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SCIENTIFIC BACKGROUND

Knee osteoarthritis (OA) is a prevalent source of impairment worldwide and is often addressed in primary care settings (Cui, A. et al. 2020 PMID: 34505846). In the UK, approximately one in twenty-five individuals seek medical consultation for knee osteoarthritis each year (Yu, D. et al. 2015 PMID: 26163287).

Regular exercise is recommended by all major clinical guidelines for managing knee OA pain and is typically the first-line treatment offered in primary care (Moseng, T. et al. 2024 PMID: 38212040). Should an exercise intervention prove ineffective in enhancing pain perception, patients are directed for physiotherapy. Following a thorough evaluation by physiotherapists, a range of exercise therapies has been recommended, differing in modality, intensity, and duration, yet yielding inconsistent outcomes.

The intervention used in this trial is part of a web-based version of the Supported Osteoarthritis Self-Management Programme (SOASP), developed in Sweden. From 2008 to 2017, over 75,000 patients participated, with 2,339 physiotherapists and occupational therapists trained to deliver it. SOASP is currently offered in 700 clinics across Sweden and has been rated good to very good by 94% of participants for its effectiveness, safety, and acceptability (Jönsson, T., et al 2019 PMID: 31536554). Given the high prevalence of knee OA, there is a clear need for therapies that are both effective and cost-efficient. However, barriers such as adherence, limited mobility, and healthcare costs challenge implementation. Digital delivery of SOASP via Joint Academy has proven equally effective and widely accepted in Sweden, and our previous UK-based work has also shown strong effectiveness for this approach (Gohir et al 2021 PMID: 33620447).

Chronic knee OA pain is influenced by systemic inflammation and metabolic factors such as poor diet, excess weight, and metabolic syndrome, which contribute to “meta-inflammation” through dysregulation of adipokines, cytokines, and lipids (Zhang et al. 2024 PMID: 38243159). A systematic review and meta-analysis of 73 studies show significant reductions in self-reported pain severity following nutrition interventions (Brain, K. et al. 2019 PMID: 30294938) and prebiotics may hold promise for the management of knee OA in adults with obesity (Fortuna, R. et al. 2024 PMID: 38713231). In addition, the endocannabinoid (EC) system plays a central role in pain regulation and emotional response to chronic pain (Woodhams, S. G., et al. 2015). PMID: 25846617). Prebiotic fibre supplementation may support gut health, reduce systemic inflammation, and improve biomarkers linked to OA and chronic pain, complementing the effects of exercise.

Emerging evidence links gut microbiome composition to OA-related knee pain, with studies indicating its role in pain intensity, progression, and sensitivity- including neuropathic pain - largely through inflammation modulation (Ding, W. et al. 2021 PMID: 32889847). Short chain fatty acids (SCFAs), produced by bacterial fermentation of dietary fibre, mediate many of the microbiome’s anti-inflammatory effects. However, the interactions between physiotherapy exercise, prebiotic

inulin supplementation, pain modulation, inflammatory biomarkers, and the gut microbiome remain poorly understood. Specifically, the effects of inulin and exercise on pain, microbiome composition, inflammatory markers, and circulating SCFA levels in individuals with knee OA have yet to be explored.

Rationale: This trial will adopt a 2x2 factorial design to assess the individual and combined effects of exercise and prebiotic inulin supplementation over six weeks. The study will evaluate their effect on knee osteoarthritis (OA) pain, as well as molecular and gut microbiome parameters.

STUDY OBJECTIVES

PRIMARY OBJECTIVE

1-To assess the magnitude of the effect of prebiotic supplementation (inulin) side by side with physiotherapy exercise versus placebo (maltodextrin) on knee pain

SECONDARY OBJECTIVES

1-To assess the combined effects of exercise and prebiotic inulin supplementation (synergistic effect) over six weeks

2-To elucidate the molecular pathways involved in pain relief induced by exercise and gut microbiome modulation in individuals with painful knee osteoarthritis

STUDY DESIGN

The INSPIRE study is a 2x2 factorial randomised controlled trial in the community setting at Nottingham with participants identified as having knee arthritis, 1:1:1:1 randomised to web-based exercises, inulin, exercise and inulin or placebo and usual care.

