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ORIGINAL ARTICLE

Exercise in knee osteoarthritis: do treatment outcomes relate to bone marrow lesions? A randomized trial

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ABSTRACT

Purpose: Exercise is effective for reducing knee osteoarthritis (OA) pain but effect sizes vary widely. Moreover, not all knee OA patients perceive beneficial effects. Tailoring specific exercises to subgroups of knee OA patients may increase effectivity. Bone marrow lesions (BMLs) have been suggested as a criterion to define such subgroups.

This study aimed to investigate whether BMLs' presence/absence is related to treatment outcomes in a group of knee OA patients who exercised for 18 weeks.

Methods: Subjects with symptomatic knee OA started a strength or walking exercise program. BMLs' presence at baseline was assessed. Pain was assessed before and after the intervention with the intermittent and constant osteoarthritis pain (ICOAP) questionnaire. Also the global perceived effect (GPE) on the patient's complaints was rated.

Results: Thirty-five patients (strength ($N = 17$) and walking ($N = 18$)) were analyzed for BMLs. BMLs were present in 25 (71%) knees. Five (14%) patients dropped out and 19 (54%) improved (GPE $\geq$5). All dropouts had BMLs, but no difference was seen between dropouts and retainers ($p > 0.05$). Pain scores did not differ between intervention groups ($p > 0.05$) or between patients with BMLs and without BMLs ($p > 0.05$).

Conclusions: Pain scores and GPE was not different between knee OA patients with and without baseline BMLs in this sample.

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KEYWORDS
Osteoarthritis; bone marrow lesion; exercise; knee; pain; global perceived effect

➤ IMPLICATIONS FOR REHABILITATION

- Both walking and strengthening exercises are effective means of improving pain in patients with knee osteoarthritis.
- In a relatively small sample, this study shows that the presence or absence of subchondral bone marrow lesions, as seen on magnetic resonance images, is not related to treatment outcomes.

Introduction

Osteoarthritis (OA) is a heterogeneous and progressive disease of the joint, characterized by several structural changes.[1,2] OA has become one of the most widespread joint problems in Western society and will become increasingly prevalent due to ageing of the population.[3]

Because until now OA is an irreversible condition, the treatment is focused on reducing disability, and controlling pain while minimizing the potentially harmful side effects of medications.[4] In this context, exercise therapy is considered an effective treatment for knee OA-related pain and disability[5–8] and recommended as "first choice conservative treatment" by several clinical guidelines.[9–11]

However, effect sizes of exercise for reducing pain in literature vary widely, ranging from 0.34 (95%CI: 0.19–0.49) to 0.63 (95%CI: 0.39–0.87) [9,12] and not all knee OA patients seem to perceive beneficial effects.[6] For example, Veenhof et al. reported a positive global perceived effect in 41% and 36% of the patients after two different exercise programs [13], and Knoop et al. reported a positive effect in 87% of patients following stability training and in 73% of patients after strengthening exercise.[14] As not all patients perceive similar effects, exploring the underlying mechanisms for the beneficial effects of exercise, may provide information to explain the high variability of effect sizes. Moreover, it may help to increase exercise effect sizes by tailoring specific exercise protocols to specific subgroups of patients. Patients who did not perceive a beneficial effect in the above mentioned studies, may not have received an optimal exercise program according to their specific profile. A frequently suggested mechanism to explain the beneficial effects of exercise on pain and function is that stronger muscles after training may unload the knee.[15] This mechanism has mainly been attributed to strengthening exercises and not to walking, presumably because walking, on the contrary, increases knee load (i.e., by 200–300% of the patient's bodyweight).[16,17]

Interestingly, bone marrow lesions (BMLs) have been significantly associated with mechanical knee load.[18,19] BMLs can be observed in 57–82% on magnetic resonance imaging (MRI) [20–22] already before symptoms appear in people who are at risk of developing knee OA.[23] High compartmental load

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(knee adduction moment, knee alignment (varus, valgus)) and structural lesions (meniscal, anterior cruciate ligament, cartilage) increase the risk of BMLs. Body weight increases the risk of BML to a lesser extent. BMLs have also been significantly and independently associated with pain in patients with knee OA.[24] In cross-sectional studies, it has been reported that patients with larger BMLs have higher pain scores with odds ratios ranging from 2.0 to 5.0.[25–27] In longitudinal studies, changes in BMLs volume have been associated with fluctuations in knee pain in patients with knee OA.[25–29] Therefore, BMLs are of particular interest as a target for preventive and therapeutic interventions to counter knee OA.[28,30].

