Title of Study:

Feasibility of Pain Informed Movement for people with knee osteoarthritis

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Introduction

Knee OA

The prevalence of osteoarthritis (OA), of which the knee is the most affected joint, continues to increase[1] and will significantly contribute to the use of healthcare resources, with an estimated 1.45 trillion in healthcare costs by the year 2040[2 3]. The severity of pain and its impact on function have been identified by people living with knee OA as two of the most important effects of the disease[4], contributing to reduced quality of life[3]. Uncontrolled OA joint pain is associated with increased healthcare use, therefore improving pain management for OA in Canada may result in a significant healthcare expenditure savings of up to $488 billion[3]. Understanding the underlying mechanisms of OA pain is critical to effectively manage knee OA. The pain experience and its associated mechanisms in people with knee OA are known to be complex and multidimensional[5], with alterations in pain signaling playing a major role in susceptibility to the development of persistent pain[6 7], and non-responsiveness to guideline-based physiotherapy[8]. The current understanding of OA pain mechanisms is incomplete, resulting in limited pain management strategies.

While it has become clear that pain sensitization is a common feature of knee OA,[6 9-11] the role of descending modulation has been relatively less studied. Importantly, changes in nervous system sensitization to nociceptive input do not necessarily correlate with changes in self-reported pain, demonstrating that other factors modulating pain, a top down process, are at play[12,13 14]. Thought to have distinct neurophysiological mechanisms from exercise induced analgesia, descending modulation from the central nervous system can facilitate or inhibit nociception[14 15]. There is highquality evidence that suggests the use of a wide variety of exercise for people with knee OA can provide benefit in terms of a meaningful reduction in pain and improving quality of life, with modest improvements in physical function[16 17]. A recent review concluded that these effects are unlikely to be changed by future research and could be regarded as true. Current guidelines for conservative management of knee OA only recently acknowledged the potential benefit of mind body therapies, such as yoga or tai chi, with the latter receiving stronger support[18-21]. The conditional recommendation for yoga is largely due to the relative paucity of studies examining its effects and their low quality[22]. However, there is promising evidence to support that yoga for those with knee OA may improve pain intensity, function, and stiffness, compared to exercise and non-exercise control groups with moderate to large effect sizes[23 24]. Considered safe for people with comorbidities, yoga has the additional benefit of addressing overall well-being through its combination of physical postures, breathing exercises, meditation, and relaxation[20]. It is hypothesized that this unique combination of activities modifies the experience of pain by regulating input into the many physiological systems involved in the modulation of nociceptive signals[25]. There is evidence that yoga exerts this effect partially by changing patients' cognitions by reducing pain catastrophizing[26] and increasing pain acceptance modifying patients' relationships to their pain[27], as well as improving psychological dimensions of disability, such as anxiety and fear of falling, even when compared to conventional exercise[28]. Furthermore, recent research has shown that prolonged yoga interventions can have significant influence on serum levels of Brain Derived Neurotrophic Factor (BDNF), a molecule known to play a role in central nervous system neuroplasticity[29]. There is a need to further our understanding of the impact on mind-body etchniques on pain mechanisms to inform the improvement of pain management among individuals with knee OA. This study will be the first to examine the feasibility and effects of a

focused pain informed movement program[30] on this innate and integrated pain modulating pathway and will explore its impact on related BDNF and Nerve Growth Factor (NGF). Altered levels of BDNF and NGF have been observed in patients with knee OA[31 32] and both are implicated in peripheral and central pain processes in OA, with the former involved in neuroplasticity and anti-NGF therapies being highly studied and considered for FDA approval[29 33-35]. Multiple reviews have indicated that medication used to inhibit NGF have improved function and decreased pain in patients with knee OA [36 37], but there is evidence that non-medical treatments such as conventional and mind-body exercise can also impact the levels of NGF as well as BDNF [38-40], indicating another potentially promising intervention.

Objectives

The aim of this study is to establish the feasibility of a pain informed movement program, that includes neuromuscular lower extremity strengthening exercises and pain neuroscience education aimed at improving pain modulation. The data collected will be used to inform a pilot and feasibility randomized controlled trial (RCT) prior to a multi site RCT to assess the program's effectiveness with the primary outcome of descending modulation as a mediator of change in pain severity.

