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Feasibility of high dose medical exercise therapy in patients with long-term symptomatic knee osteoarthritis

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ABSTRACT

Purpose: High repetition high dose medical exercise therapy (MET) is a promising treatment for patients with musculoskeletal pain. However, little is known regarding the feasibility of MET in patients with symptomatic knee osteoarthritis (OA). The aim of this study was to investigate the feasibility of MET in patients with symptomatic knee pain with radiographic verified OA.

Methods: Patients with symptomatic knee osteoarthritis were recruited to a group-based high repetitive high dose MET intervention for 12 weeks in a primary health care setting. Indicators of feasibility included processes (recruitment, program adherence, and exercise compliance), and scientific feasibility (safety and pain evaluated by using the Visual Analogue Scale (VAS)).

Results: Out of 31 individuals with symptomatic knee OA, 29 (93%) were included in this study. A total of 26 patients (90%) completed the intervention and 83% reached an attendance rate of ≥ 30 treatments. No adverse events were reported, and a majority of the patients reported a pain intensity < 30 mm (VAS) throughout the intervention period. The results showed a 70% reduction of median pain intensity between baseline (33 mm, IQR: 39), and post-assessment (10 mm, IQR: 25, $P = .003$).

Conclusion: These findings support an overall positive feasibility of MET for patients with symptomatic knee OA. The results also demonstrated that achieving a high dose of exercises might be challenging for this population. Thus, individual variations in exercise dose may be a confounding factor when evaluating high dose MET in future clinical studies.

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KEYWORDS

Knee pain; OA; high repetition high dose exercise therapy; medical exercise therapy; feasibility

Introduction

Knee osteoarthritis (OA) is traditionally considered a progressive disorder of articular cartilage and remodeling of the underlying bone (Torstensen et al., 2018). Emerging evidence suggests that pain from knee OA result from peripheral sensitization and central sensitization of the nervous system (Torstensen et al., 2018). The pain may result from peripheral sensitization where nociceptors from deep somatic tissue become sensitized by inflammation. Pathological neural signals from the joint causing changes in the central nervous system known as central sensitization may also contribute to the pain experience (Fingleton et al., 2015). There is strong evidence that aerobic and resistance exercises decrease pain and improve function in individuals with symptomatic knee OA (Fransen and McConnell, 2008; Pedersen and Saltin, 2015; Tanaka, Ozawa, Kito, and

Moriyama, 2015). However, several questions remain unanswered, particularly regarding what type of exercises, a combination of exercises, and what exercise dose is most effective in reducing pain and improving function. Medical exercise therapy (MET) is a branch within exercise therapy. High repetition high dose MET treatment consists of nine to 11 exercises lasting between 70 and 90 minutes. MET is known as a treatment based on the framework of the biopsychosocial model. The framework of the biopsychosocial model is commonly used in the treatment of chronic pain. In the biopsychosocial model, pain is understood as a psychophysiological pattern of behavior that cannot be categorized separately within biological, psychological, and social factors (Torstensen et al., 2018). High repetition high dose MET is based on the principles that: (1) exercises are self-paced; (2) exercises are graded pain-free or close to