Since OA is widely accepted as a heterogeneous disease, stratification of OA patients into subgroups (phenotypes), has recently been suggested to optimize treatment effects.[31–35] Therefore, tailoring specific exercise modalities to specific subgroups of knee OA patients may increase the effect sizes.[31–33] BMLs have been suggested as a specific criterion to define such OA subgroups [34], but it remains unclear whether these stratification techniques are efficacious to predict responses to exercise.

Considering the fact that walking increases the mechanical knee load and that strength exercises may unload the knee; given the correlations between BMLs and mechanical knee load and between BMLs and knee pain and since exercises (both walking and strengthening) have the potential to decrease the knee pain of osteoarthritic knees, patients presenting with or without BMLs may react differently to a walking or a strengthening program. However, this has not been investigated yet.

Therefore, this study aimed to investigate whether the presence or absence of BMLs influences treatment outcomes in a group of OA patients who underwent an 18-week walking or strengthening program.

Materials and methods

This prospective randomized controlled parallel trial was approved by the internal human institutional review board and participants provided written informed consent.

Patients

Community-dwelling volunteers aged 50 or older with a painful knee in the last 30 days and radiographic tibiofemoral osteoarthritis were recruited through advertisements (posters and local media). Selection criteria were based on the criteria defined by the American College of Rheumatology for knee OA.[36] Exclusion criteria include inability to come to the hospital for assessments and therapy, intra-articular steroid injections in the previous six months, a (systemic) arthritis condition other than OA, contraindications for physical exercise, or an unstable medical condition. All participants were initially screened by telephone for eligibility, and if appropriate, they were invited for a radiologic examination and a medical screening with an orthopedic surgeon in the university hospital UZ Brussel.

Imaging before exercise

Knee alignment was assessed on full-limb anteroposterior radiographs and was defined as the measure of the angle formed by the intersection of the line connecting the centers of the femoral head and intercondylar notch and the line connecting the centers of the ankle talus and tibial spines. Knees were considered "neutral" if angles were less than 5° in a varus or valgus direction and "misaligned" if the angle was 5° or more.[37] MR images were obtained at baseline on a 3.0T Philips Achieva system in the sagittal plane using a fat-saturated proton density fast spin echo sequence (TR: 7612 msec; TE: 15 ms; slice thickness: 3 mm; 27 sections; bandwidth: 357) and in the coronal plane using a fat-saturated proton density (fast spin echo) sequence (TR: 2733 ms; TE: 15 ms; slice thickness: 2.5 mm; 22 sections; bandwidth: 437).

Image analysis

The presence of subchondral BMLs was assessed dichotomously by an experienced radiologist who was blinded for patients' clinical information, group allocation, and pain scores.[38] BMLs were reported "present" if minimum one was seen in weight-bearing regions of the femur and tibia of the (most) painful knee. BMLs were defined as "areas of ill-delineated signal within the trabecular bone that are hypointense and hyperintense on T1- and T2-weighted fat-suppressed (fs) images and associated sub articular bone marrow cysts".[38]

Allocation

After baseline assessments, subjects were randomly allocated to the treatment groups (1:1) by a researcher that did not intervene with baseline measurements. To keep both intervention groups balanced, randomization was stratified by age, sex, knee alignment, and Kellgren and Lawrence (KL) grades. The reason for not considering BML as a stratification factor in the randomization of the subjects is related to practical issues since – although the MR images were taken before the start – the information (based on postprocessing of the MRI data) regarding the presence or absence of BML was not yet available at the time of the start of the exercise programs. In addition, adding BML presence/absence as a stratification factor would possibly have increased the risk of overstratification.[39] Randomization was performed in blocks of two (one for each intervention group), using a computer-generated table of random numbers. The reason for not considering BML to group the subjects was mainly inspired by practical issues since the MRI analyses regarding the presence or absence of BML were not available at the time of the start of the exercise programs. Allocation was revealed to the physiotherapist at the time the participant presented the first time for treatment.

