The Canadian Arthritis Research Conference: Research with Impact

Virtual Event

POSTER SESSION ABSTRACTS

February 16 | 11:40 – 3:30 ET

February 17 | 12:00 – 3:30 ET

Listed in alphabetical order by last name

Nada Abughazaleh

BIO

My name is Nada Abughazaleh. I am a Ph.D. student from the University of Calgary Department of Biomedical engineering. I have a bachelor's degree in biomedical engineering from The Hashemite University in Jordan. I came to Canada in 2010 and earned a master's degree in biomedical engineering. During my master's, my research focused on determining the effect of different types of exercise on chondrocyte viability and cartilage degeneration and Osteoarthritis. My work has been published in Clinical biomechanics journal. Currently, I am working in the Human performance lab at the University of Calgary under Dr. Walter Herzog's supervision to identify the effect of obesity and the associated systemic inflammation and imbalance in the microbial community with musculoskeletal degeneration and a specific phenotype of osteoarthritis.

ABSTRACT: Effect of prebiotic fibre supplementation introduced after three weeks of starting a high-fat sucrose diet on body composition, bone mineral content and bone mineral density

Background: It was shown in a rat model that a high fat/high sucrose (HFS) diet produces knee OA reliably and consistently (Collins et al., 2018), significantly increase the percentage of body fat (Rios et al., 2019), and increase bone mineral density (BMD) and bone mineral content (BMC) (Malvi et al., 2014). Furthermore, previous studies demonstrated that prebiotic fibre diet interventions superimposed on the HFS diet entirely prevent knee OA and prevent increased body mass when the intervention was started at the onset of the HFS exposure. In contrast, there was no prevention or slowing of the rate in progression of knee OA when the fibre diet intervention was started 12-weeks following HFS exposure (Rios et al., 2019). These results suggest a critical time window when fibre diet intervention is successful and can be safely applied.

Primary Objective: To explore if introducing the fibre supplement after three weeks of starting the HFS diet will prevent the changes in percent fat and lean mass, BMD, and BMC compared to HFS and control groups.

Method: Thirty-six, twelve-week-old Sprague-Dawley rats were randomized into three groups: chow-sedentary control group, a group fed a HFS diet, and a group fed a HFS diet combined with prebiotic fibre (HFS+F) introduced to the HFS diet after three weeks. Changes in weight, BMD, BMC, percent of fat and lean mass were monitored through the 12 weeks.

Results: Body weight and percent of body fat were significantly lower in rats fed HFS+F diet compared to rats fed the HFS diet. Simultaneously, introducing the fibre decreases the loss in lean mass significantly compared to the HFS diet. Both HFS and HFS+F groups showed a significant increase in BMD and BMC compare to chow at 24 weeks. The next step is to evaluate the Knee joint score using Modified Mankin score.

Conclusion: Prebiotic fibre diet intervention superimposed on the diet after three weeks of introducing HFS diet can successfully prevent a dramatic increase in body weight and body fat, also decrease lean mass loss while maintaining the positive effect on the bone.

KEYWORDS

Obesity, Fibre, Osteoarthritis, BMD, BMC

Vahid Anwari

BIO

Vahid Anwari is a 2nd year Master of Science student at the Rehabilitation Sciences Institute of the Faculty of Medicine, University of Toronto. His thesis is supervised by Dr. Andy Kin On Wong, Assistant Scientist at the Joint Department of Medical Imaging (JDMI), Toronto General Hospital Research Institute (TGHRI), University Health Network. Vahid's research objective is to measure perfusion kinetics at the knee joint using dynamic contrast-enhanced MRI images in a cohort of postmenopausal women with knee osteoarthritis pain. Vahid is the recipient of the Canada Graduate Scholarship – Master's Awards.

ABSTRACT: The association between knee pain and perfusion kinetics at the knee joint in non-overweight postmenopausal women

Background: Cartilage loss is a hallmark of weight-bearing knee osteoarthritis (OA). However, non-overweight individuals with knee pain have been poorly studied. It is known that bone marrow lesions (BMLs) are associated with pain regardless of a weight-bearing component. BMLs have been shown to have higher perfusion, especially in later stages of disease. Knee pain has also been associated with pro-inflammatory cytokines, originating within fat. At the knee, the infrapatellar fat pad (IPFP) represents a source of fat, and therefore potential contributor to inflammation and pain. While studies have shown the relationship between pain and synovitis on MRI, little is known about how perfusion properties of BMLs, synovium, and IPFP each contribute to knee pain.

Purpose: To study perfusion properties of the subchondral bone, the synovium, and infrapatellar fat pad as correlates of knee OA pain among non-overweight postmenopausal women. It is hypothesized that higher blood flow within these regions is associated with worse knee-specific pain.

Methods: Women 50 to 85 years of age, with BMI <= 25 kg/m2, with varying degrees of knee pain (as assessed by the Knee OA Outcome Score) were recruited as a convenience sample. Those with rheumatoid arthritis, existent joint replacements, or contraindications to MR imaging were excluded. T1-weighted, sagittal dynamic contrast-enhanced (DCE)-MR images were obtained with Gadolinium injection. BMLs were identified and manually segmented. The synovium was manually segmented into suprapatellar, intercondylar (notch), and infrapatellar (fat pad) regions. Pharmacokinetics of Gadolinium arrival was calculated using Toft's model, yielding a fluid transfer constant, Ktrans (min-1) which reflects the permeability of blood to the region. Statistical analysis: Ktrans measured at each region was related to KOOS pain (dichotomized as ⇢ 3) using a binary logistic regression model, reporting odds ratios (OR) and 95% confidence intervals per standard deviation in Ktrans. All models accounted for age.

Results: Among 41 participants, mean age was 61.5±8.8 years and BMI 22.69±3.29 kg/m2. Intercondylar (OR: 2.39(1.08,5.31)) and IPFP (OR: 7.11(1.49,33.91)) Ktrans were each associated with an increased odds for having knee pain. Suprapatellar Ktrans showed only a marginally significant association with knee pain (OR: 2.39(0.96,6.01)). Among two participants with BMLs, the Ktrans signal (~0.308) was larger than the mean IPFP (0.013±0.018) or intercondylar (0.013±0.013) values.

Conclusions: Greater perfusion within IPFP, intercondylar, and possibly suprapatellar synovial regions was associated with greater knee pain. These inflammatory indicators within different regions of the joint may separately contribute to pain in knee OA.

KEYWORDS

knee osteoarthritis contrast-enhanced MRI pain chronic diseases imaging

Pavlos Bobos

BIO

Pavlos Bobos is a professionally trained clinician (physiotherapy) and a clinical epidemiologist. His graduate studies were conducted at the Bone and Joint Institute at Western University and the Dalla Lana School of Public Health at University of Toronto. Currently, he is a Postdoctoral fellow at the Applied Health Research Centre of Li Ka Shing Knowledge Institute of St. Michael's Hospital in Toronto funded by The Arthritis Society of Canada.

ABSTRACT: Effectiveness and safety of non-steroidal anti-inflammatory drugs and opioid therapy for the treatment of knee and hip osteoarthritis: a network meta-analysis

Background: Non-steroidal anti-inflammatory drugs (NSAIDs) and opioids are commonly used in the treatment of osteoarthritis pain. We assessed the efficacy and safety of different doses and preparations of NSAIDs, opioids, and acetaminophen for the treatment of osteoarthritis pain and physical disability.

Methods: We searched Cochrane Central Register of Controlled Trials, regulatory agencies' websites, and ClinicalTrials.gov from their inception until January 20, 2019. We included randomized trials with ⇢100 patients per group, evaluating NSAIDs, opioids, and/or acetaminophen for the treatment of osteoarthritis. The prespecified primary outcome was pain. We also assessed physical function and safety outcomes. We used Bayesian random-effects models for network meta-analysis for all analyses. Effect estimates are comparisons between active treatments and oral placebo.

