further suggest exercising caution in attempting to harmonise differing longitudinal pain PROM data within or between participants and studies. It may be that a dichotomisation at harmonised PASS threshold on a PROM, as proposed in our systematic literature review, may have greater tolerance to allow comparisons between different pain PROMs datasets, which will be tested in corresponding research.

10
DEVELOPMENT OF AN INTERVENTION TO IMPROVE IDENTIFICATION AND MANAGEMENT OF CONCOMITANT KNEE OSTEOARTHRITIS IN PERSONS WITH TYPE 2 DIABETES AND PHYSICAL INACTIVITY

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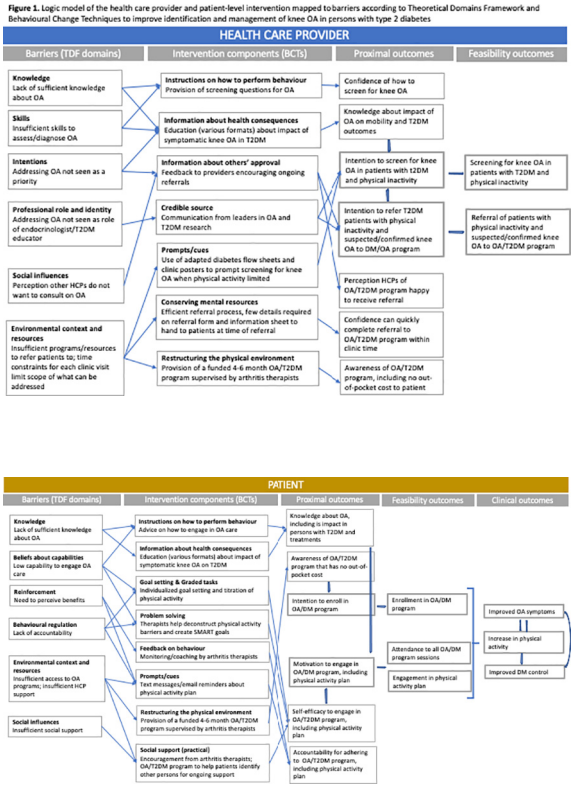
Purpose: Guideline recommendations exist for the management of knee osteoarthritis (OA) yet uptake of evidence-based OA care is suboptimal. In persons with type 2 diabetes (T2DM), the presence of concomitant symptomatic knee OA leads to functional impairments and physical inactivity which increases the risk for diabetes complications and cardiovascular events. Yet, these individuals are less likely to receive OA care due to the competing clinical demands of their T2DM. Improving uptake of knee OA care in persons with T2DM represents an opportunity to not only improve OA outcomes for under-treated individuals but also improve T2DM outcomes for a population at high risk of cardiometabolic sequelae. Implementation interventions seek to put evidence-based care into practice. The use of theory in developing complex interventions focuses on identifying determinants of behaviour and linking them to mechanisms of change to maximize intervention effectiveness. Involving stakeholders in a user-centered co-creation process can increase impact and sustainability. Our aim was to use a systematic process combining theory, stakeholder involvement and existing evidence for knee OA care to develop a multifaceted implementation intervention targeting both health care providers (HCPs) who treat T2DM and patients with T2DM and knee OA, to improve the uptake of evidence-based OA care in persons with T2DM and knee OA who are physically inactive. A broader aim was to outline this process of systematically developing a complex intervention that seeks to change behaviours of HCPs and patients to provide template for researchers tackling other problems.
Methods: The TOP-DM (Treating Osteoarthritis in Persons with Diabetes Mellitus) intervention development followed a systematic stepped process informed by the UK Medical Research Council (MRC) guidance for developing complex interventions informed by theory. First, we identified target behaviours through consultation of a User Advisory Panel (UAP) composed of stakeholders from family medicine, endocrinology, patients, physical therapy, rheumatology, and Arthritis Society, a Canadian non-profit organization offering an existing arthritis rehabilitation program. Second, we interviewed HCPs who treat T2DM (family physicians, endocrinologists, diabetes educators; n=18) and patients with T2DM and knee OA (n=18) to identify determinants of: 1) Assessing and treating knee OA (HCPs); and 2) Seeing and engaging in OA care (patients) using the Theoretical Domains Framework (TDF). We mapped identified TDF domains to operationalizable literature-supported behavioural change techniques (BCTs) to determine potential intervention components. Third, we conducted semi-structured stakeholder meetings with members of our UAP, individually and in groups, to ascertain acceptability and feasibility of identified BCTs, including content and modes of delivery. Fourth, the research team selected final intervention components informed by the prior steps, and constructed a logic model.
Results: Together with our UAP, we identified modifiable target behaviours at the HCP and patient level. At the HCP level, barriers to assessing and treating knee OA were: lack of sufficient knowledge and skills to assess OA, no intention to address OA, OA care not seen within the professional role and identity for some providers (endocrinologist/diabetes educator), perceiving that other HCP may not want to treat OA, and paucity of government-funded OA resources and programs to refer patients to for treatment. At the patient level, barriers to seeking and engaging in OA care were: insufficient knowledge and belief in personal capability to engage in OA care, need for reinforcement, social support and behavioral regulation, including accountability, insufficient support from HCPs, and paucity of accessible programs and resources for OA care. These barriers were mapped to BCTs and found to be acceptable by interviewed stakeholders; we modified content/delivery in response to stakeholder feedback. The final intervention components incorporated a range of BCTs at the HCP and patient level. These include, at the HCP level: provision of screening questions to help in the assessment of knee OA, education about the impact on symptomatic OA in persons with T2DM, cues in the work environment to prompt OA screening in persons with physical inactivity, development of an OA/T2DM program for persons with T2DM in conjunction with Arthritis Society, and an efficient referral process to the OA/T2DM program; and at the patient level: education about OA (multiple modes of delivery), the Arthritis Society-delivered OA/T2DM program that comprises goal setting, problem solving, feedback on behaviour, and support to enable engagement in the program including individualized physical activity plan. We present a logic model of the proposed intervention in Figure 1.
Conclusions: We integrated theory and stakeholder involvement to develop a multifaceted intervention to increase identification of knee OA in persons with T2DM and physical inactivity within diabetes care and improve uptake and engagement in evidence-based OA management. The final intervention leverages the existing government-funded Arthritis Society arthritis rehabilitation program infrastructure that supports potential spread, scalability and sustainability. The feasibility of the intervention components will be assessed and refined using a rapid-cycle improvement strategy before further evaluation in a cluster randomized pilot trial.