Global perceived effect and pain

At baseline and after 18 weeks of training, the intermittent and constant osteoarthritis pain questionnaire (ICOAP) was used to rate the patients' knee pain.[40] This instrument contains 11 items that are scored on a 5-point scale (0–4). The total pain score ($ICOAP_t$) is calculated by summing the scores of two subscales (constant pain ($ICOAP_c$; 5 items (maximum score 20) and intermittent pain ($ICOAP_i$; 6 items (maximum score 24)). Higher scores indicate more pain. The ICOAP has been shown to be a valid, reliable, and responsive measuring instrument.[40,41] The difference between pre- and postintervention pain scores (post–pre) was also calculated for the total ICOAP ($dICOAP_t$) and its subscales ($dICOAP_c$ and $dICOAP_i$). The patient's global perceived effect (GPE) was recorded on a seven-point Likert scale, ranging from 1 (worse than ever) to 7 (full recovery) with 4 as neutral (no change). After the 18 weeks intervention period, patients were asked the following question: "To what extent are your complaints changed since the start of the treatment?" This method has been widely used and accepted for assessing individual meaningful improvements.[42] Intraclass correlation coefficient values of 0.90–0.99 indicate excellent reproducibility of the GPE scale.[43]

Assessors were blinded to BMLs analyses and group allocation. Dropout was registered.

Intervention

Participants were allocated to one of two standardized exercise programs: strength training (ST) or walking training (WT). Both exercise programs were performed three times weekly. The total intervention period consisted of 54 training sessions over a period of 18 weeks among which 18 sessions were supervised at the university hospital and 36 sessions were unsupervised at the participants' homes. The first three weeks, all participants trained three times per week under supervision of a trained physiotherapist at the University hospital. Afterwards, the number of weekly supervised sessions was gradually reduced as shown in Table 1. During the last 12 weeks, participants were invited to 4 booster sessions once every three weeks to assess their ability to precisely replicate the exercises. The strength training (ST) sessions lasted 45 min each and consisted in seven exercises that focused on strength and functional performance of knee extensors, hamstring, hip abductor, and hip adductor muscles. These exercises were chosen based on strengthening programs that previously showed beneficial effects on pain and function [44–47] and because they could easily be performed at home without extra materials. The WT was based on a walking program that also previously showed beneficial effects on pain and function.[48] The WT program consisted of walking for 40 min at an intensity of 14 to 17 on a Borg scale.[49] This is in accordance with a heart frequency equaling the sum of the heart frequency in rest and 50–80% of the heart reserve frequency (i.e., maximum heart frequency minus heart frequency in rest).[50]

Statistical analysis

An intention to treat analysis was performed to ensure the integrity of the randomization. Normality was checked via the Shapiro–Wilk test. Missing values of the baseline ICOAP questionnaire of two subjects were replaced by the mean scores of the group that scored the same GPE rating (i.e., 4) or that dropped out. Differences between pre and postintervention ICOAP scores within subgroups (BMLs, no BMLs) were analyzed with Wilcoxon signed rank tests for the total group and both intervention groups separately (ST, WT). Differences between BMLs groups (BMLs, no BMLs) were analyzed with Mann–Whitney U-tests or Fisher's exact test for the total group and both intervention groups (ST, WT). The effect sizes (r) were calculated by dividing the Z score of the Wilcoxon signed rank test by the root of the number of observations ($r = Z/\sqrt{N}$).[51] Effect sizes of (0).10; (0).30 and 0.50 should be interpreted as small, medium, and large effects.[52] Significance level was set at $p < 0.05$.

Table 1. Baseline descriptives of patients that were eligible for MRI.

N	Total group 35	ST 17	WT 18
Age, years	61.8 (8.88)	63.7 (8.08)	60.1 (9.48)
Sex male - female			
– Male	17 (49)	6 (35)	11 (61)
– Female	18 (51)	11 (65)	7 (39)
BMI, kgm^{-2}	28.0 (3.87)	28.0 (4.68)	28.0 (3.07)
KL grade			
– 1&2	25 (71)	12 (71)	13 (72)
– 3&4	10 (29)	5 (29)	5 (28)
Knee alignment			
– Valgus	3 (9)	3 (18)	0 (0)
– Neutral	22 (63)	11 (65)	11 (61)
– Varus	10 (29)	3 (18)	7 (39)
BMLs			
– Present	25 (71)	13 (76)	12 (67)
– Absent	10 (29)	4 (24)	6 (33)

Data are presented as mean (standard deviation) or numbers (percentage); kg: kilogram; m: meter.

Results

Thirty-seven patients were allocated to the intervention groups (ST ($n = 19$) and WT ($n = 18$)). One patient in the ST group was not able to start the exercises due to an accident that happened between baseline assessment and the start of the intervention period. BMLs images of one were not assessed due to MRI data loss ($n = 1$). Five subjects dropped out during the intervention period. Consequently, 30 subjects were included in the analysis (Figure 1). No significant baseline differences were found between both intervention groups (Table 1). Between group analyses showed no differences of the proportion of participants with BML between both intervention groups at baseline ($chi^2(1) = 4.12$, $p = 0.711$).