Results: We included 188 trials comprising 99,928 participants examining 84 different active preparations/doses (62 for NSAIDs, 19 for opioids, and 3 for acetaminophen). Five oral preparations (diclofenac 150mg/day, etoricoxib 60mg/day and 90mg/day, and rofecoxib 25mg/day and 50mg/day) had ⇢99% probability for more pronounced treatment effects than the minimal clinically relevant reduction in pain. Diclofenac topical (75-81mg/day and 160mg/day) had ⇢90% probability, and all opioids had ⇠54% probability for more pronounced treatment effects than the minimal clinically relevant reduction in pain. 18%, 13%, and 83% of the oral NSAIDs, topical NSAIDs, and opioids, respectively, had an increased risk for dropouts due to adverse events (AE). 21%, 0%, and 84% of the oral NSAIDs, topical NSAIDs, and opioids, respectively, had an increased risk of any AE.

Conclusions: Etoricoxib 60 mg/day and diclofenac 150 mg/day are the most effective NSAID treatments for pain and function in osteoarthritis, with a mild increase in the risk of AEs for both, and an increased risk of dropouts due to AEs only for the latter. Topical diclofenac at 75-81 mg/day has the best effectiveness/safety profile among topical treatments. The clinical benefit of opioid treatment, irrespective of dose or preparation, does not outweigh the harms it may cause in the average patient with osteoarthritis.

KEYWORDS

Osteoarthritis, opioids, Non-steroidal anti-inflammatory drugs (NSAIDs), pain, function

Pavlos Bobos

BIO

Pavlos Bobos is a professionally trained clinician (physiotherapy) and a clinical epidemiologist. His graduate studies were conducted at the Bone and Joint Institute at Western University and the Dalla Lana School of Public Health at University of Toronto. Currently, he is a Postdoctoral fellow at the Applied Health Research Centre of Li Ka Shing Knowledge Institute of St. Michael's Hospital in Toronto funded by The Arthritis Society of Canada.

ABSTRACT: The effectiveness of virtual interventions targeting mental health in people with chronic musculoskeletal pain: A Systematic Review and Network Meta-Analysis

Introduction: The coronavirus (COVID-19) infected 3,526,178 people worldwide by April 5, 2020. While mild and symptomatic cases exist, severe cases of COVID-19 may lead to pneumonia, multiple organ failure, and death. Given the lack of any treatment, governments enacted highly restrictive social distancing policies and other infection control procedures. These policies have placed non-emergency traditional treatment programs on hold, and clinicians have struggled to provide interim services without clear direction on how these should be delivered remotely. One of the most challenging nonemergency issues is what to do with the large number of people living with chronic musculoskeletal (MSK) conditions that have persistent physical and psychosocial symptoms. It is estimated that 1 in 5 Canadians live with chronic pain.5 Evidence suggests not only an association between mental health and chronic pain, but also that shared mechanisms exist.

Objective: We aimed to evaluate the effectiveness of virtual biopsychosocial interventions in comparison to sham, traditional, or alternative virtual treatments in patients with concurrent chronic pain and mental health symptoms using a network meta-analysis approach. Methods: Two investigators independently screened (assessed eligibility) in a 2-stage process (title/abstracts and full-texts) using DistillerSR software. Risk of bias for each study was assessed with the Cochrane Risk of Bias tool. For statistical analysis, a Bayesian random effects model based on Markov chain Monte Carlo methods with minimally informative prior distributions was used.

Results: 76 studies were included in this review. Each study arm was classified by the primary delivery method (wait-list control, usual care, mobile applications, internet, telemedicine, or text education). For pain outcomes, we analyzed data from 45 studies including 6 modes of remote interventions that were evaluated in 6,287 patients with chronic pain. For mental health outcomes (depression), we analyzed data from 27 studies including 5 interventions that were evaluated in 3,152 patients with chronic pain.

Conclusions: Our results indicate that internet and telemedicine biopsychosocial treatments that target both physical and mental health symptoms improve chronic musculoskeletal pain, whereas mobile interventions are likely to be effective. Three interventions—internet, telemedicine, and mobile application—are moderately effective when compared to wait-list control. Despite multiple studies, substantial gaps remain, particularly with respect to the efficacy of mobile applications. For mental health outcomes, internet therapy can improve depression outcomes with a very large effect and a 70% probability of being the best treatment when compared with other modes of delivery.

KEYWORDS

Chronic pain, remote interventions, tele-rehabilitation, musculoskeletal pain, mental health

Mable Wing Yan Chan

BIO

I did my PhD in experimental medicine at McGill university working on signal transductions in neutrophils. My first postdoc at Saint Michael's hospital, Toronto involved investigation of mechanism of action of mesenchymal stromal cells in pre-clinical model of sepsis. This sparked my interest and enthusiasm in building a career in clinical and translational research. So, in 2018, I started my second post-doc at arthritis program at UHN, Toronto to elucidate the pathology of osteoarthritis as well as therapeutic efficacy of mesenchymal stromal cells in treatment of osteoarthritis.

ABSTRACT: Differential effects between pro-inflammatory versus pro-resolving monocytes/macrophages within a human osteoarthritic joint explant cartilage-synovium environment

Background/Purpose: Osteoarthritis (OA) is a heterogenous disease in its progression and presentation. The complexity of OA involves all the tissues of the joint; further, there is evidence that infiltrating immune cells, such as monocytes, contribute to chronic, mild inflammation. We have shown that infiltrating monocytes are pro-inflammatory and correlate to severity of patient-reported disease outcomes. There remains a gap in knowledge regarding the full role of these monocytes, their relationship with joint-resident synovial macrophages, and influence on the joint tissues.

Monocytes and macrophages (MΦ, as a mixed population) shift within a spectrum of pro-inflammatory and inflammation-resolving functions to maintain homeostasis. However, they drive inflammation without resolution when dysregulated. Understanding their role in OA will identify their feasibility as therapeutic targets or therapeutic agent. We aim to investigate the effect of exogenously polarized pro-inflammatory versus inflammation-resolving MΦwithin a representative human OA joint explant cartilage-synovium co-culture.

Methods: Cartilage and synovium are obtained from late-stage OA knee replacement. Full-depth punch-cut cartilage and minced synovial tissue are distributed into 24-wells and transwell inserts and cultured together as the cartilage-synovium baseline. Treatment groups of 48-hour cytokine-polarized CD14+ peripheral blood MΦ(IFN-ΦLPS, pro-inflammatory; IL-10+TGF-Φ, inflammation-resolving) are co-cultured with the joint explants for 2 days. Tissue and conditioned medium are harvested for tissue gene expression (matrix catabolism, anabolism, inflammation, fibrosis) by RT-qPCR and secreted protein levels by immunoassay. The panels were curated for select key OA-related genes and proteins.

Results: Our 26-gene panel of cartilage expression changes shows differential profiles of cultures treated with pro-inflammatory versus inflammation-resolving MΦ(N=6). Pro-inflammatory MΦdownregulate anabolic gene expression (COL2A1, ACAN, PRG4) while upregulating catabolic (ADAMTS4, MMP1) and inflammatory (NOS2,IL6, COX2) genes. Inflammation-resolving MΦ had a distinct effect in anabolic genes, most clearly in upregulation of TIMP1 and PRG4. Gene expression outcomes translated to significant differences in protein levels of TIMP1 between these two groups and the cartilage-synovium baseline (N=6). Presence of other secreted factors were detected in culture, including adipokines (resistin, adiponectin, adipsin) and chemokines (CCL2, CXCL8). Differences in protein level were mainly donor dependent, rather than by MΦreatment group.

Discussion/Conclusion: We observed differential gene and protein effects between addition of pro-inflammatory versus inflammation-resolving MΦwithin a co-culture system that facilitates crosstalk between OA cartilage and synovium in their native matrix. We are currently limited by tissue donor variability. Our current results support that that infiltrating or resident MΦcan impact matrix metabolism and inflammation in OA.