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IDENTIFICATION AND FUNCTIONAL CHARACTERIZATION IMBALANCED OSTEOARTHRITIS ASSOCIATED FIBRONECTIN SPLICE VARIANTS

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Purpose: Transcriptome-wide analyses demonstrated *FN1* is the highest expressed gene in articular cartilage and is significantly upregulated with ongoing OA pathophysiology. *FN1* encodes fibronectin, a dimeric glycoprotein, particularly localized in the pericellular matrix directly surrounding the chondrocytes. Fibronectin mediates a wide variety of cellular interactions by binding to extra cellular matrix proteins and to chondrocytes via integrins. The main integrin-binding domain of fibronectin is the RGD motif, which binds multiple integrin heterodimers, including the classic fibronectin receptor integrin $\alpha5\beta1$. *FN1* can give rise to 27 different splice variants, which can occur at three major sites, called extra domain A (A), extra domain B (B), and variable region

(V). Such splicing variants provides cells capacity to generate protein isoforms with different binding properties hence functions. Among the *FN1* splice variants is the intact 70 kDa N-terminus of the full length protein, also known as migration-stimulating factor (MSF), which has been associated with tumor progression in multiple cancers. Despite being prominent in articular cartilage, it is unknown whether *FN1* transcripts are involved in the OA pathophysiology. We, therefore, aimed to identify *FN1* transcripts associated with OA pathophysiology and investigated downstream effects upon modulation of transcripts relative to full length *FN1* expression in our 3D *in vitro* organoid cartilage model with human primary chondrocytes.

Methods: *FN1* transcriptomic data was obtained from our previously assessed RNA-seq dataset of lesioned and preserved OA cartilage samples (N=35, RAAK study). Differential transcript expression analysis was performed on all 27 *FN1* transcripts annotated in Ensembl database. Pearson's correlations were calculated to generate a co-expression network between *FN1* and our previously reported differentially expressed genes in OA cartilage. Human primary chondrocytes obtained from the RAAK study were transduced with lentiviral particles containing shRNA targeting full length *FN1* transcripts or non-targeting shRNA. Subsequently, matrix deposition was induced in our 3D in vitro neo-cartilage model. Effects of changes in *FN1* transcript ratio on sulphated glycosaminoglycan deposition were investigated by Alcian blue staining and dimethylmethylene blue assay. Moreover, gene expression levels of eight cartilage relevant markers and three highly correlating genes with *FN1* were determined by RT-qPCR.

Results: We identified 22 *FN1* transcripts to be robustly expressed in OA cartilage. In line with previous findings, the highest expressed protein-coding transcripts were EDA$^-$ variants, while EDA$^+$ variants were less abundantly expressed. To identify specific *FN1* transcripts associates with the OA process, differential expression analysis was performed on these 22 transcripts between lesioned and preserved OA cartilage, resulting in 16 FDR significantly upregulated transcripts. Of these 16 transcripts, 5 were protein-coding and 11 non-protein coding, suggesting these non-protein coding transcripts may play a role in OA pathophysiology. Notably, *FN1-208*, encoding Migrating Stimulating Factor (MSF), was the most significantly upregulated protein-coding transcript. Upon downregulation of full length *FN1* in our 3D in vitro neo-cartilage model, we generated an increased ratio of *FN1-208* relative to full length *FN1* transcript, as such mimicking cartilage in OA affected state. This resulted in decreased cartilage sulfated glycosaminoglycan deposition (Figure 1), as well as significantly decreased *ACAN* and *COL2A1* and increased *ADAMTS-5*, *ITGB1*, and *ITGB5* gene expression levels, implying a detrimental effect on neo-cartilage deposition. Moreover, *NT5E* expression was downregulated as a result of *FN1* downregulation, indicating *NT5E* expression is regulated downstream of *FN1* signaling.