Global perceived effect and pain

Of the 35 patients that were included in this analysis, five (14%) dropped out and 19 (54%) indicated to be improved (GPE-score ≥ 5) (Figure 2). Significant improvements in ICOAP pain scores were found in the total group ($ICOAP_c$, $ICOAP_i$, $ICOAP_t$ ($p < 0.05$)), in the ST group ($ICOAP_i$, ($p < 0.05$)) and in the WT group ($ICOAP_i$, $ICOAP_t$ ($p < 0.05$)). Differences between pre- and postintervention pain scores ($dICOAP_c$, $dICOAP_i$, $dICOAP_t$) did not differ between both intervention groups.

Role of BMLs presence

BMLs were present in 25 (71%) patients. Although all dropouts had BMLs, there was no statistical difference for the presence of BMLs between dropouts and adherers ($p > 0.05$). No significant differences for pain measures ($ICOAP_c$, $ICOAP_i$, $ICOAP_t$) were found at baseline between subjects with and without BML, neither in the total group nor in each intervention group separately. Significant improvements in ICOAP pain scores were found only in subjects of the ST group with BMLs ($ICOAP_i$ & $ICOAP_t$ ($p < 0.05$)) (Figures 3, 4, and 5). Effect sizes can be found in Table 2. Differences between pre- and postintervention pain scores ($dICOAP_c$, $dICOAP_i$, $dICOAP_t$) did not differ between subjects with BMLs and subjects without BMLs (Figures 3, 4, and 5).

Three patients of the ST group and two of the WT group dropped out; no significant difference was seen between both proportions. Of all subjects that indicated to be improved after the program ($N = 19$), seven had no BMLs, accounting for 70% of the group without BMLs and 12 had BMLs, accounting for 48% of the group with BMLs. No significant differences were found between these groups. Comparable results were found in both intervention groups.

Discussion

In this study, we investigated whether the presence of BMLs influences treatment outcomes in a group of knee OA patients who exercised for 18 weeks. We found that the effect of exercise on pain and global perceived effect was not different between knee OA patients with and without baseline BMLs. To our knowledge, the presence of BMLs has not yet been investigated as a potential influencing factor of exercise-related outcomes. We investigated