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pain-free corresponding Visual Analogue Scale (VAS) from 0 to 1; and (3) the treating physiotherapist is present in the exercise room. There is increasing evidence that exercise therapy should focus on treating pain-related knee OA such as peripheral and central sensitization from a biopsychosocial perspective rather than impairment like muscle strength (Torstensen et al., 2018). With increasing knowledge that exercise therapy is a form of cognitive therapy modulating a homeostatic emotion like pain (Strigo and Craig, 2016), it is important to consider psychosocial variables when grading exercises, such as motivation, level of self-efficacy for exercise, anxiety, depression, and fear of movement (Torstensen et al., 2018). The primary aim is to modulate the patients' pain experience and improve function by using a high exercise dose (high number of repetitions in sets) (Torstensen et al., 2018; Torstensen, Meen, and Stiris, 1994). When the pain experience decreases, impairments such as range of motion, muscle strength, and coordination improve (Lorås, Østerås, Torstensen, and Østerås, 2015). The theoretical basis for high repetitive high dose MET is to activate the descending pain modulating system, decreasing local and central sensitization, minimizing negative psychological variables; catastrophizing, fear of movement, anxiety, and depression. The rationale is that high repetitive high dose MET exercise for 70–90 minutes may result in an increased production of endogenous neuropeptides in the spinal cord, the brain stem, and in the brain, resulting in a decreased sensation of pain, and improved function of the knee (Torstensen et al., 2018). Pain is a sensory and emotional experience that is substantially modulated by psychological, social, and contextual factors (Carlino, Frisaldi, and Benedetti, 2014). The pain information in the central nervous system is controlled by ascending and descending inhibitory systems. The high volume of repetitions in MET seems to be essential to reduce pain and improve function in contrast to fewer repetitions with higher exercise load as this has shown to be effective for a variety of musculoskeletal disorders such as low-back pain (Torstensen, Meen, and Stiris, 1994); subacromial pain (Østerås, Torstensen, and Østerås, 2010); and anterior knee pain (Østerås, Østerås, Torstensen, and Vasseljen, 2013). Promising results have also been demonstrated for high repetition high dose MET in patients with symptomatic knee pain after arthroscopic meniscus surgery (Østerås, Østerås, and Torstensen, 2014). On the other hand, a pilot study in patients with symptomatic hip osteoarthritis (Østerås et al., 2017) showed no difference comparing high repetition high dose MET versus low repetition low dose MET. The aim of this study was to investigate the procedural feasibility (i.e. recruitment, protocol adherence,

and exercise compliance) and scientific feasibility (i.e. safety and preliminary results) of high repetition high dose MET in individuals with symptomatic long-term knee osteoarthritis.

Methods

Design and ethics

The current study was a feasibility study with a pre-post interventional design including repeated measures throughout a 12-weeks intervention. The study was approved by the Regional Committee for Medical and Health Research Ethics and was registered Clinicaltrials.gov identifier: NCT02024126. Prior to entering the study, patients received both verbal and written information, and those giving their consent to participate went through a clinical assessment of the painful knee. Patients who fulfilled inclusion criteria and gave their written consent to participate were included in the study.

Study participants and recruitment

Patients with long-term symptomatic knee OA were recruited from physiotherapists, orthopedic surgeons, and general practitioners in Trondheim, Norway. All patients who fulfilled the criteria were asked to participate. The inclusion criteria were; (1) age between 45 and 85 years, (2) living in the defined geographic area of Trondheim, (3) history of knee pain for at least 3 months' duration with decreased function (reduced knee mobility and functional performance), and (4) radiographic verified OA of Kellgren and Lawrence grade 1–3 (Kellgren and Lawrence, 1957). Exclusion criteria were: (1) physiotherapy treatments three months prior to inclusion; (2) a history of major knee trauma; (3) known inflammatory joint disease or hip symptoms more aggravating than the knee symptoms; (4) scheduled for knee replacement surgery within the next six months; and (5) comorbidities (e.g. cardiovascular, respiratory, and systemic, or metabolic diseases) preventing aerobic exercises.

Medical exercise therapy

The high dose MET intervention was performed in groups of three to five patients, three times a week for 12 weeks at a physiotherapy clinic in a primary health care setting. Each treatment consisted of 70–90 minutes of dynamic exercise therapy with a combination of global, semiglobal, and local exercises (Torstensen et al., 2018).