KEYWORDS

osteoarthritis, monocytes, macrophages, explant, cartilage, synovium, inflammation

Denis Choquette

BIO

Dr. Denis Choquette completed his medical training at the University of Montréal in 1979. He subsequently completed specialized training in rheumatology at the University of Montréal and McGill University. Dr. Choquette practised for three years at the CHRDL in Joliette and the Montreal General Hospital until 1986. He completed a fellowship in fundamental immunology in the service d'immunologie clinique et fondamentale of Hôpital Necker (Paris), directed by Professor Jean-François Bach. Dr. Choquette later joined the Université de Montréal and the rheumatology department of Notre-Dame Hospital (CHUM) until today. He has been a member of the CHUM service for 35 years. He held the position of director of the rheumatology program at the University of Montréal until 2007. He was director of the Canadian Rheumatology Society from 2005 to 2011 and president of L'Association des Médecins-Rhumatologues du Québec for six years' (ad 2014). He is a founding member of l'Institut de Rhumatologie de Montréal and l'Institut de Recherche en Rhumatologie de Montréal, where 15 rheumatologists collaborate in multiple clinical research projects as well as participating in the collection of data for the clinical database and registry Rhumadata®.

ABSTRACT: Discontinuation Rate of Tofacitinib as Monotherapy is Similar Compared to Combination therapy with Methotrexate in Rheumatoid Arthritis Patients: Pooled Data from two Rheumatoid Arthritis Registries in Canada

Background: Tofacitinib (TOFA) is an oral, small molecule drug used for rheumatoid arthritis (RA) treatment and is prescribed alone or with methotrexate (MTX). We previously reported the similarity in retention between TOFA monotherapy and TOFA with MTX using data from two different registries separately; the Ontario Best Practices Research Initiative (OBRI) and the Quebec registry RHUMADATA®.

Objectives: To increase the study power, we propose to evaluate the discontinuation rate (due to any reason) of TOFA with and without MTX, using pooled data from these two registries.

Methods: RA patients enrolled in the OBRI and RHUMADATA initiating their TOFA between 1st June 2014 (TOFA approval date in Canada) and 31st Dec 2019 were included. Concurrent MTX use was defined as MTX use for more than 75% of the time while using TOFA. Multiple imputation (Imputation Chained Equation method, N=20) was used to deal with missing data for covariates at treatment initiation.

Time to discontinuation was assessed using Cox regression models. To deal with confounding by indication, we estimated propensity scores for selected covariates with an absolute standard difference greater than 0.1. We then adjusted Cox regression models for propensity quantile to compare the discontinuation of TOFA with MTX versus TOFA without MTX.

Results: A total of 493 patients were included. Of those, 244 (49.5%) and 249 (51.5%) were treated with MTX and without MTX, respectively. Compared to TOFA monotherapy, the TOFA with MTX group had a significantly lower mean HAQ-DI, fatigue score, and the number of prior biologic use at the time of TOFA initiation. A lower proportion of positive ACPA (59% vs. 66%), prevalence of hypertension (31% vs 37%), and concomitant use of Leflunomide (11% vs. 23%) were also observed for patients using TOFA with MTX.

Over a mean follow-up of 19.0 months, discontinuation was reported in 182 (36.9%) of all TOFA patients. After adjusting for propensity score quantile across 20 imputed datasets, there was no significant difference in discontinuation between treatment groups (adjusted HRs: 1.12, 95% CI: 0.83-1.51; p=0.49).

Conclusion: In this pooled real-world data study, we found that in patients with RA, the retention of TOFA is similar if it is used as monotherapy or in combination with MTX.

KEYWORDS

Small molecule drug, monotherapy, combination therapy with methotrexate, discontinuation rate

Denis Choquette

BIO

Dr. Choquette is the initiator and has been the scientific and administrative director of Rhumadata® since 1998. This registry has collected clinical data on more than 6,000 patients diagnosed with rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. It is the origin of over 150 scientific presentations made at national and international congresses. He has over 60 original publications in peer-reviewed journals.

ABSTRACT: Discontinuation rate of Tofacitinib is similar when compared to TNF inhibitors in Rheumatoid Arthritis Patients: Pooled Data from two Rheumatoid Arthritis Registries in Canada

Background: Tofacitinib (TOFA) is an oral, small molecule drug used for treating rheumatoid arthritis (RA). It is used as an alternative to biologic disease-modifying antirheumatic drugs (bDMARDs), including tumor necrosis factor inhibitors (TNFi). The similarity in retention of TNFi and TOFA was previously independently reported by the Ontario Best Practices Research Initiative (OBRI) and the Quebec cohort RHUMADATA®.

Objectives: To increase the study power, we propose to evaluate the discontinuation rate of TNFi compared to TOFA, using pooled data from both these registries.

Methods: RA patients enrolled in the OBRI and RHUMADATA initiating their TOFA or TNFi between 1st June 2014 (TOFA approval date in Canada) and 31st Dec 2019 were included. Time to discontinuation was assessed using adjusted Kaplan-Meier (KM) survival and Cox regression models. To deal with confounding by indication, we estimated propensity scores for covariates with a standard difference greater than 0.1. Models were then adjusted using stratification and inverse probability of treatment weight (IPTW) methods. Multiple imputation (Imputation by Chained Equation method, N=20) was used to deal with missing data for covariates at treatment initiation.

Results: A total of 1318 patients initiated TNFi (n=825) or TOFA (n=493) with mean (SD) disease duration of 8.9 (9.3) and 13.0 (10.1) years, respectively. In the TNFi group, 78.8% were female and mean age (SD) at treatment initiation was 57.6 (12.6) years. In the TOFA group, 84.6% were female and mean (SD) age at treatment initiation was 59.5 (11.5) years. The TNFi group was less likely to have prior biologic use (33.9%) than the TOFA group (66.9%). At treatment initiation, the mean (SD) CDAI was significantly (p<0.05) lower in the TNFi group [20.0 (11.7)] compared to the TOFA group [22.1(12.4)]. Physical function measured by HAQ-DI was also significantly lower (p<0.05) in the TNFi compared to the TOFA group (1.2 vs.1.3).
Over a mean follow-up of 23.2 months, discontinuation was reported in 309 (37.5%) and 182 (36.9%) of all TNFi and TOFA patients, respectively. After adjusting for propensity score deciles across 20 imputed datasets, there was no significant difference in discontinuation between treatment groups (adjusted HRs: 0.96, 95% CI: 0.78-1.18; p=0.69). The results were similar for two propensity adjustment methods. Figure 1 shows IPTW adjusted KM survival curves comparing discontinuation rates in patients treated with TNFi and TOFA.

Conclusions: In this pooled real-world data study, we found that TNFi and TOFA retention are similar in RA patients.

KEYWORDS

Small molecule drug, TNF inhibitors, discontinuation rate

Kelsey H. Collins

BIO

Kelsey received her PhD in Biomedical Engineering in 2017 in Dr. Walter Herzog's lab at the University of Calgary. Kelsey was supported by multiple fellowships and her work on diet-induced obesity in a preclinical model of osteoarthritis was acknowledged with a J.B. Hyne Innovation Award. In the Guilak Laboratory at Washington University in St. Louis, Kelsey has created a niche in adipose-cartilage signaling, stem cell biology, synthetic biology, and drug delivery to evaluate systemic contributors and novel therapeutic strategies in osteoarthritis and rheumatoid arthritis. Kelsey's work on a mouse model of lipodystrophy was accepted at Proceedings of the National Academy of Sciences and was acknowledged with a New Investigator Recognition Award from the Orthopaedic Research Society. In 2020, Kelsey was named among the inaugural class of Rising Stars in Engineering in Health by Columbia University. As an independent investigator, Kelsey will test specific mechanistic hypotheses to separate inflammation, metabolic disorders and musculoskeletal health using tissue engineering and regenerative medicine approaches to generate novel disease-relevant therapeutic targets for osteoarthritis.