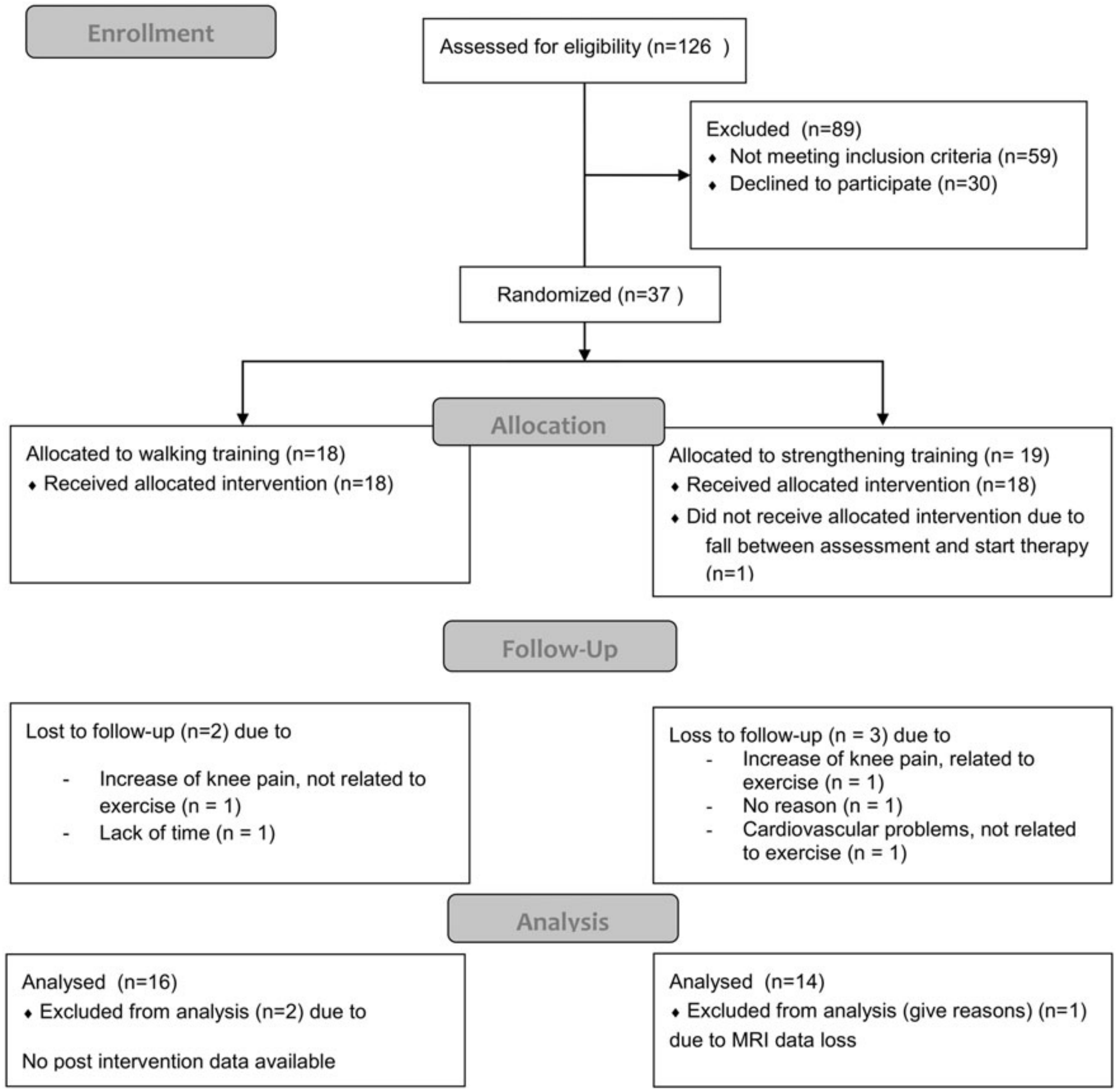

Figure 1. CONSORT flow diagram.

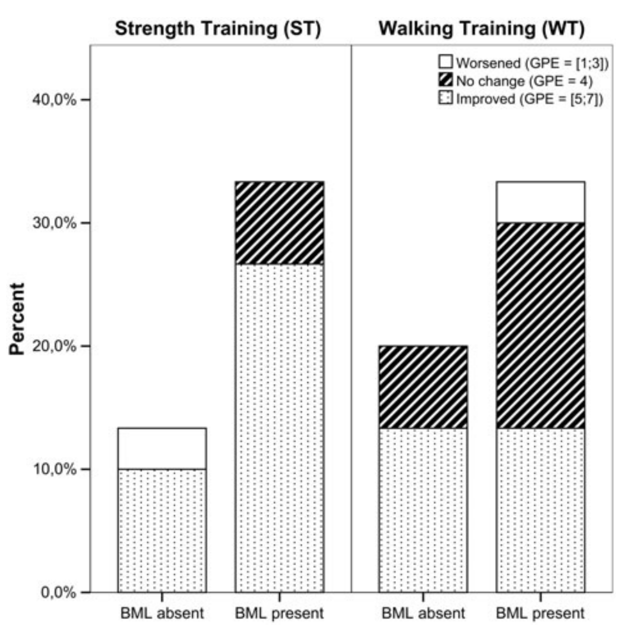

Figure 2. Global perceived effect combined scores for each BMLs presence subgroup (BMLs absent, BMLs present) of both intervention groups (ST, WT).

whether the presence of BMLs at baseline influenced pain and dropout in two 18 week during exercise programs. As expected, the pain scores were significantly lower after the exercise program and no differences in dICOAP were found between both intervention groups. These findings related to pain are in line with previous studies.[5,8] However, the research question in the present study was whether the presence or absence of BMLs is related to treatment outcomes. When we compared subjects with BMLs at baseline with those without, we were not able to detect significant differences of pain scores. Nevertheless, pain decreased significantly following ST in those patients with BMLs, but not in those without BMLs. This was not observed in the WT group. This finding might indicate that patients with BMLs might respond better to strength training for pain outcomes. Identification of BMLs before designing an exercise program might therefore be clinically relevant. However, our findings need to be confirmed in studies including a larger sample size, especially for the group without BMLs. Although the prevalence of BML in our sample (71%) was in line with the prevalence reported in literature [21], our results might have been skewed due to the uneven distribution between those having BML (71%) and those without BML (29%). Our findings may be in line with the hypothesis that strength exercises can induce beneficial effects in subjects with knee OA by means

