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Exercise in knee osteoarthritis – preliminary findings: Exercise-induced pain and health status differs between drop-outs and retainers

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ABSTRACT

Background: Exercise effectiveness is related to adherence, compliance and drop-out. The aim of this study is to investigate if exercise-induced pain and health status are related to these outcomes during two exercise programs in knee osteoarthritis patients.
Methods: Symptomatic knee osteoarthritis patients were randomly allocated to a walking or strengthening program (N = 19/group). At baseline, patients were categorized according to their health status. Exercise adherence and compliance were calculated and drop-out rate was registered. For exercise-induced pain, patients rated their pain on an 11-point numeric rating scale (NRS) before and after each training session. Before each session the maximal perceived pain of the last 24 h (NRS_{max24}) was assessed. Patients rated their global self-perceived effect (GPE) on a 7-point ordinal scale after the intervention period.
Results: 53% of the participants felt they improved after the program, 6 patients dropped out. The mean adherence and compliance rates were higher than .83 in both groups. Worse health and higher exercise-induced pain were seen in drop-outs. NRS_{max24} during the first 3 weeks did not significantly increase compared to baseline, but correlated negatively with adherence during the home sessions ($-.56$, $p < .05$). Lower adherence during supervised sessions was significantly related with higher pre-exercise pain scores ($\rho = -.35$, $p < .05$).
Conclusion: Patients who drop-out show a worse health condition and higher exercise-induced pain levels compared to patients that retained the program.

1. Introduction

Osteoarthritis (OA) is characterized by a degeneration of articular cartilage in synovial joints. Pain and disability due to OA of the knee or hip occur in 40% of people aged 65 and over (Dawson et al., 2004; Mannoni et al., 2003). Because OA is considered as an irreversible condition, the treatment is focused on reducing physical disability and controlling pain while minimizing the potentially harmful side effects of pharmacotherapy (Zhang et al., 2007).

Exercise therapy is considered effective for knee OA-related pain and disability (Fransen and McConnell, 2008), and recommended as 'first choice conservative treatment' by several clinical guidelines (Bruyere et al., 2014; Fernandes et al., 2013; McAlindon et al., 2014). In the recent update of the Osteoarthritis Research Society International (OARSI) guideline for knee OA, treatment recommendations are provided for four clinical phenotypes of knee OA (McAlindon et al., 2014). These subtypes are based on whether OA is seen solely in the knee joint or in combination with other joints being affected. They are also based on the presence or absence of co-morbidities. Chan et al. reported on average 3.2 co-morbidities in knee OA patients: 78% had at least one musculoskeletal and 82% had at least one non-musculoskeletal co-morbidity (Chan et al., 2009). The rationale for the stratification of patients in the aforementioned guideline was that co-morbidities might influence treatment choices. However, the available information concerning the impact of co-morbidities on exercise outcomes in patients suffering from knee OA is limited and, therefore, exercise is recommended in the OARSI guidelines as a core treatment for all phenotypes.

Although several meta-analyses found short-term benefits of exercise in knee OA patients, effect sizes are small to moderate (Fransen and McConnell, 2008; Iversen, 2012; Jansen et al., 2011a). Moreover, not all knee OA patients that participate in an exercise program perceive a beneficial effect. For example, Veenhof et al. reported that only 37 of 90 (41%) and 37 of 102 (36%) knee OA patients reported to be improved after 13 weeks of following a behavioral graded activity exercise program, respectively a usual care program including exercises (Veenhof et al., 2006). Bennel et al. reported that 59% of knee OA patients indicated to be improved after 12 weeks of receiving a physiotherapy program (including exercises) (Bennell et al., 2005). A sufficiently high adherence, i.e. the number of sessions attended divided by the number of sessions prescribed, has been shown to be an important prerequisite for the exercise-induced benefits (Holden et al., 2014; Marks, 2012;

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Roddy et al., 2005). Moreover, non-adherence is suggested as an explanatory factor for the declining positive effects of exercise when patients are followed-up over time (Bennell et al., 2014; Marks, 2012; Pisters et al., 2010). Adherence may be influenced by several factors. In his literature review, Marks reported personal factors that influence exercise adherence in the patients with knee OA, including the ability to tolerate exercise-induced discomfort and impaired general health status (Marks, 2012). Adherence should be distinguished from drop-out which can be defined as patients that withdraw before completing an exercise program or study (Cyarto et al., 2006). In a randomized controlled trial, Thomas et al. reported that only 48% of the 226 subjects with knee pain that were allocated to receive exercise therapy, completed a two year home based exercise program that was designed to maintain and improve the strength of muscles acting around the knee, the range of motion at the knee joint, and locomotion function (Thomas et al., 2002). The most common reasons for drop-out were related to pain (of the back and/or hip) and lack of time. Moreover, patients that dropped out were more likely to be aged over 75, and have higher baseline pain scores as reported in a postal questionnaire. In a phenomenological study, the presence of pain has indeed been shown to be an important barrier to initiate and continue exercise in people with osteoarthritis (Petursdottir et al., 2010). Effectiveness of exercise therapy may be related to adherence and drop-out, but also to the extent to which patients comply with the prescribed program (e.g., in terms of duration, intensity, frequency) (Cyarto et al., 2006). Ettinger et al. reported that pain and function improved in a walking and in a strengthening group with an increased adherence, defined as the number of exercise sessions completed, divided by the total number of sessions prescribed (Ettinger et al., 1997). Moreover, the Cochrane meta-analysis of Fransen et al. reported that the number of supervised sessions influenced the effect sizes for pain and physical function (Fransen and McConnell, 2008). This finding was empowered by the more recently published meta-analysis of Juhl et al., although only for aerobic interventions (Juhl et al., 2014).