SETTING

Home based - Community Setting

PATIENT AND PUBLIC INVOLVEMENT

The study design came as a result of analysis of 18 long qualitative interviews with participants of the iBEAT-OA trial who had completed the physiotherapy intervention. Analysis of these interviews showed a significant interest and desire on the part of individuals affected with knee OA to use nutritional strategies to improve their pain outcomes. Thus the idea of improving gut microbiome health to improve pain relief was incorporated into the digital physiotherapy protocol. This project was discussed with two patient collaborators whose input was used for drafting the first protocol. The final versions of the participant facing documentation (PIS, consent form, invitation letter and flyer) were reviewed by two patient representatives (TM and LW) who have revised them and commented on them, all their feedback was incorporated.

RECRUITMENT

Participants with knee pain who had consented to be contacted for future research will be invited from existing Academic Rheumatology, City Hospital Nottingham's databases (Millar, B. et al. 2020 PMID: 32199451) to participate in the study. Nottingham Post adverts will be used to make up for any recruitment shortfalls. All eligible individuals will be sent the participant information sheet and if they are interested they will contact the research centre to be recruited.

INCLUSION AND EXCLUSION CRITERIA

Inclusion criteria:

- Participants with any pain in or around a knee on most days for more than 3 months
- Participant is willing and able to give informed consent for participation in the study

· Participant eligibility includes those aged >18 years who have a body mass index (BMI) between 18.5 and 39.9 kg/m^2

Exclusion criteria:

The participant may not enter the study if ANY of the following apply:

· Have psychosocial or gastrointestinal (e.g. malabsorptive conditions such as IBS/IBD, coeliac)

· Are taking the following medications: immunosuppressants, anticoagulants, amiodarone and/or perhexiline

· Are currently following or anticipated to commence a specialised commercially available weight loss diet and/or programme

· Pregnant or breastfeeding

· History or current psychiatric illness (including clinical depression)

· History or current neurological condition (e.g. epilepsy)

· Those undergoing revision, having severe hip OA, inflammatory arthropathies

· Diagnosed non-OA cause of knee pain (e.g. rheumatoid arthritis)

· Neuropathy or diabetes mellitus

· Having taken part in a research study in the last 3 months involving invasive procedures or an inconvenience allowance

RANDOMISATION AND BLINDING

Randomisation will be done using a computer-generated randomisation and allocation concealment software called “sealed envelope” (**https://www.sealedenvelope.com/**). At least thirty participants will be divided equally between the treatment arms. Blinding for the exercise intervention is not feasible at this stage since participants will be informed if they have been randomly assigned to one of the exercise groups. Because this might affect the motivation of

participants who were randomly assigned to the non-exercise arms, they will be offered access to the web-based exercise programme after completing the trial. Although it is challenging to blind exercise intervention studies, both the research examiner and the participants will be blind to the intervention and the food supplementation.

MATERIALS

Inulin fibre (20g) in powder form, maltodextrin (10g) in powder form, Joint Academy app, faecal sample kit, blood sample collection materials.

PHYSIOTHERAPY INTERVENTION

INSPIRE will use a web-based exercises platform known as Joint Academy (JA) as a previous RCT from our group demonstrated promising results for this platform (Gohir et al 2021 PMID: 33620447). The Swedish face-to-face self-management programme "Artrosskolan" (The Osteoarthritis School), which offered structured information and exercises for knee arthritis to a relevant population with the condition, served as the model for this programme. The JA company has granted permission for this study to be carried out using their digital platform.

The exercise intervention has been described in detail previously (Gohir et al 2021 PMID: 33620447). It is focused on a mixture of concentric and eccentric exercises with open and closed-chain movements, for strengthening the legs including the muscles around the hips and knee joints as well as exercises to improve balance. An open kinetic chain is defined as “a combination of successively arranged joints in which the terminal segments can move freely” (Karandikar et al 2011 PMID: 21871418), while closed chain exercises are those in which the proximal joints move while the distal portion of the extremities is in a stationary position (Karandikar et al 2011 PMID: 21871418). The programme also includes educational sessions covering the fundamentals of OA, its treatment, self-managing symptoms of OA and the benefits of maintaining a healthy lifestyle.