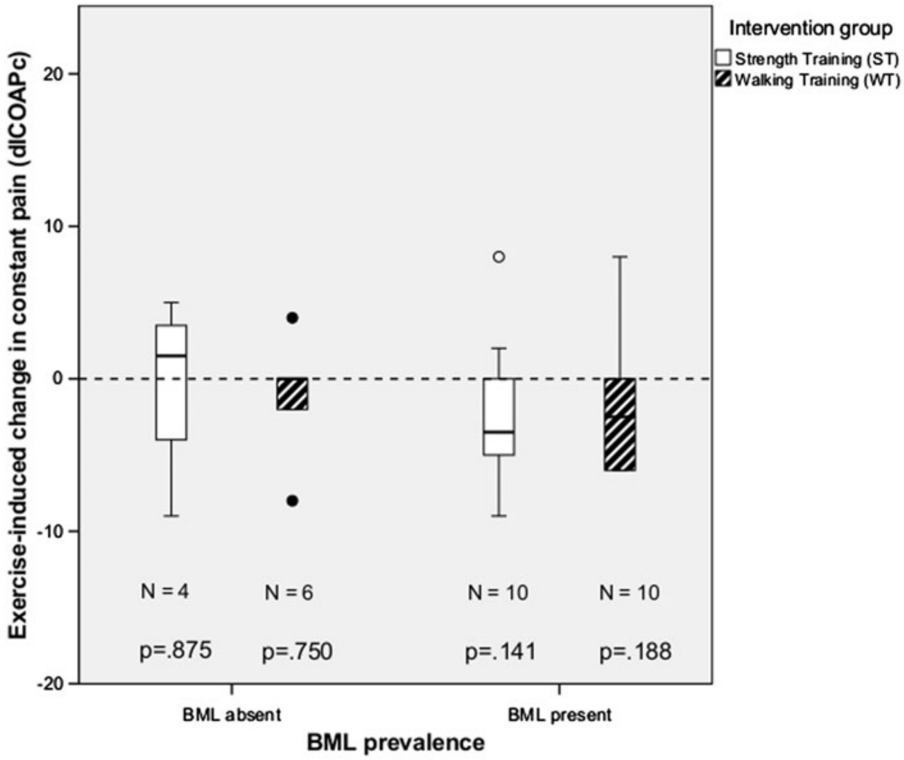

Figure 3. Difference between pre- and postintervention constant pain (dICOAPc) for each BMLs presence subgroup (BMLs absent, BMLs present) of both intervention groups (ST, WT). Scores below the striped line indicate a decrease in pain after the exercise program. Boxes indicate interquartile range (IQR), whiskers indicate the minimum and maximum of data. Dots represent outliers (>1.5 × IQR). No significant between differences were found. *p* values refer to within group pain changes (ICOAPc: Intermittent and constant Osteoarthritis Pain subscale for constant pain).