The study presented here is a sub study of the Knee Osteoarthritis Exercise Therapy (KNOET) study which aims to compare the effect of an aerobic and a strengthening exercise program on the volume of bone marrow lesions in the tibiofemoral joint and serum inflammatory parameters. The KNOET study was approved by the internal human institutional review board and participants provided written informed consent. Recruitment for the KNOET study is done in blocks of maximum 20 patients. At the moment, recruitment is still ongoing and 3 blocks of patients (n = 39) have finished the study. The aim of the present sub study is to investigate the relationship between the patient's adherence, compliance and drop-out and exercise-induced pain which was considered a safety variable (adverse event) in the KNOET study, since it may cause drop-out. Additionally, the present sub study also assed the influence of baseline health condition (including health category and comorbidities). The interim-analyses presented here were performed to anticipate adverse events, drop-outs, low adherence and/or compliance in the next recruitment waves of the KNOET study.

2. Methods

2.1. Participants and randomisation

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 osteoarthritis (Altman, 1995). 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, contra-indications 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. All subjects were involved in a stratified parallel-group intervention study with balanced block randomization of the patients [2:2] and blinded assessment. After baseline assessment, subjects were randomly allocated to one of two treatment groups. To keep both intervention groups balanced, randomization was stratified by age, sex, knee alignment and Kellgren and Lawrence (KL) grades. Randomization was performed in blocks of two (one for each intervention group), using a computer generated table of random numbers. Hence, we used two boxes: one for each sex. In each box, subgroups were made for three age categories: [50–65 years]; [65–75 years]; [75 + years]. In each age category, subgroups were made for knee alignment: neutral, >5° varus and >5° valgus. In each alignment subgroup, two subgroups were made for KL grades: one for grades 1 and 2; and another for grades 3 and 4. The numbering of the cards started at one and ended at 72. Each number corresponded to the allocation to one of both intervention groups. At the start of the study, each KL category contained one allocation card to each intervention program. Each time a new patient was included, a card was taken out of the corresponding box and the card number was written on the intervention form. When the two cards of one category were used, both were put back in the box, so that a second round could start. A list of card numbers and the corresponding treatment was provided to the therapists but not to the researchers enrolling and assessing participants. Allocation was revealed to the treating physiotherapist at the time the participant presented the first time for treatment.

Data was collected at the University Hospital Brussels (Universitair Ziekenhuis Brussel) from April 2012 to March 2014. The medical ethics committee of the University Hospital Brussels (Vrije Universiteit Brussel) approved the study protocol (B.U.N. 143,201,213,184) and all participants provided a written informed consent.

2.2. Exercise intervention

Participants were allocated to one of two standardized exercise programs: strength training (ST) or walking training (WT). Both programs were performed three times weekly. The total intervention period consisted of 54 training sessions over a period of 18 weeks, among which 18 supervised sessions at the university hospital and 36 unsupervised sessions 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 ST sessions lasted 45 min each and consisted in 7 exercises that focused on strength and functional performance of quadriceps, hamstring, hip abductor and hip adductor muscles (Table 2).

The WT program consisted of walking for 40 min at an intensity of 14 to 17 on a Borg scale (Borg, 1982). This is in accordance with a heart frequency equalling 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) (Leurs et al., 2000). Each participant was asked to avoid co-interventions during the study period. Due to

Table 1
Exercise scheme of the supervised and home sessions (data are presented as frequency per week).

Week n°	Supervised sessions	Home sessions
1–3	3	0
4–5	2	1
6	1	2
7–18	1 booster session/3w	3

Table 2
Overview of strength exercises, including exercise volume.

Muscles	Exercise description	Exercise volume	Number of repetitions
Quadriceps/Hamstrings	Isometric knee extension with a rolled towel under the knee	3 × 10 × 5 s	30
	'Straight leg raise' from long-sitting	3 × 15	45
	Knee extension, sitting on a chair	3 × 15	45
	'Sit to stand' (Bilateral knee extension from a chair)	3 × 15	45
Hip ad- & abductors	Hip abduction and external rotation in side-lying	10 × 10s	10
	Hip abduction in side-lying position (straight knee)	3 × 15	45
	Bilateral isometric hip adduction (pushing in towel between knees), sitting on a chair	3 × 10 × 5 s	30
		Total	250

ethical considerations, analgesia and non-steroidal anti-inflammatory drugs were permitted and registered in a logbook.

2.3. Outcome measures

All outcome assessors were blinded for the participants' group allocation. All participants underwent a medical screening with an orthopedic surgeon. OA grading was performed using the Kellgren-Lawrence criteria by evaluating x-ray changes observed in anteroposterior knee radiography. 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 "malaligned" if the angle was 5° or more (Sharma et al., 2003).

At baseline and after 18 weeks of training, the Intermittent and Constant Osteoarthritis Pain questionnaire (ICOAP) was used to rate the patients' knee pain (Hawker et al., 2008). 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 (Goncalves et al., 2012; Hawker et al., 2008). The difference between pre and post intervention pain scores (post – pre) was also calculated for the total ICOAP ($dICOAP_t$) and its subscales ($dICOAP_c$ & $dICOAP_i$).