It is important to distinguish between the compliance to exercise dose between global and semiglobal/local exercises, as they possibly address different treatment mechanisms. Global exercises involve body movements that activate large muscle group, aiming to increase the endurance capacity and local circulation in the knee joint. In this study stationary bike was used three times during each treatment. In order to activate the endogenous pain inhibiting systems, the targeted total duration of global exercises per treatment was 40 minutes. Semiglobal exercise was defined as an exercise involving the hip, knee, and ankle in a kinetic chain. Examples of semi-global exercises are step up, step-down exercises, and squatting. A local exercise was defined as an exercise that activates a single joint in a kinetic chain dynamically, such as an open-kinetic chain knee exercise in a seated position performed with limited resistance to extension (Torstensen et al., 2018). Each patient performed an individualized exercise program tailored in relation to his or her clinical symptoms and functional level. Lower extremity muscles were targeted (Table 1). To be able to reach a high number of repetitions, the principle of de-loading was applied. A weight stack from a pulley apparatus was used to deload a part of the weight of the body/lower extremity, resulting in a decrease of compressive forces in the knee joint decreasing mechanical allodynia. The MET exercise equipment used in the present project consisted of different form of pulleys, exercise benches, dumbbells, and barbells. All equipment was adoptable to the patients' clinical picture in order to optimize the exercise dosing and grading (Figure 1). The principles of de-loading made it possible to perform high repetitive, high dose exercises pain-free or close to pain-free corresponding

VAS from 0 to 1. The patient was supervised by an experienced physiotherapist in performing MET. The physiotherapist had an active role before and during the treatment program. The grading of exercises and baseline settings was based on initial clinical assessment, such as; range of motion, level of pain during the day/week, possible local and central sensitization, and tolerance for weightbearing activities measured with VAS. The physiotherapist guided the patient to grade and dose the exercises, aiming to fulfill the targeted dose of global, semiglobal, and local exercises. The clinical assessment and supervision of the treatment program was done by the same experienced physiotherapist in performing MET. Information from the clinical assessment was used to choose a starting position for exercise, range of motion, and loading matching the patient's ability to perform the exercises pain-free or close to pain free. Baseline of an exercise was found by asking the patient to perform 30 repetitions. After 10 repetitions, the patient had to evaluate if starting position and active range of motion was appropriate to reach 30 repetitions. This evaluation would assess level of pain such as peripheral and central sensitization of mechanical allodynia from every exercise in the program. A treatment dose was reached as the patient performed three sets of 30 repetitions with 30–60 seconds rest between each set. The treatment expected a progression during the exercise program, such as increased time during each exercise session and increased total training volume per exercise session. In order to adjust an optimal progression, the patient involvement in the program was done continuously; they influenced the progression/regression through explaining the reaction after each treatment session. As a general rule, there should be no increased pain and swelling more than 24 hours after treatment.

Table 1. Specificity of target muscles.

Intervention	Target muscles
Global exercise, stationary bike	Quadriceps, Hamstrings, Gastrocnemius, Soleus, Gluteus Maximus
Semiglobal exercise, closed chain squat	Quadriceps, Gluteus Maximus, Adductor Magnus, Soleus, Hamstrings, Gastrocnemius
Local open chain exercise, deloaded knee extension	Quadriceps, Hamstrings
Semiglobal exercise, closed chain step up	Quadriceps, Hamstrings, Gluteus Maximus
Global exercise, stationary bike	Quadriceps, Hamstrings, Gastrocnemius, Soleus, Gluteus Maximus
Semiglobal closed chain exercise, step down	Quadriceps, Hamstrings, Gluteus Maximus
Local open chain exercise, deloaded knee extension	Quadriceps, Hamstrings
Local open chain exercise, knee extension	Quadriceps, Hamstrings
Global exercise, stationary bike	Quadriceps, Hamstrings, Gastrocnemius, Soleus, Gluteus Maximus

Feasibility of high repetition high dose medical exercise therapy

The feasibility typology described by Thabane et al. (2010) was used for the evaluation of process feasibility (i.e. recruitment, protocol adherence, and exercise compliance) and scientific feasibility (i.e. safety and preliminary results). For the recruitment domain, we assessed the number of individuals with symptomatic knee OA who were willing to participate in the high dose MET treatment with respect to the number of individuals who declined to participate. To capture protocol adherence, the number of participants dropping out of the study were monitored, along with the reasons for dropping out. We defined 70% as sufficient protocol adherence. As proxies for exercise compliance, the time spent performing global