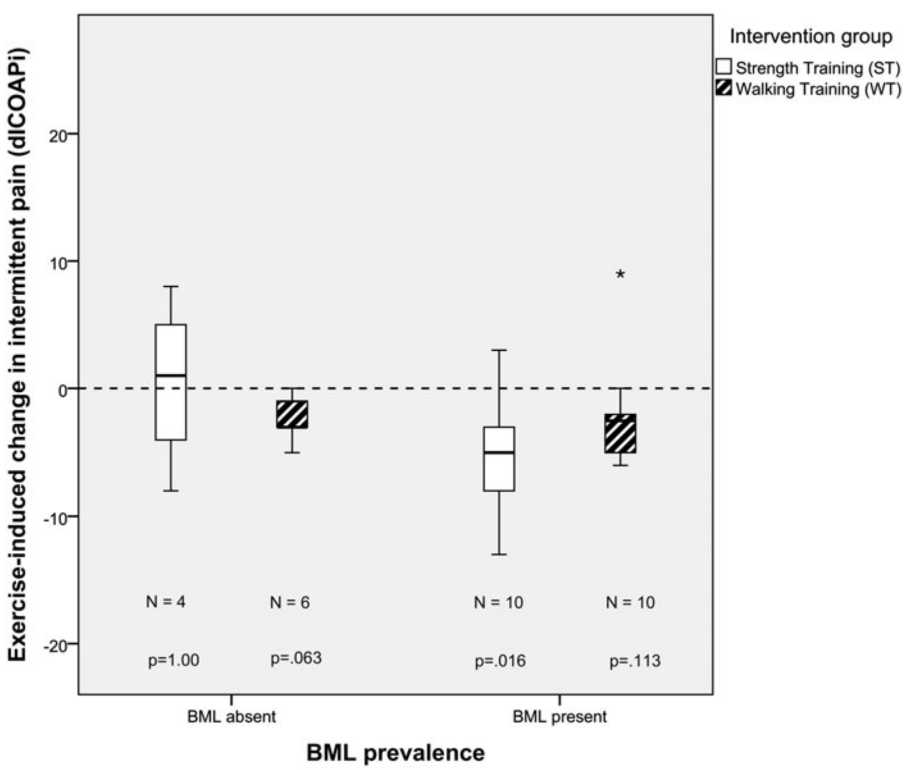

Figure 4. Difference between pre- and postintervention intermittent pain (dICOAPi) for each BMLs presence subgroup (BMLs absent, BMLs present) of both intervention groups (ST, WT). Scores below the striped line indicate a decrease in pain after the exercise program. Boxes indicate interquartile range (IQR), whiskers indicate the minimum and maximum of data. Dots represent outliers (>1.5 × IQR). No significant between differences were found. *p* values refer to within group pain changes (ICOAPc: Intermittent and constant Osteoarthritis Pain subscale for constant pain).

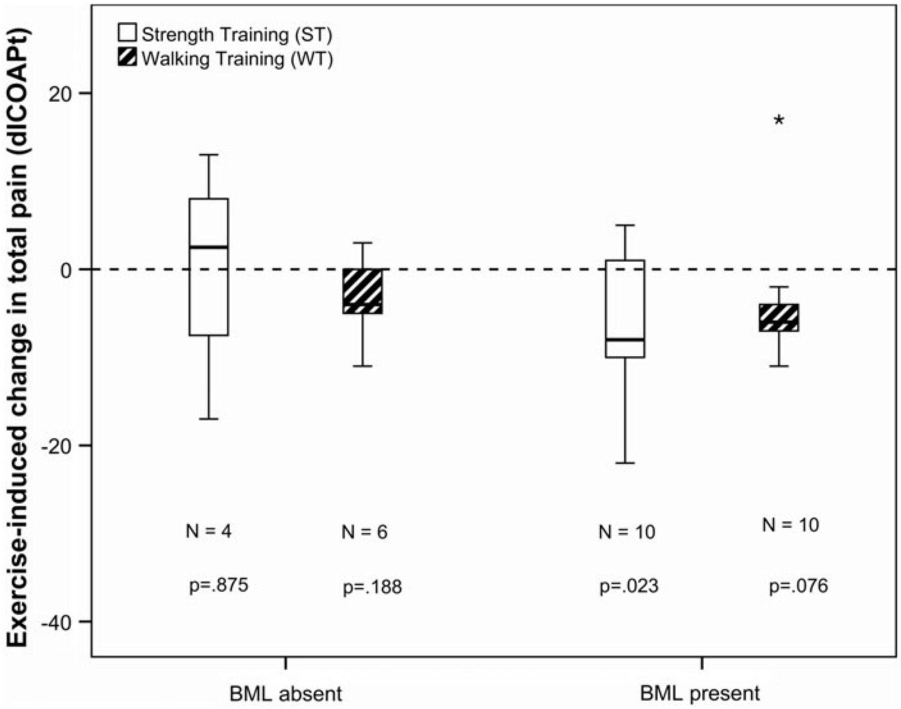

Figure 5. Difference between pre- and postintervention total pain (dICOAPt) for each BMLs presence subgroup (BMLs absent, BMLs present) of both intervention groups (ST, WT). Scores below the striped line indicate a decrease in pain after the exercise program. Boxes indicate interquartile range (IQR), whiskers indicate the minimum and maximum of data. Dots represent outliers ($>1.5 \times$ IQR). No significant between differences were found. *p* values refer to within group pain changes (ICOAPc: Intermittent and constant Osteoarthritis Pain subscale for constant pain).

Table 2. Effect sizes for ICOAP questionnaire.