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 shown to be clinically relevant and stable for assessing individual meaningful improvements (ten Klooster et al., 2006). Intra-class correlation coefficient values of 0.90–0.99 indicate excellent reproducibility of the GPE scale (Kamper et al., 2010).

2.3.1. Patient adherence

At the start of the study, all subjects were given 18 appointments for the supervised exercise sessions. Patient adherence for the supervised sessions was calculated as the ratio of the number of training sessions that were actually carried out versus the number of prescribed sessions. For the home sessions, exercise adherence was calculated as a ratio of the number of training sessions that were actually carried out at home (as indicated by the subjects in a personal log book) versus the total number of prescribed home sessions (N = 36).

2.3.2. Compliance

For the WT, compliance was calculated as the ratio of the total training duration (recorded in the logbooks) versus the prescribed total training duration, multiplied by 100. The prescribed total training duration was respectively 720 min (18 sessions × 40 min) and 1440 min (36 sessions × 40 min) for the supervised and home sessions. For the ST, the total number of repetitions was divided by the prescribed total number of repetitions. The prescribed total number of repetitions was respectively 4500 (18 sessions × 250 leg movements/session) and 9000 (36 sessions × 250 leg movements/session) for the supervised and home sessions.

Patient drop-out and the reason for withdrawal were registered.

2.3.3. Maximal pain during the last 24 h

At baseline and before each supervised training session, subjects were asked to rate their maximal pain during the last 24 h on an 11-point numerical rating scale (NRS). These scores of the first three intervention weeks (NRSmax24-3) and of the period between week 4 and 18 (NRSmax24-18) were averaged. This variable was chosen to investigate whether an increase of maximal pain during the first weeks was a barrier to continue with the exercise program. The NRS has an excellent ability to detect change and a reduction of 2 points or 30% on NRS scores is considered to be clinically important (Farrar et al., 2001; Hawker et al., 2011; Salaffi et al., 2004). Elderly prefer the NRS above other pain measure instruments (Peters et al., 2007).

2.3.4. Exercise-induced pain

Before and after each training session, subjects were asked to rate their current pain on an 11-point NRS. For each training day, the pre-training NRS score was subtracted from the post-training score to obtain the exercise-induced pain. Each pre, post and exercised induced NRS score was then averaged to obtain NRS_{pre}, NRS_{post} and $NRS_{post\text{-}pre}$ respectively. We a priori defined NRS post-pre as the average between the start of the program until the end of the program or until the time of drop-out. To examine the variation of each subject's exercise-induced pain (or pain relief) across repeated exercise sessions, the modulus (absolute value, i.e. the numerical value without regard to its sign) of each $NRS_{post\text{-}pre}$ was calculated ($|NRS_{post\text{-}pre}|$).

2.4. Health status

All subjects were categorized according to their risk for complications during physical exercise using a *health classification system* for elderly persons as described previously (Bautmans et al., 2004, 2005) (see Table 3 for description of health categories).

2.5. Comorbidity

For all participants the age-adjusted *Charlson Comorbidity Index* (*CCI*) (Charlson et al., 1987) was computed. The CCI predicts the ten-year mortality for a patient who may have a range of comorbid conditions. Each condition is assigned a score of 1, 2, 3, or 6, depending on the associated risk of mortality. Scores are summed and age-adjusted to provide a total score.

2.6. Statistical methods

An intention-to-treat analysis was performed to ensure the integrity of the randomization. Normality was checked via the Shapiro-Wilk test.

Table 3
Baseline descriptives (data represent median (interquartile range) or numbers (percentage); BMI: Body Mass Index; ECG: Electrocardiogram; 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; kg: kilogram;KL: Kellgren & Lawrence; m: meter; ST: Strength Training; WT: Walk Training.

	Total group	ST	WT
N	38	19	19
Age (years)	60 (10.25)	61 (10)	60 (10)
Sex			
-male	17 (45)	6 (32)	11 (58)
-female	21 (55)	13 (68)	8 (42)
BMI (kgm^{-2})	27.3 (6.38)	27.1 (7.9)	27.9 (5.2)
KL grade			
−1&2	25 (66)	12 (63)	13 (68)
−3&4	13 (34)	7 (37)	6 (32)
Knee alignment			
-valgus	4 (11)	4 (21)	0 (0)
-neutral	24 (63)	12 (63)	7 (37)
-varus	10 (26)	3 (16)	12 (63)
Health category			
-A	–	–	–
Completely healthy, no or only preventive medication			
B1	27 (71)	12 (63)	15 (79)
Functioning normally; presence of stabilized, no cardiovascular disease; absence of cardio-vascular abnormalities			
B2	8 (21)	4 (21)	4 (21)
Functioning normally; using medication with cardiovascular effect, no overt cardiovascular disease other than normalized arterial hypertension			
C	1 (3)	1 (5)	–
History of, or stabilized cardiovascular pathology, or abnormal ECG			
D	2 (5)	2 (11)	–
Presenting signs of acute or active disease at themoment of examination			
Charlson's Comorbidity Index			
0	27 (71)	14 (74)	13 (68)
1	–	–	–
2	2 (5)	–	2 (11)
3	5 (13)	3 (16)	2 (11)
4	3 (8)	1 (5)	2 (11)
5	1 (3)	1 (5)	–