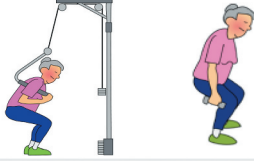

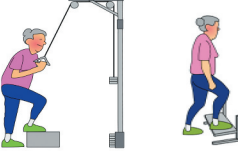





EXERCISE	HIGH DOSE MET (70-90 MIN)	DOSE
1		GLOBAL 20 min
2		SEMI GLOBAL CLOSED CHAIN 3x30 reps
3		LOCAL OPEN CHAIN 5 min
4		SEMI GLOBAL CLOSED CHAIN 3x30 reps
5		GLOBAL 10 min
6		SEMI GLOBAL CLOSED CHAIN 3x30 reps
7		LOCAL OPEN CHAIN 5 min
8		LOCAL OPEN CHAIN 3x30 reps
9		GLOBAL 10 min

Figure 1. Intervention high repetitive high dosage medical exercise therapy (MET).

exercises, and a number of repetitions of local and semi-global exercises were assessed. The exercise dose was assessed in relation to the targeted levels of 40 min of global exercises and 720 repetitions of local and

semiglobal exercises. For the safety domain, we recorded a number of adverse events during the intervention. Adverse events were defined as any reported negative side effect from the intervention itself. The patients

rated their knee pain intensity before the intervention and at six time points throughout the intervention period (after the 6th, 12th, 18th, 24th, 30th, and 36th treatment), using VAS. We defined a VAS score at 3 as an acceptable level of pain across the intervention.

Statistical analysis

Statistical Package of Social Sciences (SPSS, version 24) was used for the analysis. Descriptive statistics mean (min–max) and numbers (percentages), was used to present demographics at baseline. For exercise compliance, the mean time spent performing global exercises was calculated as well as the number of repetitions of local and semiglobal exercises for epochs summarizing five consecutive treatments (i.e. seven time points for assessment across the 12 weeks treatment period). Pain intensity, using a VAS scale, was presented as median (interquartile range). Feasibility outcomes were analyzed descriptively except for changes in pain intensity between pre- and posttest which was analyzed with the Wilcoxon rank test (alpha level set at ≤ 0.05). In a feasibility pilot study like this, there were not relevant to do a priori power analysis. To be able to use quantitative analysis we included 29 patients.

Results

Process feasibility

Out of 31 individuals with symptomatic knee OA assessed for eligibility, 29 (93%) were included in this study (Figure 2). The results showed that three patients dropped out of the study. Reason for the dropout was that

the exercise intervention was too painful to continue, lack of time to participate, and medical condition making the intervention difficult to complete. The patient's characteristics are presented in Table 2.

We observed a 38–58% increase in time spent performing global exercises and the number of repetitions of semiglobal-/local exercises from the first to the third training epochs (Figure 3a–b). A plateau in exercise dosage was observed from the third time point (11–15 treatment sessions) and throughout the intervention period. For this plateau, the average dose for global exercises was 37 min and 565 number of repetitions for semiglobal/local exercises corresponding to 92% and 79% of the targeted training dose of global and semi semiglobal-/local exercises, respectively. As shown in Figure 3b, we identified two clear clusters regarding the dosage of semi semiglobal and local exercises; one cluster of patients that achieved an exercise dose close to the targeted level and one cluster that demonstrated a lower exercise dose.

Scientific feasibility

Figure 4 shows self-reported pain at baseline, throughout the intervention period, and at the posttest. The

Table 2. Patients characteristics (number = 26) at baseline.^a

Variables	
Gender, female/male	16 (55)/13 (45)
Age (year)	60 (10)
Weight (kilogram)	82.6 (14.4)
Height (meter)	1.75 (0.07)
Body Mass Index (kilogram/metres ²)	26.9 (4.0)
Pain (visual analogue scale)	36.6 (23.5)

^aContinuous data are presented as mean (standard deviation) and nominal data as number (percentage).