		Baseline	Postintervention	ES	*p*
Total group					
BML ($N = 20$)	ICOAPc	4.9 (3.35)	2.7 (3.60)	−0.32	0.046[a]
	ICOAPi	8.0 (3.61)	4.9 (4.30)	−0.45	0.003[a]
	ICOAPt	12.9 (6.25)	7.6 (7.55)	−0.45	0.003[a]
no BML ($N = 10$)	ICOAPc	5.2 (4.54)	4.5 (4.60)	−0.06	0.844
	ICOAPi	8.9 (5.11)	7.6 (4.74)	−0.27	0.250
	ICOAPt	14.1 (9.33)	12.1 (8.88)	−0.20	0.406
ST					
BML ($N = 10$)	ICOAPc	3.8 (3.45)	1.2 (2,49)	−0.35	0.141
	ICOAPi	7.6 (4.59)	2.9 (2.73)	−0.54	0.016[a]
	ICOAPt	11.4 (7.15)	4.1 (5.15)	−0.49	0.023[a]
no BML ($N = 4$)	ICOAPc	7.5 (5.07)	7.3 (5.91)	−0.13	0.875
	ICOAPi	9.8 (6.85)	10.25 (5.91)	−0.10	1.000
	ICOAPt	17.3 (11.87)	17.5 (11.82)	−0.13	0.875
WT					
BML ($N = 10$)	ICOAPc	6.0 (2.95)	4.1 (4.07)	−0.31	0.188
	ICOAPi	8.5 (2.24)	6.9 (4.77)	−0.36	0.113
	ICOAPt	14.5 (4.91)	11.0 (8.41)	−0.40	0.076
no BML ($N = 6$)	ICOAPc	3.7 (3.83)	2.67 (2.66)	−0.15	0.750
	ICOAPi	8.3 (4.23)	5.83 (3.19)	−0.59	0.063
	ICOAPt	12.0 (7.67)	8.5 (4.37)	−0.47	0.188

[a]Significant difference between baseline and postintervention.
Data represent mean (standard deviation); ES: effect size (Z score/$\sqrt{N}$);
ICOAPc: intermittent and constant osteoarthritis pain subscale for constant pain); ICOAPi: intermittent and constant osteoarthritis pain subscale for intermittent pain; ICOAPt: intermittent and constant osteoarthritis pain total pain; ST: strength training; WT: walk training.

of decreasing the mechanical focal peak loading of the cartilage due to its impact on neuromuscular components.[15] In our study, the strength of exercises aimed primarily to increase the strength of the knee extensor and the hip abductor muscles. It has been hypothesized that stronger knee extensors may absorb more of the energy that would otherwise be transferred across the joint.[53,54] The eccentric work of the knee extensors at heel strike during gait, has been suggested to reduce the mechanical knee load at heel strike.[55] Moreover, quadriceps activity has been found to be delayed during stair descent (eccentric) but not ascent (concentric) in patients with symptomatic knee OA compared to asymptomatic controls.[56] Chang et al. observed that a greater hip abduction moment during gait at baseline had a protective effect against ipsilateral medial OA progression after 18 months follow–up.[57] The explanation that was provided by the authors was that during the single-limb stance phase of gait, weakness of the hip abductor muscles (of the stance limb) causes excessive pelvic drop towards the contralateral side, thereby shifting the body's center of mass towards the swing limb and consequently increasing forces across the medial tibiofemoral compartment of the stance limb. Therefore, it has been hypothesized that stronger hip abductors may reduce the compressive force at the knee.[58] However, intervention studies, aiming to investigate the effect of strengthening hip abductor muscles found contradictory results on mechanical knee load.[45,59,60]

A potential limitation of this study is the low sample size, and therefore, the results do not allow us to generalize. Our findings need thus to be confirmed in larger studies. Since this is the first study investigating BMLs as a potential influencing factor in exercise programs, future studies may use our data for calculating sample sizes. We have used the presence of BMLs in this study because recognizing a BMLs is a method that does not require an extensive knowhow. Consequently, it can easily be implemented in clinical practice since it is relatively time efficient. However, using dichotomous variables may lead to several problems among which the loss of important information,[61] As a consequence, statistical power to detect a relation between the variable and the patient outcome may be reduced,[61,62] More extensive MR image analyses can be used to quantify the volumes of BMLs.[63,64]

However, this was beyond the scope of the present study, where we focused on the prognostic value of BMLs presence on exercise outcomes in knee OA patients.

To our knowledge, this is the first study that investigates the effect of two exercise programs in relation to the presence or absence of BMLs in knee OA. Results of this study improves our knowledge of the underlying mechanisms of beneficial effects of exercise on pain and function in knee OA patients. In addition, understanding the interrelations between the presence/absence of BMLs and the effect of different exercise programs on pain and function may help to identify subgroups of knee OA patients who may benefit more from a specific program and thus increasing the effect sizes of exercise therapy.

Conclusion

We conclude that the effect of exercise on pain (ICOAP) and global perceived effect was not different between knee OA patients with and without BMLs in weight-bearing regions of the femur and tibia the start of an 18 week during exercise program.

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