ABSTRACT: Fat Talks to Cartilage

Changes in biomechanical loading due to increased body mass do not account for the severity of obesity-induced knee osteoarthritis (OA). While body fat and adipokines are consistently associated with OA severity, the exact contribution of the adipose tissue signaling network in OA has been difficult to determine due to the complex interactions between metabolic, biomechanical, and inflammatory factors from obesity. To separate and directly test some of these factors, we employed lipodystrophic (LD) mice, which completely lacks adipose tissue. The purpose of this study was to determine if fat-free LD mice are protected from OA, and then evaluate if susceptibility to OA can be reintroduced to LD mice using transplantation of a small adipose graft. To create LD mice, we crossed adiponectin-Cre mice with homozygous lox-stop-lox-ROSA-diphtheria toxin A (DTA) mice. DTA/+ (WT) littermates were maintained as controls. Fat was transplanted in subgroup of LD mice either via murine embryonic fibroblast transplant (MEF-R) or WT fat transplant (WF-R, n=7-10 animals/sex/group). At 16-weeks, mice underwent surgery for destabilization of the medial meniscus (DMM). Prior to sacrifice at 28-weeks of age, pain was measured (hyperalgesia evaluated by small animal algometer at the knee joint, and mechanical allodynia by paw withdrawal by Electronic Von Frey testing). To evaluate cartilage damage, stained sections were assessed using the Modified Mankin Criteria. Data were analyzed by repeated measures ANOVA (genotype, limb, diet) and post hoc testing. Body mass was similar between LD, WT, WF-R and MEF-R mice as compared to chow-fed LD. Male and Female LD mice were protected from DMM-induced cartilage damage. The severity of joint damage in either of the fat-rescue LD mice was similar to DMM damage in WT control animals, demonstrating reversal of the cartilage protection LD phenotype. Furthermore, LD mice were protected from the onset of hyperalgesia and mechanical allodynia, which was restored in the DMM limbs of MEF-R and WT-R mice. As transplantation of a small amount of adipose tissue restores susceptibility to knee joint cartilage damage and pain in rescued LD mice, these data suggest cartilage damage can be influenced and controlled by tissues outside of the joint. We demonstrated that the addition of metabolically healthy fat distally can restore susceptibility in OA-resistant animals, implicating adipokine signaling – and not body weight – as a mediator of joint degeneration. This controlled model of lipodystrophy confirms a direct relationship between adipose tissue and the onset and progression of OA, independent of biomechanical changes.

KEYWORDS

adipocyte, obesity, post-traumatic osteoarthritis, systemic inflammation

Christie Costello

BIO

Christie Costello completed her Bachelor of Science (Honours) at Memorial University of Newfoundland in 2017 and is currently completing her PhD in Genetics in the Division of Biomedical Sciences (Faculty of Medicine) at Memorial University of Newfoundland. She is partially supported by the Arthritis Society.

ABSTRACT: Individual Participant Data Meta-Analysis of Metabolomics on Refractory Knee Pain in Primary Osteoarthritis Patients

Purpose: Knee pain resulting from osteoarthritis (OA) is a common but complex condition, acting as a major driver for OA patients to seek healthcare. Around 10-20% of patients experience refractory knee pain when conservative and surgical pain interventions failed. Urgent attention is required to reveal the mechanism underlying this treatment-resistant pain. We conducted an individual participant data meta-analysis of metabolomics on refractory knee pain integrated with genome-wide association analysis (GWAS) to reveal potential mechanisms.

Methods: Two independent cohorts from St. John's, NL, Canada (n=430), and Toronto, ON, Canada (n=495) were included in the study. Refractory knee pain, defined as knee pain occurring one or more years after total knee replacement (TKR) due to primary OA, was assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) pain subscale (five questions). Those who answered yes to all five questions were considered to have refractory pain. Metabolic profiling was performed on fasted plasma. Associations between refractory knee pain and individual metabolites (n=137; Φ0.00037) and pair-wise metabolite ratios (n=18,632; Φ2x10-5) were tested in each of the cohorts by regression modeling with adjustment for age, sex, and BMI and then meta-analyzed with random effects model. A genome-wide association (GWAS) was performed to identify genes associated with the identified metabolite and ratios (Φ5x10-8).

Results: In the individual metabolite meta-analysis, one metabolite, phosphatidylcholine (PC) diacyl (aa) C28:1 was significantly associated with refractory knee pain (OR=0.66, p=0.00026). In the metabolite ratio meta-analysis, three metabolite ratios, PC aa C32:0 to PC aa C28:1, PC aa C28:1 to PC aa C32:0, and tetradecadienylcarnitine (C14:2) to sphingomyelin C20:2, were significantly associated with refractory knee pain (ORs=1.59, 0.60, 1.59, respectively; all p<2x10-5). These results suggested an increased oxidation of PCs. In the GWAS, five SNPs in high LD located in glutathione s-transferase alpha 4 (GSTA4) were significantly associated with PC aa C28:1 to PC aa C32:0 (all p=8x10-10). GSTA4 plays a key role in detoxification of lipid peroxidation products, especially produced by oxidation of PCs.

Conclusions: Our results are novel and suggested that the increased oxidation of PCs and/or inability to detoxify lipid peroxides play significant roles in refractory knee pain. Though further investigations are needed, our results provided potential biomarkers and drug targets which could be modified pre-operatively to improve knee pain and surgical response to TKR. Follow-up experiments are currently underway.

KEYWORDS

metabolomics, genome wide association, refractory pain, knee pain, knee osteoarthritis

Etienne Doré

BIO

Etienne Doré is a PhD student from the ARThrite Research Centre at Université Laval, Quebec City, under the supervision of Dr. Eric Boilard. Before his doctoral studies, he completed his Master's Degree in 2020 within the same research group, during which he investigated the interactions between an endogenous bactericidal enzyme and the intestinal microbiota in the spontaneous dysregulation of the immune system. With the support of The Arthritis Society, he is currently exploring how the interplay between this bactericidal enzyme and the intestinal flora affects the severity of inflammatory arthritis.

ABSTRACT: An endogenous enzyme promotes arthritis severity through the intestinal flora

Background: Rheumatoid arthritis (RA) is an autoimmune systemic disease characterized by joint inflammation and bone and cartilage erosion. Despite its prevalence, the etiology of this disease remains elusive. Intriguingly, accumulating evidence suggests that the intestinal flora (microbiota) plays an important role in the pathogenesis of RA. Given that patients display an altered microbiota, we are studying endogenous intestinal proteins able to promote microbial imbalances, a process known as dysbiosis. One of those candidate proteins, the secreted phospholipase A2-IIA (sPLA2-IIA), is a bactericidal enzyme that hydrolyzes phospholipids from bacterial membranes. Elevated levels of sPLA2-IIA are found in the blood and synovial fluid of RA patients. Moreover, transgenic mice overexpressing human sPLA2-IIA (sPLA2-IIATGN) are more susceptible to induced arthritis than control mice (WT) lacking the enzyme.

Hypothesis: We hypothesize that sPLA2-IIA enhances arthritis severity through its activity on the intestinal microbiota.

Methods And Results: The contribution of the intestinal flora to the enhanced arthritis severity found in sPLA2-IIATGN mice was investigated. Broad spectrum antibiotics were administered to mice via oral gavage to deplete their intestinal microbiota before arthritogenic K/B×N serum was injected to induce arthritis. Interestingly, the enhanced susceptibility of sPLA2-IIATGN mice to inflammatory arthritis was abolished upon depletion of their microbiota. This suggests that the enzyme promotes arthritis through its activity on the microbiota.

To determine whether an alteration of the intestinal flora by sPLA2-IIA could be promoting this enhanced inflammatory process, a fecal microbiota transplantation was performed. The microbiota of mice was depleted using antibiotics, then reconstituted by gavage of resuspended feces from mice expressing or not the enzyme. Interestingly, while the transplantation of the sPLA2-IIATGN flora failed to promote arthritis in WT mice, the introduction of the WT flora in sPLA2-IIATGN mice attenuated arthritis severity. The WT flora may therefore have protective effects against inflammatory arthritis in this model.

sPLA2-IIA activity on bacterial membranes may release bioactive lipid metabolites. We thus used mass spectrometry to perform a lipidomic analysis on stool samples from sPLA2-IIATGN and WT mice. We observed profound alterations in the fecal lipidome of sPLA2-IIATGN mice compared to control mice, suggesting that sPLA2-IIA could promote arthritis through the release of lipid metabolites via its activity on bacterial membranes.