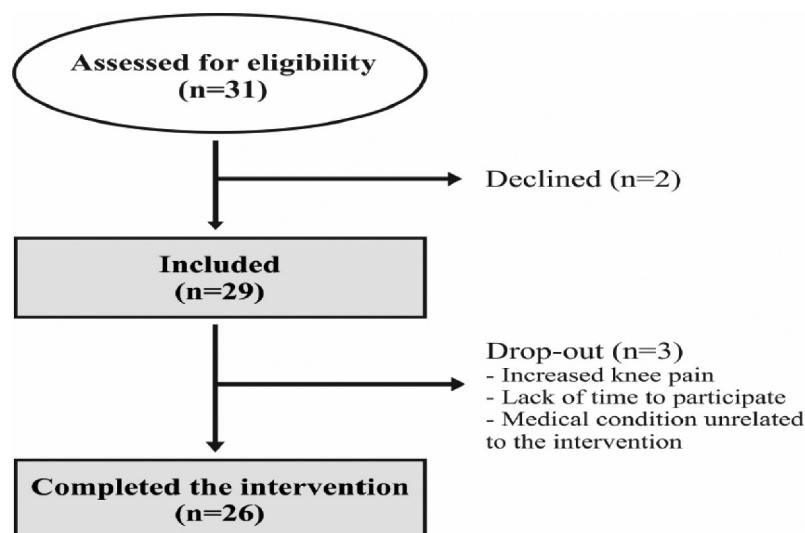


Figure 2. Study flowchart.

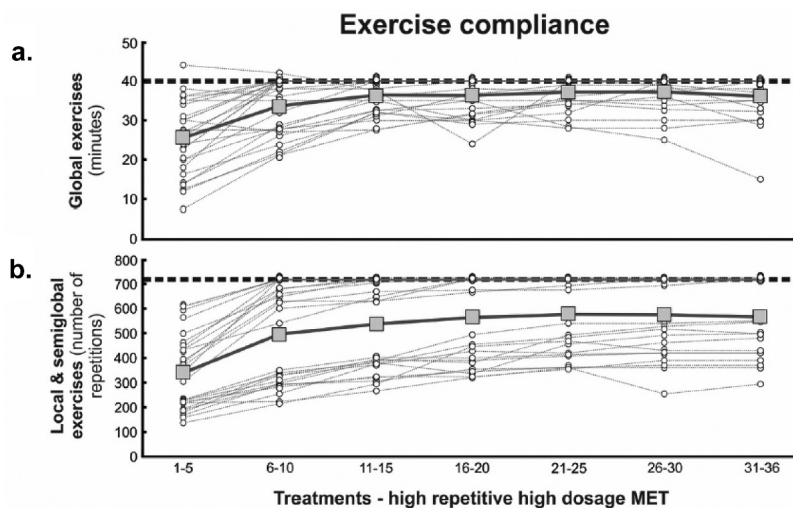


Figure 3. a) Time (min) spent performing global exercises and b) Number for repetitions of local- and semiglobal exercises during the intervention period. Data are plotted as group and individual mean values. Horizontal vertical lines reflect the targeted level of treatment dose.

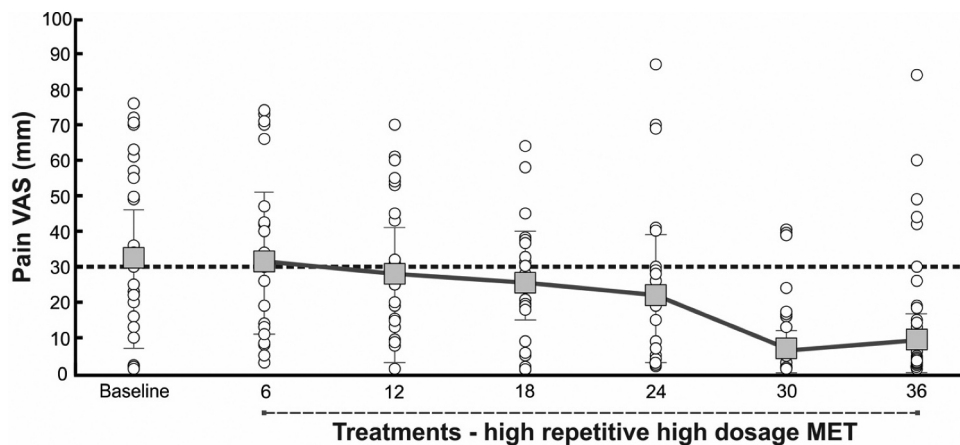


Figure 4. X-axis reflects number of treatments of high repetitive high dosage medical exercise therapy. The horizontal dotted line reflects the acceptable level of pain across the intervention (i.e. Visual analog scale score (VAS) of 3).