Research questions:
1) Is the pain informed movement program feasible in terms of recruitment rate, treatment adherence, timelines, data collection procedures, patient follow-up and resources required? 2) Is the pain informed movement program feasible in terms of patient's satisfaction and acceptability?

Literature Review

Impact of exercise on individuals with knee OA

Exercise is regularly utilized as a first-line treatment for knee osteoarthritis, and its use is supported by high quality evidence to improve pain and function[16]. Multiple clinical practice guidelines for individuals with knee OA recommend the use of aerobic and strength training for the reduction of pain and improved physical function [20 41] Other studies have supported the use of a variety of exercise types in the management of OA[17]. A Cochrane review on exercise for knee OA identified a moderate effect size of exercise compared to no exercise in reducing pain and improving physical function[42] and more recently a review of the available literature concluded that this moderate effect size was unlikely to be changed by future research [21]. Thus, the evidence supporting the use of exercise in improving physical function and reducing pain for people with knee OA is well supported and widely accepted.

Exercise leads to improved outcomes for knee OA via a number of pathways. Reductions in perceived pain can be explained in part by exercised-induced analgesia [43-46] which is thought to be mediated via numerous endogenous pathways, such as the endogenous opiate system[43] along with the endocannabinoid system[44]. Furthermore, decreased nervous system sensitivity to noxious stimuli, measured via pressure pain thresholds seem to play a role in the decreased pain experience of individuals who engage in exercise[45], as well as increased body awareness which may cause individuals to focus their attention on alternate body sensations than pain. This in turn may contribute to the diminished pain experience[45]. These mechanisms likely play a role in improved function and reduced pain along with the improved balance, muscle strength and flexibility that are conventionally associated with exercise[46].

Impact of yoga on pain and function

In recent years multiple guidelines for non-surgical management of knee OA have begun to include mind-body therapies, such as yoga or tai-chi, as conditional or core treatment recommendations[20] [41]. Structured yoga programs have been shown to result in decreased pain and improved function when compared to no exercise [47] and conventional exercise[28]. Two systematic reviews assessing the evidence for yoga treatment in people with knee OA found good evidence that yoga resulted in decreased pain and stiffness with moderate to large effect sizes [23] [48]. Both reviews indicated the need for future research to improve the methodological quality for studies on yoga effectiveness and to determine the mechanisms by which yoga leads to pain reductions in individuals with knee OA. Currently, there is evidence for involvement of numerous pathways involving multiple mechanisms. Some of those include changing patients' cognitions by reducing pain catastrophizing and increasing pain acceptance[26], changing patients' relationships to their pain[27], as well as improving psychological dimensions of disability, such as anxiety and fear of falling, even when compared to conventional exercise[28]. There is also evidence that yoga may have a beneficial impact on inflammatory pathways and assist in reducing symptoms stemming from inflammatory disorders[49]. Additionally, evidence suggests that yoga may provide many of the same benefits of conventional exercise, including improved strength, flexibility and balance[50] along with improvements in cardiovascular fitness that may exceed that obtained from conventional exercise alone[51].

Brain Derived Neurotrophic Factor

BDNF is a neurotrophin that appears to play an important role in the central modulation of pain in adults[52], and altered expression of BDNF is likely to play an important role in the pathophysiology of chronic pain[53] [54]. Individuals with knee OA have been shown to possess altered levels of serum BDNF compared to healthy controls, indicating that BDNF may be implicated in the pain experience of patients with knee OA[31]. Thus, BDNF has been identified as a therapeutic target in the treatment of pain resulting from central sensitization[34]. One systematic review showed that exercise increased peripheral BDNF concentrations in elderly individuals with and without health impairments[38] and another study reported that an aerobic exercise program in elderly women with knee OA resulted in increased BDNF plasma concentrations coinciding with improvements in walking distance and pain, suggesting that BDNF may mediate these improvements[39]. These results are encouraging, but further investigation is needed in order to determine the most appropriate interventions for achieving therapeutic BDNF levels[38]. Recently, a study assessing the effect on yoga on chronic low back pain found significant increase in serum BDNF levels with concurrent decreases in pain following a 12-week intervention[29], indicating that yoga is another plausible exercise intervention that could impact BDNF levels.

