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Exercise therapy for knee osteoarthritis pain: how does it work? A study protocol for a randomised controlled trial

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ABSTRACT

Introduction Muscle strengthening training (MST) and behavioural graded activity (BGA) show comparable effects on knee osteoarthritic (KOA) pain, but the mechanisms of action remain unclear. Both exercise-induced anti-inflammation and central sensitisation are promising pathways for pain relief in response to exercise therapy in patients with KOA: MST has the potential to decrease inflammation and BGA has the potential to decrease central sensitisation. Hence, this study aims to examine inflammation and central sensitisation as mediators for the effect of MST and/or BGA on pain in patients with KOA.

Methods and analysis The Knee OsteoArthritis PAIN trial started on 10 January 2020 (anticipated end: April 2024). The three-arm clinical trial aims to recruit 90 KOA patients who will be randomly allocated to 12 weeks of (1) MST, (2) BGA or (3) care as usual. Assessments will be performed at baseline, 13 and 52 weeks after finishing the intervention. Outcomes, including pain (Knee injury and Osteoarthritis Outcome Score), were chosen in line with the OARSI recommendations for clinical trials of rehabilitation interventions for OA and the IMMPACT/OMERACT recommendations for the assessment of physical function in chronic pain clinical trials. Inflammation as well as features of central sensitisation (including conditioned pain modulation, offset analgesia, temporal summation of pain and event-related potentials following electrical stimulation), will be considered as treatment mediators. A multiple mediators model will be estimated with a path-analysis using structural equation models. In July 2023, all 90 KOA patients have been included and 42 participants already finished the study.

Ethics and dissemination This study obtained ethics approval (B.U.N. 143201941843). Unravelling the mechanisms of action of exercise therapy in KOA will not only be extremely valuable for researchers, but also for exercise immunology and pain scientists and clinicians.

Trial registration number NCT04362618.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Inflammation as mediator between exercise and pain in knee osteoarthritis has not been investigated before.
⇒ Pain physiology as mediator between exercise and pain in knee osteoarthritis has not been investigated before.
⇒ Muscle strength training and behavioural graded activity are compared with a control group.
⇒ Acute anti-inflammatory and endogenous hypoalgesic effects of exercise are investigated in (un)trained conditions.
⇒ Exercise intervention manuals and logbooks are only present in the Dutch language.

INTRODUCTION

Background and rationale

Osteoarthritis (OA) is the main cause of pain, disability and decreased daily functioning in older persons affecting over 80% of the population beyond the age 55.[1–3] International guidelines recommend exercise therapy as the first-choice non-pharmacological treatment for patients with knee osteoarthritis (KOA).[4 5] Even though exercise therapy results in comparable effects as analgesics for OA pain,[6] effect sizes are moderate at best and the between-study heterogeneity allows plenty of room for improvement.[7] Moreover, in the most recent Cochrane meta-analysis, no statistically significant difference among different modes of treatment delivery could be detected.[7] Despite the beneficial effects of exercise therapy in patients with KOA, most guidelines do not provide recommendations on the content of the exercise therapy, highlighting the lack of knowledge regarding the mechanisms of action behind exercise therapy.[8 9] Based on a systematic qualitative study of the literature, peripheral (including inflammation) and brain-orchestrated mechanisms (including endogenous analgesia and other features of central sensitisation) were suggested to explain the beneficial effects of exercise in patients with OA.[9]

Chronic low-grade inflammation with ageing, is an important contributing factor to OA.[10] When ageing, older adults develop a chronic low-grade inflammatory profile (CLIP, also coined as 'inflammaging') which is mainly due to senescence of the immune system, physical inactivity and increased

adiposity.[11 12] CLIP is characterised by low but chronically increased blood levels of inflammatory biomarkers including C reactive protein (CRP) and interleukin (IL)-6.[13] Interestingly, CLIP seems more pronounced in people with OA,[10 14 15] with higher levels of circulating pro-inflammatory cytokines associated with more pain and worse function in OA.[16] Several studies,[17–20] reported anti-inflammatory effects of exercise countering CLIP.[21–25] This can be explained by the acute exercise-induced increase of IL-6 and other myokines, and the accompanying release of inflammation-reducing cytokines, which is strongly dose-dependent (ie, higher release following more intensive and/or longer muscle activity).[26] In the long term, the repetitive acute exercise-induced increases of myokines, will reduce the CLIP and basal levels[19 27] of inflammation (such as CRP, IL-1β and IL-6), shifting older adults from an inflammaging to an anti-inflammaging profile. Therefore, muscle strengthening appears to be the preferred option for decreasing inflammation in patients with KOA.[28] Besides the potential influence of exercise on chronic low-grade inflammation, *acute* anti-inflammatory responses to a single bout of exercise may mediate the long-term change in pain in KOA patients. Data point also towards a dose-dependent *acute* exercise-induced change in circulating biomarkers for collagen turnover such as cartilage oligomeric protein (COMP)[29 30] in KOA patients,[30] where specifically the joint load might play a role. We[19 27] and others have shown that 6–12 weeks muscle strengthening training (MST) reduced significantly the basal IL-6 levels, thus reflecting lower inflammation. Therefore, MST appears to be the preferred option for decreasing inflammation in patients with KOA.[28] However, an in-depth study of the mediating role of the anti-inflammatory effect of exercise therapy on pain has never been performed in patients with KOA.[15] In addition to its potential anti-inflammatory action, MST is chosen as one of the exercise interventions under investigation here for several other reasons: (1) MST is an effective treatment for patients with KOA[31 32]; (2) knee extensor weakness is a typical feature of KOA; (3) knee extensor weakness is associated with the development of symptomatic KOA; (4) knee extensor weakness is associated with functional decline over time in people with KOA; (5) evidence from observational and pre-post exercise studies reports associations between change in knee extensor muscle strength and change in pain and self-reported physical function in people with or at risk for knee OA.[7 31]