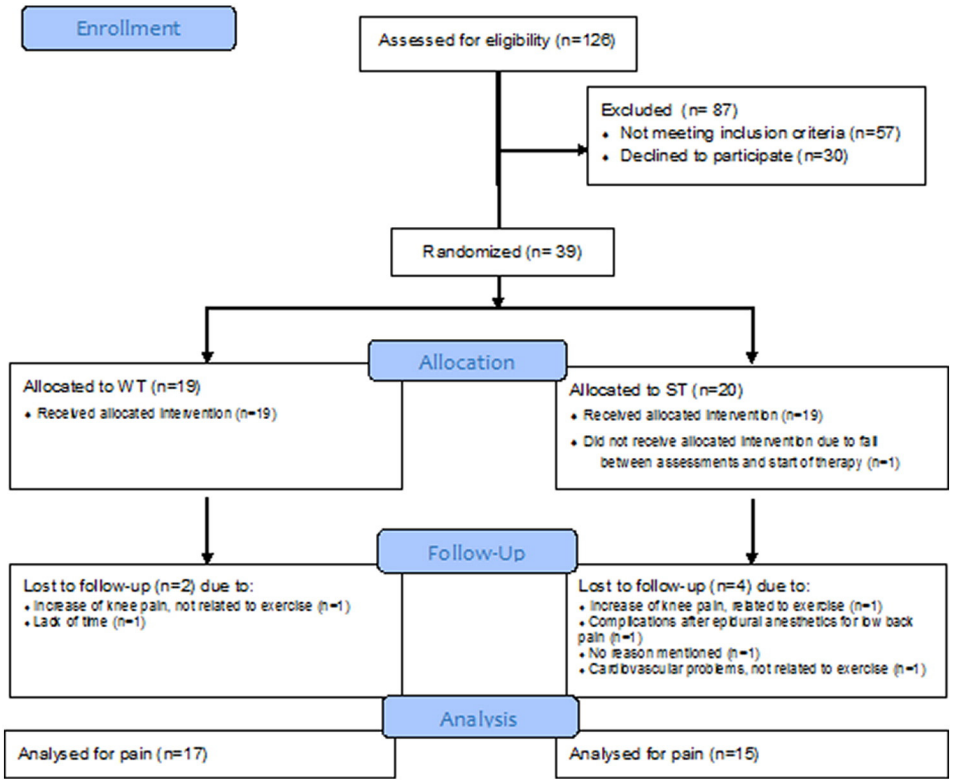

Fig. 1. CONSORT flow chart.

Non parametric test were chosen above parametric since subgroups were small and the majority of variables were not normally distributed. Missing values of the baseline ICOAP questionnaire of two subjects were replaced by the mean ICOAP scores of the group that scored the same GPE rating (i.e. 4) or the subjects that dropped out. Differences between baseline and post intervention ICOAP scores within groups were analyzed using the Wilcoxon signed rank test. 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 ($r = Z/\sqrt{N}$) (Field, 2009). Effect sizes of .10; .30 and .50 should be interpreted as small, medium and large effects (Cohen, 1992). Odds ratio for worse health and drop-out was calculated. Between group differences for exercise-induced pain, comorbidity and health status were analyzed with Mann Whitney U tests, Fisher's Exact or Kruskall Wallis tests. Changes of NRS_{max24} scores were analyzed using repeated measures ANOVA mixed design (within factor: time and between: intervention group). Bonferroni post-hoc test were performed to detect significant differences between pain scores. Correlations between outcomes were analyzed with Spearman's rho. Significance level was set at $p < .05$.

3. Results

One hundred and twenty-six people volunteered to participate (Fig. 1). Thirty people declined further participation after being informed about the study. Ninety-six persons were screened for eligibility by telephone, of whom 52 were excluded for participation. Most exclusions were due to having no clinical OA, language issues (French, Arabic) and being not able to come to the hospital for the training sessions. Consequently, 44 people were invited for medical screening and a radiologic examination after which five were excluded because they did not meet the inclusion criteria. Finally, 39 subjects were allocated to the intervention groups (ST ($n = 20$) and WT ($n = 19$)). 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.

Both groups were similar at baseline (see Table 3). ICOAP scores at baseline did not differ between health categories. Four people dropped out in the ST group and two in the WT group (Table 4). Most of the drop-outs did not return their logbooks despite of our attempts to recuperate them and thus compliance data for these subjects are missing.

Significant improvements in ICOAP pain scores were found in the total group ($ICOAP_c$, $ICOAP_i$, $ICOAP_t$ ($p < .05$)), in the ST group ($ICOAP_i$, ($p < .05$)) and in the WT group ($ICOAP_i$, $ICOAP_t$ ($p < .05$)). Effect sizes can be found in Table 5.

Differences between pre and post intervention pain scores ($dICOAP_c$, $dICOAP_i$, $dICOAP_t$) did not differ between the ST and WT group or between the health categories (Table 5). Twenty subjects (53%) indicated to be improved (GPE-score ≥5). Fisher's exact test revealed no difference between both intervention groups for being a responder (GPE ≥5) or non-responder (GPE ≤4).