Conclusion: Our findings reveal that sPLA2-IIA may contribute to inflammatory arthritis through its functional interaction with the microbiota and associated lipidome. Interfering with those interactions could lead to the discovery of new original targets for the treatment of RA.

KEYWORDS

secreted phospholipase A2-IIA, inflammatory arthritis, microbiota, lipidome, fecal microbiota transplantation, K/BxN serum

Abdellatif Elseoudi

ABSTRACT: Role of Prohibitin (PHB1) and SUMOylation in Primary Osteoarthritis

Background: Osteoarthritis (OA); is the most frequent degenerative joint disease, which represents the major cause of chronic disability in aging adults and a growing economic burden for our society. A growing body of evidence indicates that epigenetic effectors and posttranslational modifications triggered by oxidative stress may modulate gene expression and protein activities regulating chondrocyte hypertrophy and thus contribute to OA pathogenesis. We discovered that chondrocyte cells; from OA patients, cannot produce a protein termed (PITX1), which is essential for the formation of cartilage joints and hind limb bones during the development. Moreover, we observed that aberrant nuclear accumulation of mitochondrial chaperone protein Prohibitin 1 (PHB1) in OA articular chondrocytes is caused by SUMOylation, leading to the downregulation of E2F targets, such as PITX1. Indeed, we demonstrated that increased SUMOylation is associated with knee/hip OA pathogenesis.

Methods and Results: In the present study, we investigate the role of SUMOylation in the nuclear accumulation of PHB1, which may explain PITX1 suppression in OA patients. We observed increased nuclear accumulation of SUMO proteins (SUMO1 and SUMO2/3) in the cartilage of OA patients when compared to non-OA control subjects. We performed in silico and in vitro analyses of PHB1 to identify potential SUMOylation loci. Despite co-localization of nuclear PHB1 and SUMO1, PHB1 only indirectly interacts with SUMO1 proteins through a SUMO-binding motif (SBM). Deletion of the SBM prevents the nuclear accumulation of PHB1. Interestingly, Immunohistological analysis showed ubiquitin conjugation enzyme E2 (Ubc9) protein level was increased in knee OA cartilage and seems to correlate with the disease progression. Of note, UBC9 overexpression appears to stabilize and promotes the nuclear accumulation of PHB1, but this mechanism is probably indirect because the SBM presence is necessary.

Conclusion: These data might have practical implications for diagnosis, prevention, and treatment of OA; which sheds a light on the role of SUMOylation in the nuclear accumulation of PHB1 that may explain PITX1 suppression in OA patients. Moreover, our discovery may better define OA pathogenesis in terms of mitochondrial dysfunction and cellular aging.

Allison Ezzat

BIO

Dr. Allison Ezzat is a physiotherapist and postdoctoral fellow at La Trobe Sport and Exercise Medicine Research Centre in Melbourne, Australia. Allison holds a Canadian Institutes for Health Research Postdoctoral Fellowship. Her research focuses on using process evaluation and implementation science to advance the prevention of knee injuries and the non-surgical management of knee osteoarthritis.

ABSTRACT: Is previous ACLR, physical activity, or BMI associated with increased odds of recurrent or new knee injury in a cohort of young females?

Background: Anterior cruciate ligament (ACL) injuries are devastating for young, active individuals, with up to 50% developing osteoarthritis (OA) before aged 40 years. Recurrent knee injury rates are high and lead to even poorer long-term joint health. At 2-3 years after ACL reconstruction (ACLR), the relationships between known modifiable OA risk factors [e.g. moderate and vigorous physical activity (MVPA), body mass index (BMI)] and recurrent knee injury is unknown.

Objective: To determine the odds of new traumatic knee injury in a cohort of young females with ACLR 2-3 years post-surgery compared with healthy matched-controls. Secondary objectives included to (i) explore the relationships of MVPA and BMI with traumatic knee injury; (ii) document self-reported MVPA satisfaction and beliefs about future OA.

Design: Fifty-one females (aged 14-22 years) with prior (1-2 years) sport-related unilateral ACLR and 51 age-and-sport-matched controls underwent assessment of MVPA (GT3X accelerometers) and BMI. One year later, participants self-reported new or recurrent knee injuries, return to sport, MVPA satisfaction, and beliefs about OA risk. Bivariable conditional logistic regression explored the association of knee injury with (i) group (injury/control), (ii) MVPA and (iii) BMI. Beliefs about MVPA satisfaction and OA risk was reported descriptively.

Results: At 1 year follow-up (n=101), 19.6% of injured cohort and 6.0% of control participants sustained a new knee injury. The odds of traumatic knee injury for the injury group increased 7-fold over controls [OR=7.00 (95% CI=0.86,56.90)]. Odds ratios (OR) for MVPA and BMI were 0.98 (95%CI= 0.93,1.03) and 1.24 (95%CI=0.85,1.82) respectively. Just over half (55%) of injury participants and 66% of controls were satisfied with their MVPA, while 82% of injury participants believed they had increased knee OA risk compared to someone who had never had a knee injury.

Conclusions: In the 2-3 years following ACLR, one in five young females had a recurrent traumatic knee injury. Based on the point estimate, injured participants were more likely to suffer a traumatic knee injury than matched controls. BMI was not associated with increased odds of a new traumatic knee injury. Given participation in MVPA did not increase odds of knee injury and the high level of dissatisfaction with MVPA reported in this cohort, in-depth conversations between clinicians and patients who have had ACLR regarding enjoyable and sustainable MVPA participation are encouraged to promote long term joint health.

KEYWORDS

ACL reconstruction, recurrent injury, physical activity, knee osteoarthritis, body mass index

Maria Fernandes

BIO

I am an associate professor in the department of Microbiology-Infectiology and Immunology (Faculty of Medicine) at Université Laval in Québec City. After my PhD at McGill University in molecular genetics, I pursued two post-doctorates (Thomas Jefferson University and Université Laval) during which I cloned genes that code for myeloid C-type lectin receptors, studied neutrophil biology and developed an interest in arthritis. The research in my laboratory brings all of these fields of research together into one main theme: to decipher the role of C-type lectin inhibitory receptors in the immunopathogenesis of arthritis. A key discovery made by laboratory is the involvement of the inhibitory receptor CLEC12A in the pathogenesis of gout and rheumatoid arthritis. We are currently using a multidisciplinary approach to gain insight into how CLEC12A functions with the ultimate goal of eventually transferring our findings to the clinic.

ABSTRACT: Expression of the Myeloid Inhibitory Receptor CLEC12A Correlates with Disease Activity and Cytokines in Early Rheumatoid Arthritis

Background. CLEC12A is a myeloid inhibitory receptor that negatively regulates inflammation in mouse models of autoimmune and autoinflammatory arthritis. Reduced CLEC12A expression enhances myeloid cell activation and inflammation in CLEC12A knock-out mice with collagen antibody-induced arthritis. Moreover, internalisation of cell-surface CLEC12A in human neutrophils augments neutrophil activation. We thus postulated that CLEC12A expression levels on circulating myeloid cells of rheumatoid arthritis patients are associated with disease manifestations and activity. Moreover, we identified signal transduction pathways regulated by CLEC12A in human neutrophils pertinent to RA.

Methods. Circulating neutrophil and monocyte CLEC12A expression was determined by flow cytometry in 17 early rheumatoid arthritis patients at baseline and up to 18 months follow-up, and in 16 healthy donors. CLEC12A expression was compared between groups and its association with disease activity and clinical parameters determined with the generalized estimating equations model, Student's t-test and Spearman's correlation test. Plasma cytokines were measured by ELISA. Phosphoproteomics analysis was performed on human neutrophils after antibody-induced CLEC12A internalisation.