DIETARY INTERVENTION

Inulin fibre (20g) in powder form (commonly found in root vegetables such as chicory) will be randomly allocated to eligible participants in order to test specific effects on gut microbiome

composition and metabolic markers. Inulin is easily dissolvable in liquid and can be incorporated into the usual diet - by adding water, juice, smoothies, cereal, yogurt.

CONTROL PLACEBO GROUP

The control group will continue with routine self-management which is offered in the community setting and will be instructed to receive maltodextrin (10g) in powder form (commonly found in corn, potatoes, rice) which can be consumed by adding to breakfast cereal/ smoothie/ yogurt or drink of choice similar to inulin will serve as a control/placebo to compare the effects observed with inulin.

FOLLOW UP DURATION

Six weeks post-intervention.

RESEARCH ASSESSMENT

Following outcome measures will be assessed:

- Quantitative Sensory Testing – QST (Pressure pain threshold – PPT and Temporal summation – TS)
- SCFAs, EC, gut microbiome and inflammatory pain-related biomarkers
- Physical functioning (Time up and go test, 30-second sit to stand test)
- Grip strength
- Hospital Anxiety and Depression Scale (HADS)

DESCRIPTION OF INTERVENTION

The study will be communicated verbally and in writing to participants who have knee pain from OA. Participants who meet the study's eligibility requirements will sign an informed consent form and be randomly assigned to either the interventional groups or the control/placebo group.

All groups will have an assessment session with experienced staff with blood samples taken at baseline and a Numerical Rating Scale (NRS) (Hjermstad, M. J. et al. 2011 PMID: 21621130), physical functioning and other outcomes (grip strength (Roberts, H. C. et al. 2011 PMID: 21624928), Time up and go test (Barry et al 2014 PMID: 24484314), 30-second sit to stand test (Jones, C. J., et al. 1999 PMID: 10380242), Quantitative Sensory Testing (QST) (Arant, K. R. et al. 2022 PMID: 34597800)). Participants will be asked to fill in questionnaires on health and anxiety/depression (Hospital Anxiety and Depression Scale (HADS) (Zigmond, A. S. & Snaith, R. P. 1983 PMID: 6880820) that they will have been sent via post before the study visit. They will also be sent a faecal sample kit and will be asked to provide a faecal sample to bring to their baseline appointment.

The exercise interventional groups will be sent an email with a link to access the JA online platform. The physiotherapy intervention will begin once log-in and a kick-off call with an assigned personal physiotherapist is complete. The intervention will consist of a 6-week online physical therapy course that includes exercises, information, contact with a personal physiotherapist, and instruction on behavioural and lifestyle modifications, and can be accessed using a smartphone or tablet. Through frequent email prompts, the programme also promotes commitment to physical activity. Participants will first complete a physical test measuring lower limb strength and respond to an online questionnaire that covers topics like physical function, health-related quality of life, and the severity of joint discomfort. The online baseline evaluation will include this questionnaire. In addition to some functional exercises like sit-to-stand and stair climbing, the exercise intervention will include knee and hip exercises.

The placebo and inulin groups will receive pre-measured pots containing either the supplement or placebo powder for each week, along with scoops. Participants will be instructed to take either 2 or 3 scoops daily, depending on whether they are in the inulin or placebo group. They will also be provided with guidance on incorporating their daily dose into their diet, such as mixing it into smoothies or using it as a topping on yoghurts and breakfast cereals. Participants will be asked to maintain a daily dietary compliance record to track their supplement intake, including any missed doses and the reasons for not taking the supplement. If participants experience adverse effects, such as severe bloating or nausea, that prevent them from continuing with the supplement, they will be instructed to notify a member of the study team.

After the six weeks of interventions, all participants will fill in the same questionnaires and perform the physical tests, to enable evaluation. Participants and the researcher will meet in person twice: once at enrolment and again six weeks later.

OUTCOMES

Primary outcome:

- Numerical Rate Score (NRS) for pain to assess changes in response to the interventions.