NRS_{max24} during the first 3 weeks did not change significantly compared to baseline (mean difference − .96; 95% CI [−1.97;.44], $p = .07$). However, $NRS_{max24\text{-}18}$ was rated significantly lower than $NRS_{max24\text{-}0}$ (mean difference − 1.96; 95% CI [−2.88, −1.05], $p < .0001$) and $NRS_{max24\text{-}3}$ (mean difference − 1.00; 95% CI [−1.58, −.43], $p < .001$).

Exercise-induced pain, as measured by $NRS_{post\text{-}pre}$ and $|NRS_{post\text{-}pre}|$ did not significantly differ neither between the intervention groups nor between health categories.

Adherence and compliance for the supervised and the home sessions was similar for both intervention groups as well as for all health categories (Table 6).

A significantly higher dropout rate was observed for health categories B2-D compared to A-B1 (Fisher's exact test $p < 0.05$) but no difference was found between both intervention groups (Table 6). NRS_{post},

Table 4
Description of drop-outs (BMI: Body Mass Index; 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; kg: kilogram; KL: Kellgren & Lawrence; m: meter; NRS_{max24}: Maximal pain during the last 24 h; NRS_{pre}: Averaged Numeric Rating Score before training; NRS_{pos}: Averaged Numeric Rating Score after training; $NRS_{post\text{-}pre}$: Averaged exercise induced pain ST: Strength Training; WT: Walk Training.

	Subjects					
	1	2	3	4	5	6
Intervention group	ST	ST	WT	ST	ST	WT
Exercise related drop out	Yes	No	No	No	No	No
Reason for drop-out	Increase of knee pain, related to exercise	Complications after epidural anesthetics for low back pain	Increase of knee pain, not related to exercise	No reason mentioned	Cardiovascular problems, not related to exercise	Lack of time
Age	84	52	54	64	77	50
Sex	F	F	M	M	F	M
BMI (kgm^{-2})	33.3	22	24.5	31.1	30.4	30.5
KL grade	3	3	2	2	2	1
Knee alignment	neutral	valgus	varus	neutral	neutral	neutral
Health category	D	C	B1	B2	B2	B2
Charlson's Comorbidity Index	5	0	0	3	0	2
ICOAPc baseline	5	5	5	2	7	5
ICOAPi baseline	6	6	7	2	10	5
ICOAPt baseline	11	11	12	4	17	10
Adherence supervised sessions	0.11	0.56	0.69	0.83	0.61	0.72
Adherence home sessions	missing data	missing data	missing data	missing data	missing data	0.53
Compliance supervised sessions	missing data	missing data	0.61	missing data	missing data	0.72
Compliance home sessions	missing data	missing data	missing data	missing data	missing data	0.69
NRSmax24 baseline	5.0	6.0	5.0	0.0	1.0	7.0
NRSmax24 avg. weeks 1–3	5.5	5.3	3.3	0.0	4.7	6.7
NRSmax24 avg. weeks 4–18	missing data	5.3	2.8	0.1	2.3	6.7
NRSpre	5.0	2.4	1.5	0.0	1.8	2.4
NRSpost	5.0	5.1	3.4	0.0	3.2	4.6
mean NRSpost-pre	0.0	2.7	1.8	0.0	1.4	2.2
mean |NRSpost-pre|	0.0	2.7	1.8	0.0	2.3	2.5

Table 5
Effect sizes (baseline – post intervention) for ICOAP questionnaire (data represent median (interquartile range); ES: effect size (Z score/√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.

	Baseline	Post intervention	ES	p
Total group				
ICOAPc	5 (7)	3 (6)	−.26	.042*
ICOAPi	9 (5)	6 (6)	−.39	.002*
ICOAPt	13 (10.75)	9 (10)	−.37	.003*
ST				
ICOAPc	4 (9)	3 (5)	−.25	.209
ICOAPi	7 (10)	5 (6)	−.38	.045*
ICOAPt	11 (16)	8 (11)	−.31	.101
WT				
ICOAPc	6 (6)	4 (6)	−.28	.131
ICOAPi	9 (4)	7 (5)	−.43	.013*
ICOAPt	15 (10)	11 (7)	−.43	.013*

$NRS_{post\text{-}pre}$ and adherence during supervised training sessions differed significantly between subjects that dropped out and subjects that did not drop out ($p < .05$).

All correlation coefficients are reported in Table 7. During the supervised training sessions, better adherence was significantly correlated with lower NRS_{pre} scores ($\rho = -.35$, $p < .05$) (Table 7). Also, higher compliance during supervised sessions correlated significantly with lower $NRS_{max24\text{-}3}$ ($\rho = -.50$, $p < .05$) and NRS_{post} scores ($\rho = -.38$, $p < .05$). Similarly, during the home sessions, higher adherence significantly correlated with lower $NRS_{max24\text{-}3}$ ($\rho = -.56$, $p < .05$), $NRS_{max24\text{-}18}$ ($\rho = -.43$, $p < .05$), NRS_{post} scores ($\rho = -.40$, $p < .05$) and $|NRS_{post\text{-}pre}|$ ($\rho = -.42$, $p < .05$) but not with $NRS_{post\text{-}pre}$ ($\rho = -.19$, $p > .05$). Age correlated significantly with compliance during supervised training sessions ($\rho = .48$, $p < .05$) but not during home sessions ($\rho = .18$, $p > .05$). Comorbidity Index did not correlate with adherence ($\rho = -.07$ (supervised); $\rho = -.15$ (unsupervised); $p > .05$), compliance ($\rho = -.10$ (supervised); $\rho = .17$ (unsupervised); $p > .05$) nor $dICOAP_c$ ($\rho = -.03$; $p > .05$), $dICOAP_i$ ($\rho = .10$; $p > .05$) and $dICOAP_t$ ($\rho = .05$; $p > .05$).