Results. Patients with reduced neutrophil CLEC12A expression at baseline and at 3 months have an increased simple disease activity index ($p = 0.032$ and $p = 0.01$, respectively). A similar correlation between CLEC12A expression and disease activity was observed in monocytes at baseline and 3 months ($p = 0.026$ and $p = 0.01$, respectively). Low baseline CLEC12A expression also correlates with a higher SDAI at 6 months ($p = 0.046$). In contrast, a positive correlation was observed with eotaxin/CCL11 levels at baseline in neutrophils and monocytes ($p = 0.003$ and $p = 0.034$, respectively). In monocytes, baseline CLEC12A expression also correlates positively with levels of MIP-1 ϕCCL4 ($p = 0.024$) and IL-1-RA ($p = 0.043$). Moreover, neutrophil and monocyte CLEC12A expression is significantly higher in early rheumatoid arthritis patients at baseline than healthy controls ($p = 0.014$ and 0.026 respectively). Phosphoproteomics identified phopshorylation events in proteins of the PI3K, MAPK and JAK-STAT pathways in neutrophils with reduced CLEC12A expression.

Conclusion. Neutrophil and monocyte, cell-surface CLEC12A expression correlates with disease activity and cytokines in early rheumatoid arthritis patients. These observations together with the differential expression of CLEC12A on circulating neutrophils and monocytes of early rheumatoid arthritis patients compared to healthy donors are indicative of a potential regulatory role for CLEC12A in rheumatoid arthritis. This regulation may involve the PI3K, MAPK and JAK-STAT pathways.

Matei Gardea

BIO

Matei Gardea is a research intern in Dr. Andy Kin On Wong's MSK Imaging & Epidemiology Lab. His primary focus is deep learning and artificial intelligence.

ABSTRACT: Fully-Automated Bone Marrow Lesion Segmentation Using a UNET-Based Convolutional Neural Network Architecture

Background: Bone marrow lesions (BMLs) are a common hallmark of knee osteoarthritis visible on magnetic resonance images (MRI) within the subchondral bone and have been associated with pain. Pang et al 2013, using the MOAKS method to quantify BML volume, reported 24 minutes of user interaction per MR image to manually segment the region of interest (ROI). In standard of care, the test-retest imprecision and lack of sensitivity of semi-quantitative BML obscures its correlations to patient outcomes. In this study, we aimed to automate the segmentation of BMLs using a deep learning approach.

Methods: Our team validated a custom-designed UNET neural network architecture to segment BMLs within MRI slices of the knee. A subset of sagittal double echo steady state MR images at 3.0T (0.5x0.5x1.0mm) from 100 participants in the Osteoarthritis Initiative (OAI) was used. BMLs were annotated within 16,000 MRI slices from these participants using rectangular ROIs. Among all slices examined, 2184 contained one or more BMLs; 80% of these images (N=1750) were used for training and 20% (N=434) for testing. A total of 80 combinations of baseline neural network hyperparameters were investigated. The different model configurations we tested were trained for up to 100 epochs at learning rates ranging from 10-3 to 10-5, activation-layer dropout rates ranging from 10% to 50%, and ultimate training performance measured by the 1-DICE coefficient loss function. The CNN's performance was validated with the Intersection Over Union (IOU) metric. All code was developed with TensorFlow-2.1.0 on Python-3.6.7 within a Windows x64 environment.

Results: Mean age of participants was 63.2 ± 10.2 yrs, BMI: 29.67 ± 4.78 kg/m2, 6% had KL= 0 or 1, 30% KL=2, 49% KL=3, and 15% KL=4 After 72 hours of training on two 8GB GTX 1080 Ti GPUs, the best validated model achieved a minimum 1-DICE coefficient of 0.291 and a mean IOU of 0.5443 using validation images. The network also managed to segment BMLs in close proximity to one another at high spatial resolution with associated pixel confidence scores faithfully representing BMLs identified by visual inspection.

Conclusion: Despite using coarse rectangular ROIs for BML annotations, our UNET model managed to yield correct high-resolution segmentations of discrete BMLs ranging in shapes with high fidelity. Future optimization of this model will likely reduce the probability of false positives.

KEYWORDS

bone marrow lesion, grading, neural network, UNET, magnetic resonance imaging, medical imaging

Kristine Godziuk

BIO

Dr. Kristine Godziuk is a postdoctoral research fellow in the Faculty of Rehabilitation Medicine at the University of Alberta. She has a clinical background as an exercise physiologist, and her research program is focused on the intersection of three chronic and complex conditions: osteoarthritis, obesity and sarcopenia.

ABSTRACT: Patient-perspectives to inform the development of the POMELO (Prevention Of MusclE Loss in Osteoarthritis) pilot intervention trial

Background: Best practices to manage advanced knee osteoarthritis (OA) in adults with a body mass index (BMI) ⇢35 kg/m2 are undetermined. These individuals are at higher risk for complications after total knee arthroplasty (TKA), and as a result may not be eligible for this procedure unless they reduce their BMI. However, there is limited evidence for endorsing weight-loss as beneficial prior to TKA. Further, unsupervised weight-loss could increase risk for muscle loss and development of sarcopenic obesity, a condition of low muscle and low strength that negatively impacts mobility and mortality. This suggests that alternatives are needed, possibly integrating non-surgical approaches that improve strength, function and body composition. Importantly, such approaches must be designed to meet individual patient needs. Therefore, as part of a project to develop and pilot a multimodal intervention (the POMELO trial), we aimed to gather perspectives from individuals living with knee OA and a BMI ⇢35kg/m2 on the design and delivery of the proposed intervention.

Methods: Purposive and voluntary sampling was used to engage participants ⇢40 years of age, with self-reported knee OA and a BMI ⇢35 kg/m2. An electronic survey was distributed by the Obesity Canada Public Engagement Committee on social media between April-June 2020. Individuals could self-enroll and complete the survey, which included open-ended questions regarding the proposed intervention (involving targeted nutrition, resistance training exercise, and self-management support over 12-weeks). Upon survey completion, participants could optionally complete an interview to provide additional detailed perspective. Interviews were recorded and transcribed verbatim. Thematic analysis, guided by an intervention acceptability framework, was used to identify participants' recommendations.

Results: The online survey was completed by twenty individuals (100% female; 17 age <65 years) living across Canada. Participants predominantly reported bilateral knee OA (75%), with symptom onset ⇢5 years prior (85%). Ten individuals completed the interview. From aggregate survey and interview data, three key recommendations emerged from patient-perspectives: 1) the effectiveness of the intervention for improving OA-related health (i.e. mobility and pain reduction) rather than weight-loss should be emphasized to align coherence and expectations; 2) extended support offered beyond the planned 12-week study timeline, and inclusion of positive language around body-size diversity could enhance acceptance and perceived effectiveness; 3) include options for customization of intervention delivery to reduce perceived burden and support self-efficacy.

Conclusion: Incorporating these patient-recommendations in the design and delivery of the intervention may improve perceived acceptability, potentially enhancing participant enrollment and retention in the pilot trial.

KEYWORDS

Obesity, knee osteoarthritis, intervention, patient-engagement

Emily Ha

BIO

Emily Ha is a PhD student in Epidemiology at the Dalla Lana School of Public Health, University of Toronto. She completed her MSc in Public Health and Health Systems and her BSc in Honours Biology, both at the University of Waterloo. Emily's research interests are in aging, biomarkers, chronic diseases, and epidemiological methods. For her Doctoral research, Emily is interested identifying pathways that lead to musculoskeletal health outcomes in women.