In addition to systemic mechanisms such as anti-inflammation, other mechanisms within the central nervous system, like the brain-orchestrated mechanism of endogenous analgesia, have been suggested to explain the beneficial effects of exercise in patients with OA.[9] The brain holds the capacity to activate powerful descending nociceptive inhibition,[33] referred to as endogenous analgesia and resulting in less pain. In people with OA pain, the mechanism of endogenous analgesia is malfunctioning,[34–36] resulting in increased sensitivity of the central nervous system (‘central sensitisation’).[37–40] Traditionally, OA has been considered a nociceptive/inflammatory pain condition.[41 42] However, central sensitisation is a common feature of OA pain[37 43 44] and may at least partly explain the well-known discordance between pain and radiographic OA severity,[44] as markers of central sensitisation are strongest among patients with high pain in the absence of moderate-to-severe radiographic OA.[45]

Behavioural graded activity (BGA) has demonstrated to be an effective treatment for relieving pain, improving physical functioning and physical performance, and preventing joint replacement surgery in patients with OA.[46 47] BGA is a therapeutic intervention that incorporates the principles of operant conditioning to enhance the level of physical activity in the patient’s everyday life.[46] This intervention adopts a highly personalised methodology by addressing the patient’s specific activity limitations and self-identified treatment objectives through goal setting. Compared with usual care, BGA shows superior exercise adherence and more physical activity in KOA patients.[48] Besides that, BGA specifically targets psychological factors like pain catastrophising, fear and maladaptive pain coping styles, which are known to facilitate (rather than inhibit) pain,[49 50] thus preventing normal functioning of endogenous analgesia. Therefore, BGA appears to be the preferred option for activating endogenous analgesia in patients with KOA.[51–53] Additionally, the acute endogenous hypoalgesic effects are related to the type of physical exercise and pain sensitisation levels[54] which can affect the effects in the longer term.[55 56]

Even though the European Alliance of Associations for Rheumatology has identified mediators of OA outcomes as an important research priority to enable individualised healthcare in the future,[4 52 57] no studies are currently available on the underlying mechanisms of action behind exercise therapy in KOA patients.

Within the current innovative project we aim to examine whether the effect of MST and BGA on pain in patients with KOA can be explained by changes in inflammation and/or features of central sensitisation. To compare the possible changes in both exercise therapy groups with a situation where no additional exercises are incorporated into daily life, a control group will be added as a third study arm. We hypothesise that each exercise therapy programme (ie, MST vs BGA) will address both mechanistic pathways to a different extent. The current study will employ mediation analyses to understand the known relationship between exercise and pain. Mediation analysis is a statistical technique used to understand the relationship between an independent variable (exercise treatment) and a dependent variable (pain) by examining the role of intermediate variables (inflammation, endogeneous analgesia), also known as mediators. The goal is to determine whether the effect of exercise on pain is either direct or indirect, meaning it operates through the mediator.

Table 1 Consensus exercise reporting template for treatment arms behavioural graded activity (BGA) and muscle strengthening training (MST)

Item	BGA	MST
Type of exercise equipment	No (self-selected ADL)	Elastic bands
Instructor	Physiotherapists, trained in performing BGA	Physiotherapists, trained in performing MST
Individual or group	Individual	Individual
Supervision	Supervised except daily living activities	Supervised except home sessions
Registration of adherence	Logbook completed on paper and handed in during follow-up assessment	Logbook completed on paper and handed in during follow-up assessment
Motivation strategies	Goal setting, therapeutic alliance, shared-decision making, (non-verbal) reinforcement	(Non-)verbal reinforcement
Progression through exercise programme	Weekly increase (fixed) of the duration of activities (shared-decision making with patient)	Every six sessions, the 12RM is reassessed and the resistance bands adapted
Specify exercises	Individually tailored and patient-guided: participants are invited to pick activities that they are eager to return to, mostly because they like to do the activities but currently feel unable to do them (as much or for as long as they want to). This is a key feature of motivating patients for engaging in the behavioural graded activity programme. Examples: walking, getting up from chair, bending knees	Quadriceps 1. Isometric holds over a roll (supine) 2. Straight leg raises (supine) raise leg to 30° hip flexion 3. Leg press (sitting) 4. Knee extension (sitting) Hip abductor and adductor[120 121] 1. Unilateral hip abduction performed (side lying) 2. Unilateral hip external rotation (side lying) 3. Unilateral hip adduction (standing)
Home programme content	Integration of activities in the daily living (phase 3)	Analogue to exercises in hospital
Non-exercise components	Behavioural therapy (operant conditioning with exercise therapy)/time contingent ('stop after 5 min')	Pain contingent ('stop when it hurts')
Setting	Hospital and home (phase 3)	Hospital and home
Training parameters	► Duration: 12 weeks (week 1–12) ► 15–18 sessions under supervision, 18–21 session at home ► 30'/session Phase 1: identification of limitations in ADL	► Duration: 12 weeks (week 1–12) ► 18 sessions under supervision, 18 sessions at home ► 30'/session
Tailored to the individual's	Activity limitations ► Exercises are chosen by patient (phase 1) ► Baseline levels (hence: exercise intensities (phase 2)) for performing the patient's limited daily activities (phase 1)	12RM for each exercise will be assessed frequently and resistance adapted appropriately Tolerable level of pain: the patient is instructed to perform the exercises within 'tolerable levels of pain' and to 'stop when it hurts'. This will not be further specified in terms of numeric rating scale
Starting level	20% under maximal symptom-free duration of each activity	Three sets of six reps at 12RM, progressively increased every session until 3 sets of 10 reps at 12RM

w.u, warming-up.