Table 7
Correlation matrix (Data represent Spearman rho; *Significant correlation at $p < .05$; dICOAPc: difference between pre and post intervention Intermittent and constant Osteoarthritis Pain subscale for constant pain; dICOAPi: difference between pre and post intervention Intermittent and constant Osteoarthritis Pain subscale for intermittent pain; dICOAPt: difference between pre and post intervention Intermittent and constant Osteoarthritis Pain total pain; GPE: Global Perceived Effect, NRS_{max24}: Maximal pain during the last 24 h; NRS_{pre}: Averaged Numeric Rating Score before training; NRS_{pos}: Averaged Numeric Rating Score after training; $NRS_{post\text{-}pre}$: Averaged exercise induced pain).

	Supervised		Unsupervised (home)	
	Adherence	Compliance	Adherence	Compliance
Age	.32	.48*	.16	.18
ICOAPc baseline	.08	.01	−.20	−.16
ICOAPi baseline	.12	−.03	−.06	.01
ICOAPt baseline	.11	.01	−.12	−.04
dICOAPc	−.05	.01	−.11	−.1
dICOAPi	−.17	−.06	−.36*	−.36
dICOAPt	−.09	.00	−.15	−.17
NRS_{max24} baseline	−.11	−.12	−.18	−.14
NRS_{max24} avg. weeks 1–3	−.01	−.50*	−.56*	.07
NRS_{max24} avg. weeks 4–18	−.01	−.32	−.43*	−.11
NRS_{pre}	−.35*	−.24	−.25	−.20
NRS_{post}	−.29	−.38*	−.40*	−.09
mean $NRS_{post\text{-}pre}$	−.12	−.24	−.19	−.02
mean $\|NRS_{post\text{-}pre}\|$	−.07	−.35	−.42*	−.23
Health Category	−.31	−.05	−.15	−.24
Charlson's Comorbidity Index	−.07	−.10	−.15	.17
Intervention group	.21	.23	.18	.14

4. Discussion

Rather than studying the effects of exercise programs, we aimed to investigate possible exercise-related barriers that may hinder the beneficial effects of exercise in patients with knee OA. We think that our results are likely not influenced by the exercise interventions provided here, compared to other exercise studies because we have chosen exercise programs that were based on programs that previously showed beneficial effects on pain and function (Bennell et al., 2007, 2010; Ettinger et al., 1997; Evcik and Sonel, 2002; O'Reilly et al., 1999). Moreover, the first 9 sessions were supervised and all instructions on how to perform the exercises were provided to the patients in the logbooks

Table 6
Pain and potential barriers related to exercise (Data represent median (IQR) or number (%); significant difference ($p < .05$) between health categories[1]; between drop-outs and no drop-outs[2], between pre and post-intervention in the total- [3], ST-[4] and WT-[5] group; [6]significantly different from NRS_{max24} baseline and NRS_{max24} avg. weeks 1–3; dICOAPc: difference between pre and post intervention Intermittent and constant Osteoarthritis Pain subscale for constant pain; dICOAPi: difference between pre and post intervention Intermittent and constant Osteoarthritis Pain subscale for intermittent pain; dICOAPt: difference between pre and post intervention Intermittent and constant Osteoarthritis Pain total pain; ES: effect size (Z score/√N); GPE: Global Perceived Effect, NRS_{max24}: Maximal pain during the last 24 h; NRS_{pre}: Averaged Numeric Rating Score before training; NRS_{pos}: Averaged Numeric Rating Score after training; $NRS_{post\text{-}pre}$: Averaged exercise induced pain; *OR: Odds Ratio for drop-out (good health vs bad health); ST: Strength Training; WT: Walk Training).