Secondary outcomes:

- Changes in markers of pain assessed by quantitative sensory testing, and in markers of inflammation

- Changes in gut microbiome composition and serum levels of short chain fatty acids (SCFAs) in response to the interventions.

- Changes in functional outcomes (e.g., 30 second sit to stand test, get up and go test)

STATISTICAL ANALYSIS PLAN

The clinical trial data will be analysed using the appropriate parametric and non-parametric statistical tests, we will compare outcome measures (such as pain sensitivity and pain ratings) between the exercise and non-exercise groups while adjusting for baseline scores.

Secondary analyses (i.e., correlations between changes in SCFAs and changes in pain measures) will be conducted using the appropriate type of statistical test based on data normality (e.g., Spearman's).

A planned analysis of covariance (ANCOVA) will be conducted to assess differences in follow-up outcome measures among treatment groups while adjusting for baseline levels. The model will include treatment group (arm: inulin only, exercise only, inulin &exercise, control/placebo) as a categorical independent variable and baseline outcome scores as a covariate. Model assumptions will be evaluated through residual diagnostics to ensure the validity of the analysis

To further explore differences between groups, post hoc pairwise comparisons will be conducted, including comparisons between groups and an evaluation of potential interactions to assess potential synergy between treatments.

R studio and Graph Pad PRISM will be used for the statistical analyses.

SAMPLE SIZE AND JUSTIFICATION

Primary outcome is a Numerical Rate Score (NRS) for pain as used in our previous exercise intervention study (Gohir et al 2021 PMID: 33620447). The 2x2 factorial design with 30 individuals per block (total n=120) has 80% to detect differences of 0.51 SDs. In our own study delivering the exercise intervention the effect size observed was a drop of 0.84 SDs in the exercise arm compared with only 0.2 SDs in the control arm (who only received a leaflet). In addition, the study has adequate power to detect moderate main effects of inulin on pain outcomes, with 30 participants per group providing ~75–80% power to detect an effect size of Cohen's d ~ 0.6 at α = 0.05. If changes in gut microbiome via dietary supplementation can achieve a difference of 0.51 or higher in NRS, the study is powered to detect them.

Secondary outcomes: a key goal of this study is to link changes in molecular markers in serum to changes in pain and other outcomes (n=120, 60 per arm for the 2x2 intervention). For instance, the effect sizes in changes in a circulating molecular pain modulator observed previously from 0.32 to 0.71 nmol/L; SD=0.61 after 6 weeks of inulin supplementation hence yielding an effect size of 0.62 STDs. It increased from 1.61-1.82 nmol/L; SD=0.31 yielding an effect size of 0.61 STDs with the exercise intervention.

DATA MANAGEMENT

Data will be gathered during the first and last sessions of the INSPIRE trial. Trained local research personnel will compile all the data sources, and data entry in a RedCAP database will be done in a consistent manner. This will comprise data from QST, 30CST, and TUG as well as questionnaires. The data entry site will enter data from the clinical research forms (CRF) from the initial and final study visits.

ADVERSE EVENTS

Since the interventions in the current study are using components sourced from common foods and routine exercise, we foresee no adverse reaction or side effects. Increasing fibre intake may result in bloating amongst those who have a low habitual intake of dietary fibre. However, such effects are mild and not considered as a safety concern. Participants will be asked to record any side effects like bloating using the dietary compliance diary and will be advised to stop taking the supplement if they experience severe bloating. Between 2008 and 2017, 75,000 participants participated in these activities' trials, and no significant side effects were reported (Thorstensson, C. A. 2015 PMID: 25345913). An increase in back, hip, or knee pain is a remote possibility (Luan, L., 2022 PMID: 35091326). Using an online interface, we will track the patient's pain levels every week to see if there has been an increase in discomfort. The subject will be advised to discontinue

study participation and get in touch with their GP if their pain worsens to the point that they begin to struggle with everyday tasks.

Criteria for terminating the study: It is not anticipated that circumstances will arise that necessitate the termination of this study because it only consists of two assessments, does not involve investigational medications or medical devices, and the same intervention has not resulted in any serious adverse events in over 70,000 participants in Sweden.

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