Objectives

The primary goals of this trial are:

- To examine whether the effect of exercise therapy on pain in patients with KOA can be explained by changes in inflammation and/or features of central sensitisation.
- To examine whether the acute anti-inflammatory and/or endogenous hypoalgesic response to MST versus BGA versus control in patients with KOA is associated with change in pain after 12 weeks of intervention.

The secondary goals of this trial are:

- To examine whether the *acute* anti-inflammatory and/or endogenous hypoalgesic response to one session of MST versus BGA versus control in KOA patients (rather than the *overall* effect of the full 12 weeks exercise programme) is associated with change in pain after 12 weeks of intervention.
- To examine whether the *acute* anti-inflammatory and/or endogenous hypoalgesic effect is different at the beginning of the intervention (week 2, untrained

condition) compared with the end of the intervention (week 10, trained condition).
- To examine whether the *acute* anti-inflammatory and/or endogenous hypoalgesic effect is associated with changes in basal levels of inflammation (CLIP) and/or central sensitisation after 12 weeks of intervention.

METHODS

This study is substantially funded by the Research Foundations Flanders (project number G040919N), has ethics approval (B.U.N. 143201941843). The clinical trial started on 10 January 2020. The manuscript is formatted by using the Standard Protocol Items: Recommendations for Interventional Trials statement.

Trial design

A multicentre randomised controlled trial with 3-month intervention and 12-month follow-up will be conducted. The trial is designed in line with the OARSI clinical trial recommendations for rehabilitation interventions in OA patients.[58]

Study setting

All assessments and treatments will take place at the participating hospital (UZ Brussel) or at the participants' homes.

Eligibility criteria

Patients should meet the following inclusion criteria:

(1) KOA according to the clinical American College of Rheumatology (ACR) criteria.[59 60] The clinical ACR criteria[59] for KOA are: knee pain and at least three of the six following features: age ≥50, morning stiffness <30 min, crepitus, bony tenderness, bony enlargement, no palpable warmth. KOA will be confirmed with radiographs, including anterior-posterior and medio-lateral radiographs for imaging of the tibiofemoral joint, and an axial view for imaging of the patellofemoral joint. Patients with tibiofemoral (and patellofemoral) OA will be included. Kellgren and Lawrence (K&L) grading system for OA[61 62] will be applied, with K&L grade 2 or higher defined as OA; radiographic KOA is defined as definite osteophytes and possible joint space narrowing[63 64]; (2) pain, nominated by the patient as three or higher on a visual analogue scale on most days of the last 3 months[65]; (3) aged ≥50 years.

Exclusion criteria are:
- Treatment with exercise therapy or joint infiltrations (eg, corticosteroids, hyaluronic acid) in the preceding 6 months.
- Being on a waiting list for knee replacement.
- Any contra-indication for exercise therapy as established by the treating physician.
- Corticosteroid infiltrations in the last 6 months.
- Cognitive impairment (unable to understand the test instructions and/or Mini-Mental State Examination score <23/30).
- Unable to understand the Dutch language.
- Inflammation unrelated to OA (eg, due to acute or chronic infection) established by CRP >10 mg/L.
- Presence of a disorder (eg, cancer, fibromyalgia, rheumatoid arthritis) and/or medication (eg, opioids, immunotherapy, anti-epileptics) that influences pain and/or the immune system.

Interventions

Muscle strength training

Muscles of both legs are trained at 3 sets of 10 repetitions at 12 repetition maximum (12RM, that is, the maximum weight that can be lifted in 12 consecutive movements). Each set consists of short bouts of intensive concentric and eccentric muscle contractions. 12RM will be assessed at baseline and the exercise intensity will be progressively increased. The 12RM assessment involves gradually increasing the resistance until the participant reaches a load that he/she can perform the exercise for 12 repetitions but not for more. By using elastic bands, the resistance can be easily modified to meet the specific needs and goals of the individual, providing a customised and adaptable training experience. Every six sessions, the 12RM will be reassessed and the resistance of the elastic bands adapted. One session will consist of different exercises containing muscles of the hip (adductors and abductors) and the knee (extensors). More details can be found in table 1 describing all treatment arms according to the Template for Intervention Description and Replication checklist and guide.[66] Due to the COVID-19 crisis and the associated restrictions, we will give patients the opportunity to choose between physical interventions sessions (at campus) or digital sessions (tele-consults). As such, we can meet concerns regarding COVID-19 and guarantee therapy continuation. Tele-consults will be held by the physiotherapists using a secured platform that allows video calling.