results showed a 70% reduction of median pain intensity between baseline (33 mm, IQR: 39) and post-assessment (10 mm, IQR: 25, $P = .003$). Except from one patient dropping out during the treatment because of experiencing an increase in knee pain, no adverse events were reported during the intervention period.

Discussion

The feasibility of high repetitive high dose MET for patients with symptomatic knee OA was supported in this study by sufficient participation, high protocol adherence, no adverse event, and acceptable pain levels across the intervention. However, variations were observed regarding compliance to the planned exercise dose where a plateau in exercise dosage was observed from

the third time point (11–15 treatment sessions) and throughout the intervention period. For this plateau, the average dose for global exercises was 37 min and 565 number of repetitions for semiglobal/local exercises corresponding to 92% and 79% of the targeted exercise dose of global and semiglobal/local exercises, respectively. Because of the difference between individuals in exercise dose, we believe it is important in clinical studies to monitor and control the exercise dose minimizing this variable as a confounder for the outcome.

Recruitment and program adherence

According to the feasibility typology described by Thabane et al. (2010), the criteria for eligibility and number of persons recruited in this study are acceptable

(i.e. 93% of the eligible patients were included). This is higher compared to other exercise studies where the recruitment rate varies from 52% to 74% (Chang et al., 2015; Li et al., 2017) were combined exercise/transcranial direct electrical stimulation and a behavioral intervention supported by a wearable device (Fitbit flex) was assessed to promote physical activity in patients with knee OA.

In our study, the high recruitment rate could be explained by the wide inclusion criteria regarding age (45–85 years) and severity of knee OA (Kellgren and Lawrence grade 1–3), which likely resembles the clinical profile of patients suitable for exercise generally and MET specifically. This is an important issue for the execution of clinical trials of high dose MET; demonstrating sufficient reach with regards to the inclusion of patients with long-term knee OA, which is higher, compared to previous studies reporting an adherence rate between 50% and 84% (Lange, Vanwanseele, and Fiatarone Singh, 2008; Marks and Allegrante, 2005) where isolated resistance training, combined aerobic, and resistance exercises were assessed in people with knee osteoarthritis. Furthermore, the drop-out rate in this study is only 3% which is lower compared to similar exercise studies reporting a drop-out rate ranging from 8% to 10% (Rewald et al., 2015; Røgind et al., 1998). Our results showed a high level of compliance (83%) to MET which is similar to previous exercise studies of 71–87% (Fraser and Spink, 2002; Rejeski et al., 1997; Skou, Odgaard, Rasmussen, and Roos, 2012; Van Oort et al., 2013) who assessed different types of exercise therapy such as combined group education and exercises, aerobic and resistance exercises, and resistance exercises in a home-based training program in patients with knee OA. There are several possible explanations for the high recruitment and adherence rate in the present study. A possible explanation is that MET is based on a biopsychosocial model as the exercises are self-paced, graded pain-free, or close to pain-free. Also, that the physiotherapist is present in the exercise room supervising the patient (Torstensen et al., 2018) can explain the high recruitment and adherence in the present study. This makes it possible to tailor the exercises individually according to the patient's clinical picture and the patient's needs and expectations (Carlino, Frisaldi, and Benedetti, 2014). Williams (2008) pointed out that interventions including an active involvement on behalf of the patient, like being self-paced, are more likely to demonstrate high adherence compared to exercise treatments relying on a predefined scheme of exercise. Ekkekakis, Parfitt, and Petruzzello (2011) suggested that when the intensity is self-selected, it appears to foster greater tolerance to higher intensity levels.