	Intervention		Health Category				Drop-out		
	ST	WT	B1	B2	C	D	Yes	No	ES
Adherence supervised sessions[2]	.83 (.17)	.89 (.22)	0.89 (0.11)	0.86 (0.22)	–	0.42 (0)	0.65 (0.3)	0.89 (0.11)	.50
Adherence home sessions	.89 (.19)	.97 (.33)	0.94 (0.19)	0.9 (0.54)	–	–	–	0.92 (0.22)	
Compliance supervised sessions	.83 (.13)	.89 (.22)	0.83 (0.12)	0.83 (0.22)	–	–	0.72 (0)	0.86 (0.13)	
Compliance home sessions	.89 (.18)	.97 (.46)	0.94 (0.25)	0.91 (1.19)	–	0.86 (0.2)	–	0.92 (0.28)	.26
dICOAPc [3]	0 (7)	−1 (5.5)	−1.5 (5.25)	−1 (11)	–	–	–	−1 (5.75)	
dICOAPi [3,4,5]	−3 (10)	−3 (4)	−3 (6)	−3 (7)	–	–	–	−3 (5)	
dICOAPt [3,5]	−7 (14)	−5 (5)	−6 (10.25)	−4 (17)	–	–	–	−5 (11.25)	
NRS_{max24} baseline	5 (4)	6 (5)	5 (3)	7 (6.75)	–	6.5 (0)	5 (5.5)	5 (4)	.14
NRS_{max24} avg. weeks 1–3	4.67 (3)	4.33 (2.33)	3.33 (2.67)	5.17 (1.92)	–	5.42 (0)	5 (3.29)	4.17 (3)	.15
NRS_{max24} avg. weeks 4–18[6]	2.12 (2.15)	2.71 (1.53)	2.17 (1.13)	2.82 (4.69)	–	–	2.75 (4.82)	2.25 (1.69)	.12
NRS^{1}_{pre}	1.2 (1.84)	1.17 (1.2)	1.13 (0.99)	2.05 (2.27)	–	4.62 (0)	2.11 (1.92)	1.17 (1.29)	.23
$NRS^{1,2}_{post}$	1.41 (2.72)	1.53 (2.07)	1.43 (0.68)	2.37 (2.64)	–	4.88 (0)	3.98 (2.64)	1.45 (1.11)	.34
mean $NRS_{post\text{-}pre}$ [2]	−.05 (.53)	.21 (1.8)	0.04 (0.84)	−0.22 (1.69)	–	0.26 (0)	1.59 (2.29)	−0.03 (0.85)	.40
mean $\|NRS_{post\text{-}pre}\|$	.44 (.67)	.88 (1.35)	0.56 (0.7)	1.39 (1.88)	–	0.38 (0)	2.05 (2.57)	0.56 (0.9)	.19
GPE									
[1,4]	4 (21)	8 (42)	10 (37)	2 (25)	0 (0)	0 (0)	–	12 (37)	
[5,7]	11 (58)	9 (47)	16 (59)	3 (38)	0 (0)	1 (50)	–	20 (63)	
drop-out	4 (21)	2 (11)	1 (4)	3 (38)	1 (100)	1 (50)	6 (100)	0 (0)	
Health Cat. A-B1 vs B2-D							1 vs 5	26 vs 6	22*

(pictorial and written information). In our study, 53% of all included subjects indicated that they improved. This proportion did not differ between the WT and the ST group, which is in accordance with the literature (Fernandes et al., 2013; McAlindon et al., 2014). In addition, the effect sizes for pain reduction that we have found are in agreement with those that have been reported in literature, ranging from 0.34 (C.I. 0.19–0.49) (Jansen et al., 2011b) to 0.63 (C.I. 0.39–0.87) (Bannuru et al., 2012; McAlindon et al., 2014).

To our knowledge, no study has previously investigated to what extent the first sessions of an exercise program may influence knee pain as well as other factors such as adherence, compliance and drop-out in patients with knee OA. We found that the pain rating for maximum pain of the last 24 h, averaged for the first 3 weeks, did not differ from baseline. Nor did it differ between the intervention groups. However, this pain score was inversely correlated with adherence to the home sessions ($\rho = -.54$), suggesting that exercise adherence at home decreases with increasing knee pain.

We also studied exercise-induced pain and found no difference according to the type of intervention or health status. Interestingly, the exercise-induced pain was significantly higher in patients who dropped-out. Nevertheless, four of the six drop-outs had exercise induced pain but did not report that pain was the reason to stop with the program. Also other factors, such as functional limitations, daily activity, and/or psychosocial factors may be predictive of dropout in addition to exercise induced pain. However, we did not take these factors into account when performing the analyses. Moreover, the only patient that reported an increase in knee pain as a reason to stop the program, did not have exercise-induced pain as calculated by us. Maybe patients are not always honest when reporting the reason for drop-out and therefore, since our analysis showed that exercise induced pain was significantly higher in patients who dropped out, calculating the exercise-induced pain may be a variable that can be used *during* exercise programs to anticipate drop-out.

We found that NRS_{post}, $NRS_{post\text{-}pre}$ and adherence during supervised training sessions differed significantly between subjects that dropped out and subjects that did not drop out ($p < .05$). Our results regarding adherence and compliance could potentially be influenced by medication intake. Analgesics and non-steroidal anti-inflammatory drugs were permitted but patients were asked to register the intake in the logbooks. However, only 1 drop-out returned the logbook while the others did not send it back. Therefore, this data were not available for the analyses.

Additionally, we measured the fluctuations of the exercise-induced pain scores by averaging the modulus of the exercise-induced pain score of each session. This approach avoided that positive and negative pain scores would cancel each other out. We found that a higher level of exercise-induced pain fluctuation was significantly related ($\rho = -.42$) to lower adherence to the home sessions.