Behavioural graded activity

Patients will receive a behavioural treatment integrated within the concepts of operant conditioning with exercise therapy. The purpose of BGA is to increase the level of activities in a time-contingent manner and increase the level of physical activity in the patient's daily lives.[46] BGA consists of three phases: (1) education and setting the baseline, (2) treatment (pacing) and (3) integration in daily life.[46] The BGA treatment protocol is detailed in available treatment manuals,[67 68] and more details can be found in table 1.

Care as usual

Patients allocated to the control group will receive care as usual. They will be asked to maintain their current lifestyle and treatment (if any) and to refrain from other new interventions for 24 weeks. After completion of the study (W64) control patients can have the opportunity to receive an initiation/info session about MST or BGA. Just like the patients in the remaining study arms, control patients will also receive an email with the results of the

trial and contact details of possible physiotherapists after completion of the study.

Fidelity measurements

Before initiating the data collection, therapists will be trained face-to-face in providing the therapy (either MST or BGA) by experienced researchers with a clinical background. The duration of this training varies between 3 hours (MST) and 5 hours (BGA). Every 3 months, a half-day refresher course (face-to-face or online, based on therapists' preference) will be organised, allowing therapists to discuss any difficulties experienced. Additional measures taken to allow quality control of the provided treatment include developing and using a programme manual that depends on available guidelines and manuals. Also, in case of permission of the participants all treatment sessions 4 weeks before the 3-monthly refresher course of the therapists will be recorded.[69] Independent raters will successively evaluate a random selection of the tapes of each therapist using the Cognitive Therapy Adherence and Competence Scale[70] and fidelity criteria. They have a bio-/psycho-medical background and will not be involved in providing the treatments. They will be specifically trained to score the recordings of treatments. The Steering Committee, which consists of the three main investigator (IB, JN, DB) will develop a measure of fidelity criteria before the start of the interventions. The method to develop these fidelity criteria has previously been described[71] and will take into account the available guidelines and manuals. The fidelity criteria will be used to a priori inform and train therapists in providing the treatment, and they will be used to score the recordings of treatment sessions.[71]

Outcomes

Outcomes were chosen in line with the OARSI recommendations for clinical trials of rehabilitation interventions for OA[58] and the IMMPACT/OMERACT recommendations for the assessment of physical function in chronic pain clinical trials[72] (see table 2 and online supplemental appendix 1). The collection of personal characteristics (age, sex, comorbid medical conditions, etc)[73] will be carried out once at baseline. The *primary outcome* is pain severity and will be assessed with the pain subscale of the Knee injury and Osteoarthritis Outcome Score (KOOS).[74] The KOOS includes WOMAC Osteoarthritis Index LK3.0[75] in its complete and original format. WOMAC (and therefore the pain and symptoms subscale of the KOOS) is a valid tool for subjects with KOA. The KOOS is proven to generate valid and reliable scores.[76 77] The KOOS shows adequate content validity, internal consistency, reliability, content validity and responsiveness for age and condition relevant subscales.[77]

Treatment mediator: inflammation

Blood sampling will be performed at baseline (before starting the intervention), at week 2–3 during intervention (pretreatment, post-treatment and 1-hour post-treatment session), at week 10–11 during intervention (pretreatment, post-treatment and 1-hour post-treatment session), immediately after intervention (week 13, at least 48 hours after the last training session to avoid bias due to acute exercise-induced elevations of biomarkers) and at week 26 (13 weeks after intervention) for subjects allocated to the MST or BGA group.

These blood samples will be used for biomarker profiling. A panel of biomarkers for CLIP will be included: ultra-sensitivity ELISA for high-sensitivity CRP (hsCRP), IL-1β, IL-1RA, IL-6, IL-8, IL-10, MCP-1, TNFα, sTNFR1&2, CXCL-10, CX3CL-1, MIG (CXCL-9) and suPAR.

Given the involvement of advanced glycation end products (AGE, resulting from non-enzymatic condensation of glucose with an aminogroup of proteins) and the receptor for AGE (RAGE) in CLIP[78] and OA,[79–81] we will add carboximethyl-lysine, pentosidine and sRAGE to the inflammatory panel. The panel will be completed by a set of adipokines[79] including adiponectin, leptin, visfatin and resistin. In addition, the role of cytoprotective mechanisms and their modulation by physical exercise should be considered.[19 82 83] We will also include hsp27 and hsp70 (ultra-sensitivity ELISA) in our biomarker panel. Since circulating brain-derived neurotrophic factor (BDNF) is stimulated by exercise both in older healthy[84] and KOA patients,[85] we will add circulating BDNF to our panel. Finally, we will also measure circulating markers of collagen turnover including COMP, metalloproteinase-1 and metalloproteinase-3 to monitor the degenerative process as a possible source for inflammation.

At week 2–3 and at 10–11, blood will be sampled immediately before and immediately after an MST or BGA session. Additional sampling will be performed at 1 hour after the session. Eventually, a catheter placement may be considered so that the participant does not need to be pricked multiple times (>3) and/or when the participant has small vessels and is hard to puncture. This design allows to appraise changes in inflammatory biomarkers appearing early in the circulation (IL-6, IL-8, BDNF, MCP-1) which are considered as 'myokines'[86–88] secreted by exercising muscles, as well as biomarkers appearing later during and after exercise (IL-10, IL-1RA, sTNFR1&2), which are produced by immune cells as a response to stimulation by the myokines. All biomarkers (as mentioned above) will be determined at these timepoints, including the circulating markers of collagen turnover as exercise-induced changes (especially COMP) are closely related to knee joint loading.[30 89]

Subjects that are allocated to the control group, will not undergo blood sampling at week 2–3 and week 10–11. Blood will be collected at baseline and reassessed after 1 hour of rest, immediately after intervention (week 13, at least 48 hours after the last training session to avoid bias due to acute exercise-induced elevations of biomarkers) and at week 26 (13 weeks after intervention).

