICT OF INTEREST

Authors have no conflict of interest to declare.

DATA SHARING

The research team will consider reasonable requests to share patient data not stated in this article. Requests must be sent to the corresponding author. Participants have consented to use their data for other research on knee OA and stem cell therapy. The data provided are anonymous, and the risk of identification is low.

Table S1. Results of Each Patient Exercises in Non-Weight Bearing Group.

Number non- WB	Watt of stationary cycling	Quad contraction time (each set) (second)	Prone knee flexion time (each set) (second)	Ankle plantar flexion time (set) (each second)
1	50	10	30: double leg	10
2	50	10	30: double leg	10
3	50	10	30: double leg	10
4	50	10	30: double leg	10
5	50	10	30: double leg	10
6	50	10	30: double leg	10
7	50	10	30: double leg	10

Table S2. Results of Each Patient Exercises in Weight Bearing Group.

Number WB	Speed of treadmill	Squat time (each set) (second)	Squat degree (set) (each second)	Calf raise time (each set) (second)	Single leg stance time (set) (each second)
1	4	10	110	10	10
2	4.5	10	110	10	10
3	4	10	110	10	10
4	4	10	120	10	10
5	3.5	10	110	10	10
6	4	10	110	10	10
7	4	10	110	10	10
8	4	10	110	10	10

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