Nerve Growth Factor

NGF is a neurotrophin known to play a critical role in the proper development of the nervous system[55] [56]. Evidence indicates that NGF is also involved in the increased pain experience of many individuals via peripheral sensitization of nociceptive neurons[57] [58]. Furthermore, NGF levels have been shown to be elevated in a wide variety of chronic pain conditions[59] including knee OA[32]. As a result, anti-NGF therapies are being highly studied and considered for FDA approval[35] as they have significant potential to decrease pain and improve function in individuals with OA that do not respond to conventional analgesics[60]. Multiple recent reviews have indicated that interventions, such as medication, used to inhibit NGF have resulted in decreased pain and improved function

and quality of life in patients with symptomatic OA[36 37]. Additionally, there is some evidence that acute moderate exercise can alter NGF levels in people with certain conditions[40] indicating that alternative methods to medication could be explored.

Ethical Considerations: This application has been reviewed by the Hamilton Integrated Research

Ethics Board under Project #13461.

Methods

Study Design

This pre-post test mixed methods study will assess the feasibility of a pain informed movement program. All included participants will be assessed at baseline and after the intervention. All participants will also be invited to complete a satisfaction survey and take part in focus group interviews at the end of the program. These studies will be guided by the Conceptual Framework for Defining Feasibility[61] and Pilot studies and the Standard Protocol Items: Recommendations for Intervention Trials.[62]

Study Population

A convenience sample of 15 adults will be sought and is adequate to evaluate the feasibility of the program[63].

Recruitment

Participants will be recruited through the email lists of the McMaster Physical Activity Centre of Excellence (PACE) community. Recruitment posters will also be included in the McMaster Institute for Research on Aging (MIRA) newsletter. In addition, we will place postings on both PACE and MIRA social media pages.

Participants

Inclusion criteria:

- ≥40 years of age with a diagnosis of knee OA by a physician; OR
- ≥45 years of age having activity related knee joint pain with or without morning stiffness lasting 30 minutes (as per NICE criteria)
- Having an average pain intensity of 3/10 on a numeric pain scale

Exclusion criteria:

- Cannot communicate in English;
- Have inflammatory arthritis or other systemic conditions;
- Have had lower limb trauma, surgery within the past 6-month;
- Have participated in a similar knee OA exercise program in the prior 3-months;
- Have used oral corticosteroids or had a corticosteroid injection in the index knee within 6months prior to baseline assessment
- Do not have regular access to the internet for viewing of educational videos

Intervention

The proposed program will be an 8-week in-person group exercise program held twice weekly, in which participants will receive exercise instruction (60 minutes) and education (15min for the first 4 sessions). Home sessions will be facilitated by exercise handout sheets and access to video files to guide the participant through the exercises. The exercise component has been developed by a team member and will be delivered by an experienced yoga teacher. The education component will cover the following topics: The purpose of pain, basic neurophysiology of nociception and pain, common OA symptoms and risk factors, neurophysiological changes of pain, movement guidelines when pain persists, and self care techniques to impact neurophysiology and support moving with ease.

Setting

The in-person 8-week exercise program will be held twice weekly at McMaster University's Physical Activity Centre of Excellence (PACE) located in the Ivor-Wynne Centre. Participants will complete the pain assessment, and have blood drawn at PACE by PACE staff who are certified phlebotomists.

Pre-Assessment and Screening

Potential participants will contact the research coordinator, who will explain the purpose of the study and determine participant eligibility. If eligible, participants will be sent a link to our online consent form using Limesurvey. Participants will also have the option to have this consent form mailed to them.

Assessment

As part of participation in the study, participants will be asked to attend an assessment at the beginning of the study, and once again upon completing the 8-week exercise program. Participants will undergo pain modulation (CPM) testing, and the 30 Second Sit to Stand Test to determine leg strength and endurance. Lastly, participants will have their blood drawn at the beginning and end of the study.

Participants will then be asked to complete a series of questionnaires about their pain and mood. These will be completed via a link provided by the research coordinator for participants to complete on our online Limesurvey system. Alternatively, participants can have these questionnaires mailed to them to be complete and manually entered by the research coordinator. These questionnaires will be completed at the beginning and end of the study.