Serum and plasma will be collected and stored at −80°C until assayed (simultaneously for all time points). Biomarkers will be measured using ultra-sensitivity ELISA

Table 2 Outcomes of the Knee OsteoArthritis PAIN study

Primary outcome	
Pain	Knee injury and Osteoarthritis Outcome Score (KOOS)—pain subscale
Secondary outcomes	
Different subtypes of pain	Visual Analogue Scale (VAS)
	Intermittent and constant pain (ICOAP)
	Central Sensitisation Inventory (CSI)
Function in daily living	KOOS subscale: function in daily living
	KOOS subscale: functioning in sports
	KOOS subscale: functioning in recreation
	Patient Global Assessment (PGA)
Treatment adherence (treatment sessions)	Ratio of the number of treatment sessions that were actually carried out vs the number of prescribed sessions
Treatment adherence (home sessions)	Ratio of the number of training/activity sessions that were actually carried out at home vs the total number of prescribed home sessions
Treatment compliance	Ratio of the total training duration vs the prescribed total training durationx100
Healthcare cost effectiveness	Medical Consumption Questionnaire
	Productivity Cost Questionnaire
	EuroQol EQ-5D
Treatment mediators	
Inflammation	Circulating biomarkers
Endogenous analgesia	Electrical detection thresholds (EDTs) and electrical pain thresholds (EPTs)
	Temporal summation (TS)
	Offset analgesia
	Conditioned pain modulation (CPM)
Explanatory outcomes	
Pain catastrophising	Pain Catastrophizing Scale (PCS)
Pain hypervigilance	Pain Vigilance and Awareness Questionnaire (PVAQ)
Illness perceptions	Illness Perception Questionnaire-revised (IPQ-R)
Dietary intake	Food Frequency Questionnaire

The order of the outcome measurements follows a fixed structure. At baseline, postintervention (week 13) and follow-up (week 26), first self-reported measures will be completed, second, the experimental pain measurements will take place (in the following order: EDT, EPT, TS, CPM, offset analgesia), and finally, blood will be drawn. during the intervention, in week 2–3 and in week 10–11, only the electrical pain thresholds and temporal summation assessments are performed, before and immediately after the exercise session. During a second test moment in week 2–3 and in week 10–11, exercise-induced inflammatory effects will be assessed by taking a blood sample before, immediately after and 1 hour after the exercise session. Here, also the self-reported measures will be completed before the blood punctures.

and/or multiplex (Luminex platform) assays. To reduce bias due to intra-assay and inter-assay variability for each participant, samples of all time-points will be assayed on the same plate.

Treatment mediator: features of central sensitisation

Features of central sensitisation will be assessed by evaluating (1) electrical detection thresholds (EDTs) and electrical pain thresholds (EPTs),[90] (2) temporal summation (TS),[91 92] (3) conditioned pain modulation (CPM),[92–94] (4) offset analgesia[94–96] and (5) event-related potentials following electrical stimulation[97] by a single evaluator. All these assessments will be done at baseline (before starting the intervention), after the intervention (week 13) and at week 26 (13 weeks after intervention). A subset of these assessments (ie, EDTs, EPTs and TS) will be performed at week 2–3 and at week 10–11 during the intervention (pretreatment, post-treatment and 1-hour post-treatment) in a separate test moment, not together with the blood sampling and self-reported measures).

EDTs and EPTs

EDTs and EPTs will be measured (Surpass LT stimulator, EMS Biomedical, Korneuburg, Austria) at the knee (peripatellar region: 3 cm medial to the midpoint of the medial edge of patella[98]) of the symptomatic leg, and at the median nerve ipsilateral to symptomatic leg side (as remote site). The order of test locations will be randomised in everyone. Each stimulus will be a constant current rectangular pulse train consisting of 5 pulses delivered at a

frequency of 250 Hz, each lasting 1 ms.[99] Stimulation will start at 0 mA and will be gradually increased using steps of 0.5 mA[100] until the patient is experiencing a faint sensation (=EDT) and further until the stimulus is experienced as painful (=EPT). The mean EDT and mean EPT of the respectively three measurements with 30 s interval will be used for further analyses. EPTs has demonstrated to be reliable for the assessment of the sensitivity of the spinal nociceptive pathways in people with chronic pain.[101]

Endogenous pain facilitation assessed by the TS paradigm

TS will be assessed by delivering 20 stimuli[100] at the previously determined intensity of the EPT, with an interstimulus interval of 0.5 s. The same order of test location as during EDT and EPT will be used. Each test region will be assessed three times, interspersed with a 30 s rest. The patient will be asked to give a verbal numeric rating scale (VNRS) score ranging from 0 (=no pain) to 10 (=worst possible pain)[100] after the 1st, the 10th and the 20th stimulus. The outcome measures for TS will be the differences between the 10th and 1st VNRS score,[92 102] the 20th and 10th VNRS score and 20th and 1st VNRS score.