We also studied outcomes of the exercise programs in reference to baseline health status and the CCI. Exercise related pain outcomes (dICOAP) did not differ between health categories and were not correlated with CCI. This implies that health status and comorbidities at baseline did not explain the beneficial effects of exercise in our sample of knee OA patients. The health classification system that we used, has been developed to grade elderly participants according to the risk for dangerous complications during physical exercise and to allow physical therapists to adapt a scheduled program of physical exercise and lifestyle instructions. Therefore, cardiovascular abnormalities were considered to present a higher risk than non-cardiovascular conditions. This system has shown significant differences in physical exercise capacity (measured with the 6 min walking test) in the elderly. Patients with non-cardiovascular comorbidities (including musculoskeletal) are categorized as B1 unless they have also cardiovascular related disease were coexisting. In the latter case, they were categorized B2-C. Musculoskeletal disorders of other joints may be an important factor that can influence adherence, compliance and drop-out since exercise may affect these joints. Comorbidity has also been suggested as an important personal barrier for exercising in older people (17). In a cross-sectional study among 288 older adults (50–85 years) with hip or knee OA, coexisting disorders were inquired and investigated (18). Eighteen coexisting disorders occurred in more than 5% of the sample. Although some of them, e.g. diabetes (prevalence 10%) and obesity (prevalence 24%), are known to cause physiological (19) or behavioral restrictions to exercise (20), no comorbidities were taken into account when exercise was recommended in the latest OARSI guidelines (3). In our study, we investigated whether health status and comorbidity influenced treatment outcomes. Our results suggest that neither pain evolution nor adherence seemed to be affected by general health status, as measured with the health classification system developed by Bautmans et al. (Bautmans et al., 2005), or comorbidity, as measured with the CCI (Charlson et al., 1987). The CCI is an instrument that has been designed to provide clinicians and researchers with information about the associated risk of mortality of a patient's comorbidities. Given the aimed treatment outcomes of our exercise on pain and function, other comorbidity scoring systems, e.g. one that correlates better with health related quality of life (Fortin et al., 2005), may be more sensitive to capture the influence of comorbidities on exercise effects. Nevertheless, the patients in our sample who dropped out showed a worse health condition. Thus, our preliminary findings concerning comorbidities not being related to exercise outcomes, are in line with the aforementioned OARSI guideline but our findings with respect to the impact of bad health on drop-out, should require attention in future studies. We observed a significantly higher dropout rate in subjects with worse health compared to those with better health. Literature is scarce regarding health related differences between drop-outs and non-drop-outs of exercise programs aiming to reduce knee OA pain and function. However, our finding is in line with previous studies that evaluated predictors of dropout from exercise programs in patients with depression (Herman et al., 2002) and in frail older people (Schmidt et al., 2000). Depression is frequently seen in knee OA patients (e.g. 12% of 3407 knee OA people had signs of probable clinical depression) (Riddle et al., 2011). Health related factors (life satisfaction, anxiety) differed significantly between drop-outs and non-drop-outs in a group of elderly patients (Herman et al., 2002). In a group of older people that were assigned to an exercise program, drop-outs had greater disease burden and worse self-perceived physical health at baseline (Schmidt et al., 2000). In this study we aimed to measure the influence of each individual exercise session on pain. Therefore, patients were asked to indicate their pain level on a pain NRS before and after each training session. The reason to not use the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (Bellamy et al., 1988) for this purpose is that the WOMAC includes 24 questions of which only 5 concerns pain. Moreover, these questions refer to the last 48 h and thus the influence of an individual exercise bout, is not likely to be captured. It must be noted that by using the pain NRS, only one pain component is evaluated, and that the complexity of the pain experienced or improvements due to symptom fluctuations, might have been less well captured. Nevertheless, by frequently measuring the maximal pain and by calculating the modulus of the exercise-induced pain score of each session, we think that such fluctuations were taken into account.

Our study has some limitations. First, the low sample size implicates that the results should be handled with care and thus, our interim analyses need to be confirmed in larger studies. Performing sub analyses, including the low sample size it encompasses, does not allow us to generalize the results. Nevertheless, the statistically significant results are promising and more convincing results may be obtained in the future with increasing sample size. Additionally, to the best of our knowledge, this is the first study providing both qualitative and quantitative information concerning the drop-outs in an exercise intervention for patients with knee OA. Moreover, the introduction of an easy-to-calculate measure (i.e. exercise-induced pain) and a health classification system that both may have the potential to recognize drop-outs in an

early stage are extra assets of this study. As in each RCT, it is important to limit the number of drop outs to an absolute minimum. Therefore we think that the low sample size can be justified. Second, we used the WT sessions' duration to define compliance. Although we instructed the patients to walk at an intensity corresponding to a BORG score of 14, we did not register the BORG score during the exercise sessions. Therefore, in future studies, the duration of the training sessions may be added with the BORG score for intensity during walking. Third, adherence and compliance were obtained based on self-reported data and thus validity issues may be present. Fourth, we acknowledge that exercise may affect not only the patient's pain but also his functioning, daily activity and psychosocial factors. Therefore, these measures should be implemented in future studies when investigating potential barriers for initiating and continuing exercise programs in patients with knee OA. Additionally, larger studies investigating the exercise-induced pain in OA patients that are not adhering adequately to an exercise program, may be informative as well. Fifth, we did not use a control intervention group and thus it cannot be ruled out that our results are due to general confounding factors instead of factors that are specifically related to exercise. The rationale for using a second exercise program, rather than a control intervention, was that we aimed to investigate differences between strength and walking programs in patients with painful knee OA.

5. Clinical relevance

This study showed that both the health classification system as well as the exercise-induced pain measure have the potential to detect patients with knee OA at risk for dropping out an exercise program. However, this needs to be confirmed in larger studies. Starting an exercise program does not cause exacerbation of pain during the first weeks of training in our sample of people with symptomatic knee OA, and neither pain evolution or adherence seems to be affected by general health status. However, patients who drop-out show a worse health condition and higher exercise-induced pain levels. All future studies investigating the effects of exercise on knee OA should consider to take health category and exercise-induced pain as safety outcomes.

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