Time Commitment

The in-person assessments to complete the pain assessments and drawing of blood will take ~20 minutes. Participants will be asked to complete the questionnaires before beginning the exercise sessions. Completion of these questionnaires will take ~20 minutes. Twice weekly exercise sessions will be an hour and 15 minutes in duration. Participants will be given instructions to complete these exercises at home at least one other time during the week for the same duration.

In total, participants will complete an 8-week twice weekly exercise program at the university, one session at home and complete 2 series of questionnaires. The total time commitment for participants will be approximately 29 hours.

Outcomes

Outcomes will be evaluated at 2 time points: at baseline and at the conclusion of the pain informed movement program (approximately 8 weeks).

Feasibility Outcomes: Acceptability of the intervention (content, frequency, duration), burden of procedures (questionnaires, quantitative sensory testing, blood draws), recruitment rate, adherence rate, follow-up rate, self-reported adverse events, exercise completion (number and frequency completed). A priori success criteria will be used to determine feasibility.

Participant characteristics: Age, sex, race, gender, education level, marital status, height, and weight will be collected.

Pain modulation (CPM): CPM is an indicator of descending inhibitory pain modulation and a measure of the degree to which *pain inhibits pain.* Following recommended testing,[64] first an ascending measure of pressure pain threshold (PPT) inducing a verbal pain rating of 3 out of 10 will be evaluated at the anterior shin on the unaffected knee. Next a conditioning stimulus in the form of forearm ischemia will be applied to induce a minimum verbal pain rating of 5 out of 10 at the opposite volar forearm. The arm will be elevated to chest level with a blood pressure cuff around the middle of the upper arm. Systolic pressure will be determined. Next the cuff will be inflated to 20mmhg above systolic pressure and the participant will be asked to squeeze a stress ball until a pain rating of 5/10 is reported. Once pain rating is recorded, PPT at the anterior shin will be repeated as the cuff remains inflated.[15] An index will be created by calculating the percent efficiency of CPM (%CPM) as PPT2/PPT1, multiplied by 100; whereby %CPM ≤ 100 indicates inefficient pain modulation.[64 65] CPM testing has demonstrated good reliability intra-session ICC (0.75 - 0.85).[65]

Pain intensity: Pain intensity will be measured with the Numeric Rating Scale, a unidimensional single item measure of pain intensity used in adult populations[66]. The average of three questions will be used: average pain intensity in the past 24 hours, past week, and worst pain in the past 24 hours. Questions are rated on a an 11-point scale where patients select a rating between 0-10 with zero typically represents 'no pain' while 10 represents the 'worst imaginable pain'[67].

Pain catastrophizing: Pain catastrophizing will be measured using the Pain Catastrophizing Scale[68] (PCS). The PCS is a 13-item self-reporting instrument for catastrophizing in the context of actual or anticipated pain, with higher scores indicating higher pain catastrophizing. Sub-scores for the three PCS dimensions (rumination, magnification, and helplessness) will also be calculated.

Chronic pain self-efficacy: The Self-Efficacy for Managing Chronic Disease 6-item scale will be used to measure self-efficacy for chronic pain sufferers, with higher reported scores indicating higher self-efficacy[69].

Anxiety and depression: The Hospital Anxiety and Depression Scale (HADS) consists of 7 questions to measure anxiety and 7 questions to measure depression[70]. Higher scores represent increased severity in anxiety and depression symptoms. It is a brief and reliable measure of emotional distress in general and chronic populations including chronic pain and rheumatology.[71] Average sensitivity and specificity is ≥ 0.80.

Knee injury and outcomes: The Knee Injury and Osteoarthritis Outcome Score (KOOS) is a kneespecific instrument, used to assess self-reported opinions about patients' knee and associated problems, while evaluating short-term and long-term consequences of knee injury. There are 42

items in 5 scored sub scales, of which two will be used: 1) pain, and 2) function in daily living (ADL). Scores range from 0-100 with zero representing extreme knee problems and 100 representing no knee problems[72]. KOOS has adequate internal consistency (0.70-0.95) and construct validity in adults with knee OA.[73] Multiple studies have determined convergent and divergent construct validity with comparison to several instruments including the subscales of SF36 and the Lysholm knee scoring scale.[74]

Performance tests: The 30 Second Sit to Stand Test will be used to test leg strength and endurance[75]. Time will be measured with a handheld stop watch and recorded to the nearest 0.01 secs for walking. The chair stand test is a measure of sit to stand activity and of lower extremity strength and balance. The maximum number of chair stand repetitions completed during a 30 second interval will be noted along with use of any aids during testing. A standard chair height will be used for all participants (ICC 0.81-0.98).