Endogenous pain inhibition assessed by offset analgesia

Offset analgesia can be described as a disproportionately large decrease in perceived pain following slight decreases in noxious thermal or electrical intensity.[103] Traditionally noxious thermal intensity has been used by researchers in order to evoke off-set analgesia.[103] However, in this study, noxious electrical intensity will be used which has been validated to be used same as noxious thermal intensity.[94]

Electrical stimuli will be applied as a train of rectangular pulses (frequency: 100 Hz; pulse duration: 1 ms) delivered by a constant current simulator. The test site will be located and marked 3 cm distal to the elbow joint on the volar site of the dominant hand side forearm. The stimulation intensity will be stated according to electrical pain perception values (EPP) of each individual. EPP will be calculated average of three trials of giving electrical stimuli from a baseline of 0.5 mA in steps of 0.1 mA with interpulse intervals of 5 s until the participants reported the stimulus as painful stimuli. Then patients will be given the painful stimuli into three time intervals; T1 (5 s), T2 (5 s) and T3 (20 s). Intensity of the painful stimuli will be %150 of EPP at T1, %180 of EPP at T2 and %150 of EPP at T3. Finally, during each application (T1, T2 and T3) participants need to report their intensity of pain according to the visual analogue scale; 0 means no pain and 10 means maximum pain.[94]

Second, a control paradigm will be conducted with painful stimuli %150 of EPP for 30 s. It is well known that a pain reduction due to prolonged pain stimuli can be caused by the adaptation of primary afferents known to occur during prolonged stimulation, and this control paradigm was conducted to account for the adaptation. All trials will be separated by a 5 min interval in an attempt to minimise the carry-over effects on the site of the stimulation, as primary afferents have adaptive behaviours.[95 104]

Endogenous pain inhibition assessed by the CPM paradigm

To assess the efficacy of endogenous analgesia the CPM paradigm will be used. CPM is an established way of measuring endogenous analgesia.[105–107] The cold pressor task will be used as conditioning stimulus and electrical stimulation will be used as the test stimulus. Electrical stimulation (test stimulus) will consist of 20 stimuli,[108] with a variable interstimulus interval of 8–12 s, at 1.4 times EPT[109] and will be applied before and during the application of the conditioning stimulus at the knee and remote site. After 20 stimulations a VNRS score is obtained on a scale from 0 (=no pain) to 10 (=worst pain possible). In order to apply the conditioning stimulus, patients will have to put their hand (the one contralateral to symptomatic leg side) up to the wrist in a cold-water bath (VersaCool, Thermo Scientific, Thermo Fisher Scientific, Waltham, MA, USA). The bath area will be filled with distilled water circulating at 12°C[110] up to the wrist.

After applying the CPM paradigm at one body site, the participant is allowed to withdraw the hand from the cold-water bath for 15 consecutive minutes. Next, the CPM protocol will be repeated for the remaining anatomical location. The order of test locations will be the same as the randomised order in which EDTs and EPTs were determined. For each of the two anatomical locations (knee and remote site) the VNRS score after electrical stimulation will be recorded before and during immersion of the participant's hand into cold water. The CPM effect will be quantified as the absolute difference in VNRS score before and during the cold pressor test.[99]

EEG recordings during offset analgesia and CPM

During the assessment of the offset analgesia and CPM, the nociceptive evoked potentials elicited by the contact electrical stimulus will be recorded by means of scalp EEG (Sienna Digital EEG, EMS Biomedical, Korneuburg, Austria) from 32 active Ag/Au electrodes attached on the participant's head (Headcap, EMS Biomedical, Korneuburg, Austria). EEG will be used to measure voltage fluctuations along the scalp resulting from the ionic current flows within the neurons of the brain,[111] allowing us to examine differences in brain responses and brain localisation to painful stimulation between test conditions and group allocations. Participants will be asked to close their eyes and sit as still as possible during the EEG recording procedures. Sienna EEG software will be used to set high and low bandpass filters, remove remaining artefacts and perform independent component analysis.[112] The time window from −100 ms to 500 ms post-stimulation will be analysed with the accent on late evoked potentials and the maximum sampling frequency will be set at 1024 Hz. Further analyses on the averaged evoked potentials with the Brain Electrical Source Analysis software will be used to obtain 3D brain mapping with specific coordinates for each brain area. A ratio between the dorsal anterior cingulate cortex and pregenual anterior cingulate