ABSTRACT: A latent measure of subchondral bone: An opportunity for postmenopausal bone and joint care

Introduction: Knee osteoarthritis (OA) is a commonly diagnosed chronic disease in general practice, and a leading cause of pain among adults. In addition to progressive cartilage loss and joint space narrowing, subchondral bone alterations have been established as a key characteristic of knee OA. Common risk factors for subchondral bone alterations include obesity and weight-bearing stress. However, knee OA also affects non-overweight individuals, including postmenopausal women. As such, it is important to identify risk factors of subchondral bone alterations among postmenopausal women. Moreover, while computed tomography (CT) can provide a very detailed measure of subchondral bone mineral density (BMD), it is not part of the standard of care for knee OA. Therefore, alternative and accessible methods that can predict subchondral BMD may be beneficial. The objective of this study is to identify correlates of measured subchondral BMD, and to develop and validate a latent concept of subchondral bone for scenarios when CT imaging is not available.

Methods: Data from 50 postmenopausal women between 50 to 85 years were collected by convenience sampling at the University Health Network hospitals. Subchondral BMD was measured using peripheral CT. Hip and lumbar spine BMD were measured using dual-energy X-ray absorptiometry scans. Multivariable linear regression with purposeful selection (p<0.25) was used to identify significant and clinically relevant indicators of measured subchondral BMD. Confirmatory factor analysis (CFA) was used to develop a reflective latent construct for subchondral bone using the selected clinically relevant indicator variables. Model fit was assessed using absolute (Standardized Root Mean Square Residual), parsimonious (Root Mean Square Error of Approximation), and incremental (Comparative Fit Index, Tucker Lewis Index) fit indices. Correlations between measured subchondral BMD and the latent concept of subchondral bone were assessed for validation.

Results: Subchondral BMD was significantly explained by the following indicator variables: hip and spine BMD, prior fractures and/or falls, and hip-to-waist ratio. In CFA models of latent subchondral BMD, good model fit was observed as assessed by absolute (<0.08) and incremental fit indices (>0.90). Measured subchondral BMD from peripheral CT and the latent construct of subchondral bone were significantly correlated (B=0.961, SE=0.187, p<0.001).

Conclusion: Subchondral bone can be represented as a reflective latent construct comprised of indicator variables commonly collected as part of postmenopausal women's standard of care. This study provides a deeper understanding of correlates of subchondral bone and offers a unique and accessible method to represent subchondral bone in a priority population of postmenopausal women.

KEYWORDS

Bone mineral density, subchondral bone, latent construct, women's health, epidemiological methods

Chakib Hamoudi

BIO

Graduated in Pharmacy from the Faculty of Medicine of Algiers, currently I am a master student in Microbiology and Immunology at LAVAL University, in the laboratory of Dr. Fawzi Aoudjit at CRCHUL-Quebec.

ABSTRACT: The purinergic receptor P2X4 promotes Th17 development and its inhibition reduced the severity of arthritis.

Background: Purinergic signaling via P2X and P2Y receptors plays an important role in the regulation of inflammatory response and has been involved in T cell activation. Th17 cells are highly inflammatory and are implicated in the development of several inflammatory diseases including rheumatoid arthritis. However, the importance of purinergic signaling to the differentiation and activation of Th17 cells and to the development of arthritis remains poorly understood.

Methods: P2 receptor expression was evaluated by qRT-PCR analysis. We used pharmacological and gene silencing approaches to determine the implication of particular P2 receptor in the development and activation of human Th17 cells. Th17 cells were characterized by flow cytometry and the levels of IL-17 were determined by ELISA. The implication of particular P2 receptor in arthritis was carried out in the mouse model of Th17-dependent collagen-induced arthritis (CIA).

Results: P2X4, P2X7 and P2Y11 are the major functional P2 receptors expressed by human Th17 cells. Pharmacological inhibition of P2X4 with specific antagonist 5-BDBD, unlike other receptors, blocked the polarization of CD4+ T cells towards the Th17 pathway. In addition, 5-BDBD and P2X4 siRNA also decreased the production of IL-17 by anti-CD3+anti-CD28-activated polarized Th17 cells. This reduction in IL-17 levels was associated with an inhibition in the expression levels of RORc, the master regulator of IL-17 gene expression. Finally, we found that treatment of CIA mice with 5-BDBD reduced the severity of arthritis, which was associated with the inhibition of Th17 expansion and activation.

Conclusion: The purinergic P2X4 receptor plays a major role in the activation of human Th17 cells and its inhibition reduced the severity of arthritis suggesting that it could represent a therapeutic target in arthritis.

KEYWORDS

Th17 cells; Rheumatoid arthritis; Inflammation; ATP; P2 receptors; Purinergic signaling

Carly Jones

BIO

Carly is a PhD candidate in the department of Biomedical Engineering at UBC. She completed her undergraduate degree in Engineering Physics in 2017, also at UBC. Her research is based out of the Centre for Hip Health and Mobility (a UBC biomechanics research lab), where she has been working under the supervision of Dr. David Wilson since 2014. While working as an undergraduate research assistant she published two papers on the topic of modelling hip range of motion in Slipped Capital Femoral Epiphysis (SCFE), a childhood hip disorder. After completing her graduate studies, she plans to pursue a professorship. In her free time, she enjoys singing, gardening, playing with her cat, and outdoor sports such as biking, hiking and skiing.

ABSTRACT: dGEMRIC T1 is Reduced in Cartilage Overlying Bone Marrow Lesions in the Hip

Purpose: Bone marrow lesions (BML) are associated with painful and progressive OA. Quantitative MRI has found evidence of early cartilage degeneration overlying BMLs in knees, but similar work has not been done in the hip. The purpose of this study is to determine whether there is evidence of cartilage degeneration in BML overlying cartilage in hips.

Method: MRI study participants (n=128) were recruited from a cross-sectional population-based study of adults aged 20-49 years. Delayed Gadolinium Enhanced MRI of Cartilage (dGEMRIC) and proton-density weighted fat-suppressed (PDw-FS) MRI scans were acquired of one hip for each participant. dGEMRIC is a well-validated method of quantifying cartilage proteoglycan content using MRI. BMLs were identified from PDw-FS scans by a MSK radiologist, and only scans of hips with BMLs (n=32) were used in this study (age 44.4 (SD: 6.5), 62.5% F). BMLs were segmented semi-automatically from the PDw-FS scans, and acetabular and femoral cartilage were segmented manually from the dGEMRIC scans (Analyze 10 (AnalyzeDirect, KS)). The PDw-FS and dGEMRIC images were rigidly registered using landmark points to align the cartilage with the BML locations. Outlines of BMLs were projected onto the hip cartilage either radially outwards from (femoral BMLs) or towards (acetabular BMLs) the centre of the femoral head to define the BML overlying cartilage. Mean T1Gd was calculated for the BML overlying cartilage (OC) and the surrounding cartilage (SC) for the full cartilage thickness (all BMLs), acetabular cartilage (acetabular BMLs), and femoral cartilage (femoral BMLs). We tested the statistical hypotheses that mean T1Gd of OC was different from mean T1Gd of SC using a paired t-test in MATLAB (Mathworks, MA).

Results: For the combined hip cartilage, mean T1Gd was 59ms (SD: 165ms) lower in overlying cartilage than surrounding cartilage (p=0.05, n=32). For acetabular cartilage, mean T1Gd was 45ms (SD: 109ms) lower in overlying cartilage than surrounding cartilage (p=0.06, n=23). For femoral cartilage, mean T1Gd was 117ms (SD: 193ms) lower in overlying cartilage than surrounding cartilage (p=0.03, n=15).

Conclusion: Our result that mean T1Gd is lower in hip OC than SC suggests that hip OC has a lower proteoglycan content than hip SC, which is consistent with previous research of BMLs in the knee. We found the largest difference in mean T1Gd between OC and SC in the femoral cartilage. These preliminary results suggest that BML overlying cartilage in the hip has a lower proteoglycan content than the surrounding cartilage.

KEYWORDS

Osteoarthritis, Bone Marrow Lesions, Bone, Cartilage, dGEMRIC, MRI, Biomechanics, Population-based

Ania Kania-Richmond

ABSTRACT: Managing osteoarthritis – Learning from the lived experience of Albertans with knee osteoarthritis who are not candidates for arthroplasty.