Conclusions: We identified *FN1-208* as the most significantly upregulated protein-coding transcripts, which has not been previously associated with OA. We show that full length *FN1* downregulation and concomitant relative *FN1-208* upregulation was unbeneficial for deposition of neo-cartilage matrix, likely due to decreased availability of the classical RGD integrin-binding site of fibronectin. We identified *NT5E* as previously unknown *FN1* signaling downstream gene in cartilage. Together, our data highlight the importance of proper balance of *FN1* transcripts for healthy cartilage homeostasis.

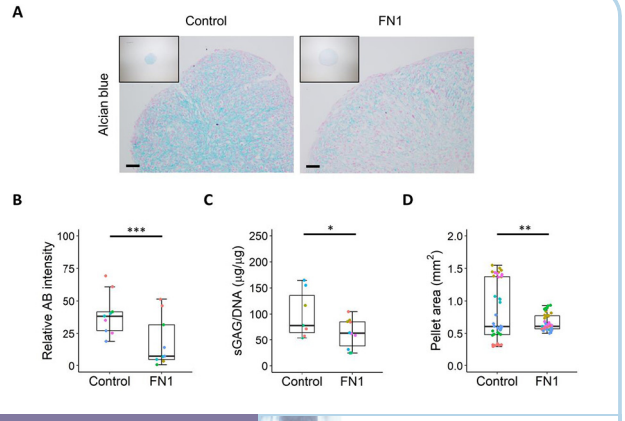

Figure 1 Osteoarthritis and Cartilage

Decreased overall *FN1* expression and change of *FN1* transcript ratios results in decreased matrix deposition in neo-cartilage pellets after three days of chondrogenesis. (A) Representative images of Alcian blue staining of neo-cartilage pellets of primary chondrocytes transduced with non-targeting shRNA (control) and FN1 targeting shRNA (FN1). (B) Quantification of Alcian blue (AB) pixel intensity staining of control and FN1 targeting shRNA transduced pellets (N=9). Colors of dots represent the different donors. (C) Sulphated glycosaminoglycan (sGAG) content normalized to DNA content in pellets of the control (N=7) and FN1 group (N=11) analyzed by dimethylmethylene blue assay. (D) Pellet area of pellets in control (N=40) and FN1 group (N=48). P values were determined by generalized estimation equations, with experimental read-out as dependent variable, and donor and group as covariate. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$.

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RELIABILITY OF WEARABLE SENSORS FOR ASSESSING GAIT AND CHAIR STAND FUNCTION AT HOME IN PEOPLE WITH KNEE OSTEOARTHRITIS

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Purpose: The COVID-19 pandemic has accelerated the adoption of digital health technologies for remote monitoring of participants in clinical trials, including measuring physical function. For trials in people with knee osteoarthritis (OA), standardized measures of function such as gait and chair stand are considered important outcomes. Wearable sensors have the potential to monitor these outcomes remotely. However, the reliability of wearable sensor metrics of gait and chair stand in participants' homes and agreement between these metrics collected in laboratory and at-home have not been reported to date. Hence, our objective was to assess the reliability of wearable sensors for remote monitoring of gait and chair stand in people with knee OA.

Methods: We used data from a substudy (n=20) embedded within an ongoing, single-arm clinical trial of an exercise intervention in people with knee OA (clinicaltrials.gov NCT04243096). Key inclusion criteria were age $\geq$ 50, BMI $\leq$ 40 kg/m^2, physician diagnosed knee OA, score $\geq$ 3 on weight-bearing questions from the Knee Injury and Osteoarthritis Outcome Score (KOOS) Pain Subscale in the index knee, and ability to walk for 20 minutes without assistance. Key exclusion criteria included other major health conditions; prior, current, or planned major knee OA treatment; prior surgeries for knee OA; and contraindications to exercise. All assessments took place prior to initiation of the intervention. Participants completed two visits, an in-person lab visit and a remote at-home visit. The order of these visits was randomized across participants, with participants completing both visits between 1 and 20 days of each other. For the remote visit, participants were provided a wearable system consisting of three inertial sensors (Opal, APDM, Portland, OR, USA), two cones connected by a 7-meter rope, and an armless chair. Identical equipment was used during the in-person lab visit. During the remote visit, researchers guided the participants via video conference. Participants self-applied the sensors on each foot and on the lower back. They performed two trials each of a standardized gait task (self-selected walk for two laps of a 7-meter path defined by the cones and rope totaling 28 meters of walking) and chair stand task (five chair stands as quickly as possible with arms across the chest) in their