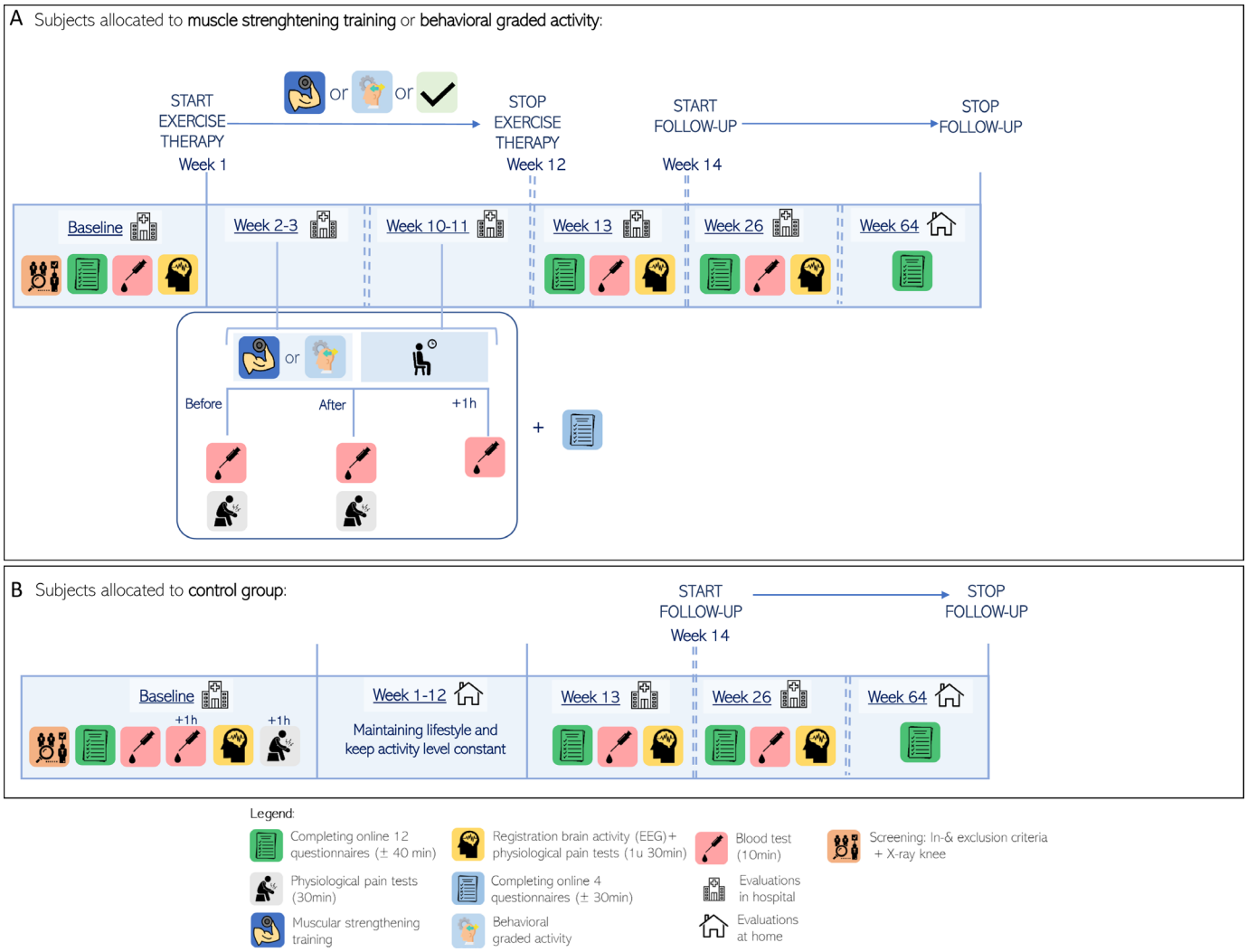

Figure 1 Overview study timeline. (A) For subjects allocated to muscle strengthening training or behavioural graded activity group. (B) For subjects allocated to control group.

cortex/ventromedial prefrontal cortex will be calculated to reflect a balance between pain supporting and pain suppressing systems.

Sample size

Sample sizes were calculated to detect a clinically relevant difference between the treatment arms and the control of 0.49 (0.39 to 59). The effect size is based on results from a recent Cochrane meta-analysis (including 44 studies, 3537 participants).[7] Because for each patient three measurements are obtained (at 0, 12 and 26 weeks), the effect size is transformed into an F-test statistic of 0.245 to be used within a sample size calculation for repeated measures analysis of variance. A sample size of 24 per treatment arm is obtained with an expected correlation over time of 0.3, allowing for a type I error of 0.025 and a type II error of 0.2. A 20% loss to follow-up is expected based on earlier studies and is added so that the total required sample size is estimated at 30 patients per study arm, resulting in 90 KOA patients to be recruited.

Recruitment

First, patients will be recruited in primary care. Therefore, all family physicians working within a 15 min travel distance from the participating hospitals will be contacted personally and invited to participate. When agreeing, physicians will receive recruitment leaflets which are displayed in the waiting areas. Interested patients can register by contacting the study team.

Second, patients will be recruited within the participating hospital (UZ Brussel), including the Department of Orthopaedics. Physicians can refer interested patients to the central study team and provide them an information leaflet of the study.

Finally, advertisements and announcements in local newspapers, pharmacies and (online or printed) publications from patient support groups will be used as additional recruitment strategies.

Patients will be informed that they will receive a gift voucher of €50 as travel reimbursement. Patients will receive the gift voucher of €50 in two parts: a gift voucher of €30 when they complete the 12-week intervention