Interventions that include active involvement by the patients is also supported by Lind, Ekkekakis, and Vazou (2008) who suggested that even a minor increase in exercise intensity beyond the self-selected level can result in a decrease in pleasure which in turn could hamper exercise adherence. Furthermore, we believe that the presence of a physiotherapist in the exercise room during each treatment made the patient feel safe, enhancing positive expectations from the exercise therapy, and minimizing possible nocebo effects (Carlino, Frisaldi, and Benedetti, 2014). Supporting this view, Williams (2008), showed positive effects from supervision on adherence to exercise in patients with knee osteoarthritis. Performing exercises pain-free or close to pain-free may be an important factor for the high compliance and low dropout rate. In addition, physiological demands from the exercise stimulus influence the affective responses related to the interpretation of physiological symptoms. This suggests that perception of control and attentional focus during treatment can be structured eliciting positive affective responses (Rose and Parfitt, 2010).

Compliance to the targeted exercise dose of global, semiglobal and local exercises

An important finding in the present study was the large individual variations in exercise dose of local, semiglobal, and global exercises. Although we observed an increase in exercise dose during the beginning of the treatment period, the dose reached a plateau below the targeted levels. We speculate that individual variations in symptoms (e.g. pain, stiffness, and decreased function) and psychosocial variables (e.g. motivation, level of self-efficacy for exercise and fear of movement) could have restricted the training dose for some patients. This finding needs to be explored in more detail in future studies, because in order to evaluate the effects of high repetition high dose MET, it is fundamental that patients perform the required planned exercise dose.

Safety and preliminary results

During the treatment mean pain decreased and no adverse events were reported, supporting safety and preliminary effects of high repetition high dose MET in patients with symptomatic knee OA. This is in line with a larger body of research demonstrating acceptance and safety for different exercise modalities in this population (Ageberg, Link, and Roos, 2010; Christensen, Bartels, Astrup, and Bliddal, 2007; Skou, Odgaard, Rasmussen, and Roos, 2012; Van Oort et al., 2013). The gradually mean reduction in pain observed

during the treatment period in our study may hypothetically reflect increased activation of the descending pain modulating system induced by the high dose MET intervention (Torstensen et al., 2018). The decrease in pain intensity by 23 mm (70%) between the pre- and post-treatment period exceeds a minimal clinical important change of 20 mm for VAS (Tubach et al., 2005). These results are in line with other clinical studies on the effectiveness of high dose MET reviewed by Lorås, Østerås, Torstensen, and Østerås (2015). However, there was also a large individual variability with regard to patterns of change in pain intensity during the intervention period, which is similar to findings by Ageberg, Link, and Roos (2010). In fact, five patients (19%) reported pain exceeding 30 mm VAS at post assessment. Thus, it is important for future studies to identify baseline characteristics associated with a positive response to the high dose MET.

Study limitations

Although the present sample size was enough to perform a feasibility study, we used convenience sampling from one primary healthcare center, which probably resulted in an inadequate representation of the heterogeneity of patients with knee OA. The generalization of our results is also limited to patients with OA grade 1–3 by Kellgren and Lawrence with a rather low pain intensity (median pain intensity of 33 mm by VAS) at inclusion. In future studies, patients with higher pain ratings should be included avoiding possible ceiling effects regarding the outcome. On the other hand, the study sample was considered to resemble a sub-group of patients with knee OA, which is often recommended physiotherapy as exercise therapy.

Conclusion

To our knowledge, the current study is the first to investigate the feasibility of high repetition high dose MET in patients with knee OA. The process feasibility of the MET intervention was supported by a high recruitment rate, protocol adherence, and an acceptable exercise compliance. The high repetition high dose MET intervention was also found safe and our results indicate a clinical meaningful reduction in knee pain intensity. Nevertheless, we also demonstrated large individual variations in exercise dose, which needs to be considered when designing and executing clinical trials. In


conclusion, we recommend future studies to evaluate the efficacy and effectiveness of high repetition high dose MET.


Competing interest

The authors report no conflict of interest.

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