Blood analysis: A maximum of 5ml of blood will be drawn for analysis of BDNF and NGF. Measurement of BDNF and NGF requires 50µL of diluted plasma as per the ELISA kit.

Exit Survey and Focus Group

A satisfaction survey will be conducted at the end of the program to evaluate the a priori feasibility criteria. Participants who indicated upon initially consenting to the study that they would like to participate in a focus group, will be contacted. Consent for participation will be obtained in person, or participants will have the option to have this consent form emailed to them. Qualitative data collection will be used to explore participants experience and perceptions of the feasibility and acceptability of the program. The interview guide has been developed by patients and practitioners.

Data Collection:

A focus group will be conducted using audio or video recording (using Zoom), lasting between 4560 minutes. Transcripts will be available and will be reviewed for accuracy by participants. The qualitative software "Dedoose" will be used to manage, store, and analyze data.

Methodological Rigor:

Member checking (participants' comments on any emergent themes), verification (researchers converge on recognizing "identical patterns" in the data), referential adequacy (providing enough quotes to ensure the findings fit the data) and maintaining an audit trail (records of decisions made), will be used to ensure methodological rigor.

Statistical Analysis Plan (SAP)

Feasibility of Pain Care Yoga: All quantitative analyses will be conducted using SPSS 26. Descriptive statistics will be used to report feasibility outcomes, and survey responses will be summarized (using descriptive statistics) to identify trends in patient-reported outcomes.

Qualitative Interviews: Qualitative interviews will be analyzed using Thematic content analysis to identify suggestions for program modification. Line-by-line reading of the transcripts will be performed by the authors and thematic patterns will be explored. Once themes and patterns are identified, each meaningful segment of text will be assigned a conceptual code. When conceptual codes become saturated, authors will build pattern codes where specific dimensions of clinicians' experiences will be clustered into recurring themes. Once the codes and themes are developed,

participant and clinician partners will be invited to contribute to blinded data analysis to broaden interpretations and provide feedback on the quotes and emergent themes.

Impact

Understand the underlying mechanisms of OA pain is critical to effective management, however our knowledge of knee OA pain mechanisms is incomplete given knee OA pain is complex and multidimensional[5]. The proposed study will be the first to examine the feasibility and effects of a focused pain informed movement program on this innate and integrated pain modulating pathway and will ultimately explore its impact on related Brain Derived Neurotrophic Factor (BDNF) and Nerve Growth Factor (NGF). Both are implicated in peripheral and central pain processes in OA, with the former involved in neuroplasticity and anti-NGF therapies being highly studied. The project will contribute to the clinical recommendations for management of OA pain using mind body therapies for clinicians across multiple sectors and will provide additional conservative pain management options for a disease that is expected to increase with the aging population. This study will lay the foundation to inform a multi-site RCT to assess the program's effectiveness with the primary outcome of descending modulation as a mediator of change in pain severity.

Timeline

Study recruitment and offering of the pain informed movement program will take place between January 2022 - September 2022. months. Meeting recruitment goals is highly feasible as based on approaching 500 members of PACE and cross-faculty MIRA institute, our recruitment rate will only need to be 3%.

Plans for Knowledge Translation:

The goal of our knowledge translation efforts will be to inform clinicians and researchers of the results of this study for research considerations and clinical recommendations. To do so, we will disseminate the results through journal article publications (e.g., Osteoarthritis and Cartilage and Arthritis Care and Research), peer review conferences (e.g., OARSI and Canadian Rheumatology Association), national professional organizations (Canadian Physiotherapy Association) and special interest groups such The Arthritis Society. We will also aim to use the results of this study to support the design of and application for funding a multicenter randomized controlled trial.

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