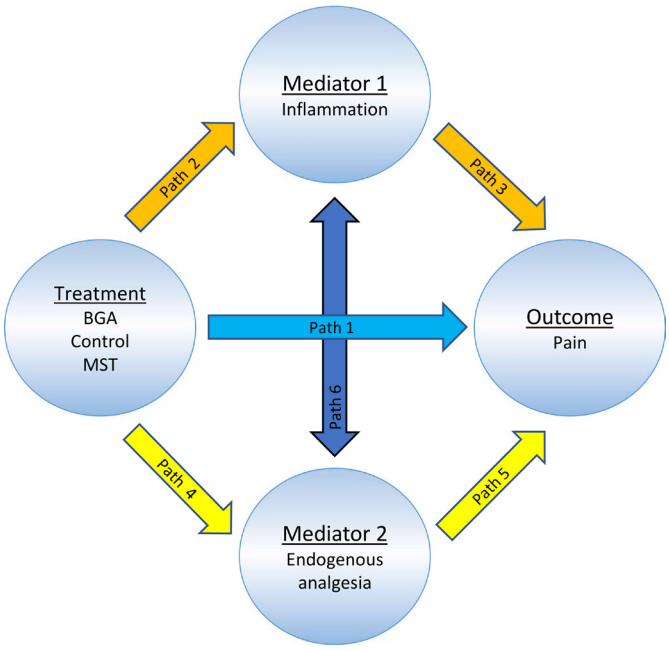

Figure 2 Theoretical model of mediation analyses. The treatment has an impact on pain (path 1) that is caused by the effect of the intervention on the mediator (paths 2 and 3) which in turn produces the change in pain (paths 4 and 5). Path 6 takes into account the interaction between both mediators. The mediation is complete if the intervention group is no longer a statistically significant predictor of the outcome variable after accounting for the effect of the change in the mediator. The mediation is partial if the intervention group remains a significant but a weaker predictor of pain after accounting for the effect of the change in the mediators. BGA, behavioural graded activity.

period, and a gift voucher of €20 after they completed the test moment at week 26. Patients who are willing to participate, will be screened by phone by a study nurse and subsequently in the hospital by a doctor for eligibility based on the predefined inclusion and exclusion criteria. During the screening by the doctor at the hospital, a blood sample will be taken to determine the hsCRP levels of the patient.

Assignment of interventions

Allocation: sequence generation

The patients will be randomly allocated to 12 weeks programme of either MST, BGA or control. Randomisation will be performed by using the method of randomly permuted blocks with random block sizes, using a computer-generated random number sequence. To keep both intervention groups balanced, randomisation will be stratified for baseline inflammation status (based on a cut-off of 3 mg/L of circulating hsCRP[113]), central sensitisation status (based on a cut-off score of 40 on the Central Sensitisation Inventory[114–117]) and sex (male vs female).

Allocation: concealment mechanism

A list with patient numbers and the group allocation that results from this randomisation procedure will be stored in a sealed envelope.

Allocation: implementation

Only an independent researcher (LLeysen) will have direct access to the randomisation list. Randomisation will take place if a patient is found eligible to participate after the screening procedure. A study nurse (LDG) will arrange all appointment times with the treating therapists (EB, CDC, LLie, IR) and the assessors (LLeemans, SP) for all outcome measures. Patients will be scheduled to receive their first assessment within 1 week of randomisation. After the first assessment, patients receive an email with their group allocation as well as a letter for their treating physician. A trained therapist will provide the intervention; each treatment arm has different therapists (ie, therapists will provide either BGA or MST).

Blinding (masking)

Patients will not know which one the experimental intervention is and which one the control intervention is; however, they will of course be aware of the intervention received and whether or not they are part of the control group. Outcome assessors (LLeemans, SP) will be blinded to the maximal extent possible. About this, patients will be asked not to communicate with the assessors (LLeemans, SP) about the intervention received. The therapists providing BGA (LLie, IR) will not be involved in providing MST (EB, CDC), and vice versa. The interventions will take place at different locations on the Brussels Health Campus (Jette, Belgium) to minimise the contamination between groups, MST sessions will be organised in the UZ Brussel (Department of Physical Medicine) and BGA sessions will be held at the Erasmus Hogeschool Brussel (Jette, Belgium). Patients will not see each other in the hospital waiting rooms. Furthermore, because of the COVID-19 crisis and the associated restrictions, patients will have the opportunity to opt for tele-consults that will be held by the physiotherapists using a secured platform that allows video calling. As such, concerns regarding COVID-19 can be met, and therapy continuation will be guaranteed. The statistician will be blinded to the allocation of the treatment groups.

Data collection

Assessments will be performed:

- T_0: within 1 week after randomisation (baseline).
- T_1: at week 2–3 (pretreatment and post-treatment session) during intervention.
- T_2: at week 10–11 (pretreatment and post-treatment session) during intervention.
- T_3: after finishing intervention (minimum 48 hours after last treatment session) (week 13).
- T_4: 13 weeks after intervention (week 26).
- T_5: 52 weeks after intervention (week 64).

A detailed overview of the study timeline can be found in figure 1 and online supplemental appendix 2.

Data management

Biomarkers will be measured using ultra-senstitivity ELISA and/or multiplex (Luminex platform) assays.

Statistical methods

All data analyses will be performed by a statistical consultant at the Interfaculty Center Data processing and Statistics. A multiple mediators model will be estimated with a path-analysis using structural equation models. The analysis proceeds in three steps as suggested by Baron and Kenny.[118] In step 1, the direct effects of the manipulated variables on the outcome will be assessed (figure 2—path 1). In step 2, the effect of these variables on the mediators (inflammation/endogenous analgesia) will be assessed (figure 2—paths 2 and 4). In step 3, the combined effect of both the manipulated variables and the mediators on the outcome (figure 2—paths 1, 3 and 1, 5) will be assessed. It will also be explored whether both mediators are related (figure 2—path 6). The importance of the explanatory outcomes will be investigated by a multiple regression analysis.

Patient and public involvement

During the preparation of the research, we made inquiries with a national patient group (Reumanet) who identified barriers for implementing the interventions.

Ethics and dissemination

This study has ethics approval (Universitair Ziekenhuis Brussel; B.U.N. 143201941843). The research team are committed to full disclosure of the results of the trial. Findings will be reported in accordance with Consolidated Standards of Reporting Trials guidelines.[119] Given the multitude of outcome parameters, results will be divided over several papers. The funder will take no role in the analysis or interpretation of trial results.

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