Background: One-third of patients with knee osteoarthritis (OA) are not surgical candidates and require on-going management of their OA-related symptoms. Understanding how these patients manage their OA from their perspective will help decision-makers align services with best practice guidelines and in response to patients' needs and lived realities.

Objectives: Explore how people with knee OA who are not candidates for arthroplasty manage their OA.

Methods: Semi-structured interviews were conducted with a convenience sample of who agreed to an interview following a telephone-administered questionnaire evaluating use of health care services. An interpretative-descriptive approach was used for the analysis. Through an iterative process, data elements were compared and contrasted, and an emergent coding framework was developed. This framework was then applied to all interview data. Based on similarities, patterns and relationships, descriptive categories were generated, and high-level themes emerged through the interpretative analysis.

Results: Twenty participants consented to the interview from the 50 who agreed to be contacted. Participants were 75% female and 90% were retired. The number of years since participants had been diagnosed with OA ranged from less than 3 years to over 30 years. Participants accessed services from a range of health care professionals, including physicians, allied health professionals, and complementary/alternative practitioners. A variety of medical (physician administered) and non-medical interventions were used to address OA symptoms. Three themes emerged that define how participants manage their OA: 1) a cyclical process that is highly individualized, 2) experimentation and willingness to "try anything", and 3) reliance on networks of peers, family members, and perceived experts for information.

Conclusions: Day-to-day management of OA is a patient-driven, highly individualized process informed by a network of sources. Effectively supporting individuals with knee OA who are not surgical candidates involves access to appropriate health care services, credible information, and self- management strategies that occur within and outside of the healthcare system.

Audrée Laroche

BIO

Science has fascinated me for as long as I can remember. I was impatient to understand the complex immunological mechanisms behind arthritis, which affects my maternal family. During my master graduate studies, my motivation led me to study the pathogenesis of systemic lupus erythematosus, an arthritic disease in which several organs and tissues are affected by inflammation. During my PhD studies, with the support of The Arthritis Society, I will continue to increase our knowledge on the mechanisms of this disease to hopefully improve the quality of life of people affected by systemic lupus erythematosus.

ABSTRACT: Immune complexes in the brain of a FcγRIIA-expressing lupus mouse model

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease affecting many organs and tissues. Loss of immune tolerance in SLE leads to the production of autoantibodies in the blood. Autoantibodies in circulation form antibodies-antigens complexes, named immune complexes (ICs), which play a major role in the inflammation observed in SLE. Most of SLE patients display mood disorders, cognitive disfunctions, memory loss, migraines and even psychosis. Neuropsychiatric systemic lupus erythematosus (NPSLE) is the name given to all the neurological and psychological manifestations caused by SLE. Blood brain barrier disruption in NPSLE leads to immune cells infiltration and inflammatory mediators, including ICs, into the brain (Schwartz, Stock et al. 2019). ICs bind FcγR receptors and trigger many biological functions such as phagocytosis and cell activation. While FcγRIIA, a FcγR, is better known for its expression in blood by platelets, neutrophils and macrophages (Bruhns and Jonsson 2015), it is also expressed by microglial cells in humans (Fuller, Stavenhagen et al. 2014). Mice are devoid of the FcγRIIA receptor. Therefore, mouse models used to study NPSLE lack the inflammatory response mediated by FcγRIIA in the brain. We recently generated a SLE mouse model expressing FcγRIIA, namely the NZBxNZW(F1)::FcγRIIATGN mice (Melki, Allaeys et al. 2020).Using this model, we showed that FcγRIIA expression aggravates nephritis in SLE. However, whether or how FcγRIIA affects the functions of the brain in SLE has never been evaluated. We hypothesize that ICs activate cells expressing FcγRIIA in the brain and thereby contribute to NPSLE.

Antibodies and FcγRIIA-expressing cells in the brain were investigated by immunofluorescence in vivo in NZBxNZW(F1)::FcγRIIATGN lupic mice. Experiments in vivo revealed the expression of FcγRIIA by brain macrophages, as well as their colocalization with antibodies in the brain of NZBxNZW(F1)::FcγRIIATGN mice.

During my thesis with the support of The Arthritis Society, the role of FcγRIIA and ICs in the entry of antibodies in the brain will be assessed by intravital imaging. The BBB permeability of FcγRIIATGN mice will be quantified by measuring leakage into the brain parenchyma in response to ICs with low-molecular weight fluorescent tracers injected intravenously and compared to FcγRIIAnull mice. BBB integrity will be monitored a different stages of lupus disease in mice. As antibodies accumulate in the brain of NZBxNZW(F1) mice, the understanding of the mechanisms that promote the localization of antibodies in the brain could reveal new targets which inhibitions could interfere in the apparition of neurological and psychological manifestations in SLE.

KEYWORDS

Neuropsychiatric lupus erythematosus, systemic lupus erythematosus, blood brain barrier, antibodies, Fc receptor

Siwen Liu

BIO

Siwen Liu is a second year Master's student at the Rehabilitation Sciences Institute at the University of Toronto. She is in the Rehabilitation Sciences program doing a Collaborative Specialization in Musculoskeletal Sciences. She is working in Dr. Andy Kin On Wong's Musculoskeletal Imaging & Epidemiology Lab at the Toronto General Hospital Research Institute. Her research interests involve studying knee osteoarthritis and identifying potential predictors of knee pain.

ABSTRACT: Patients with prevalent BMLs should not be candidates for arthroscopic knee surgery: data from the Osteoarthritis Initiative

Background: Arthroscopic knee surgery remains one of the most common orthopedic procedures. However, there lacks evidence that having meniscal tears alone prior to surgery improves knee outcomes. Knee OA properties such as bone marrow lesions (BMLs) can be gleaned from the same MR images but are not factored into surgical decision-making. It is possible that even if meniscal tears were resolved, the presence of BMLs would still result in pain persisting. It is important to consider other MRI variables before surgery because arthroscopic knee surgeries have previously been shown to be no better than exercise alone. It was hypothesized that individuals with BMLs are associated with having negative surgical outcomes despite having meniscal tears before arthroscopy.

Methods: A prospective discrete time analysis was performed using data from the Osteoarthritis Initiative (OAI), which included participants (N=4796, 45-70 years old) at risk of OA or have OA in >1 knee. Data for a subset of this cohort from baseline-108 months were included if knee arthroscopy was performed, knee outcome scores were available before and after surgery, and if MRI was completed before surgery. Coronal intermediate-weighted turbo spin-echo and 3D sagittal DESS water excitation MRI sequences were semi-quantitatively graded for BML number, size, and % of lesion that is BML (vs cyst) (MOAKS). A binary logistic regression model determined how pain changes (Knee Osteoarthritis Outcome Score (KOOS) questionnaire pain item) from before to after surgery (dichotomized to whether changes exceeded minimal clinically meaningful improvement) were associated with meniscal tears and BML scores. Odds ratios (OR) were reported with 95% confidence intervals. Models were adjusted for sex, age, education, income, analgesic use, KOOS before arthroscopy, time between pre-surgical KOOS and arthroscopy, time between arthroscopy and post-surgical KOOS, and time between pre-surgical MRI and arthroscopy.

Results: 167 participants (54.5% women, mean age=59.3±8.5 years, mean BMI=29.46+4.42 kg/m2) had knee arthroscopy, 11 of whom had it performed in both knees, resulting in 178 knees analyzed. Worse knee pain after arthroscopy was associated with a greater number of BMLs (OR=2.82(1.37,5.83)), larger BML size (OR=2.05(1.11,3.79)), and greater % of lesion that is BML (OR=2.11(1.22,3.63)), despite having had meniscal debridement. Having a meniscal tear before knee arthroscopy was not independently associated with improved knee pain.

Conclusions: The presence of BMLs remains to be a significant source of pain post-surgery even after meniscal debridement. Therefore, patients with prevalent BMLs in presurgical MRI scans should not be candidates for arthroscopic knee surgery.

KEYWORDS

knee osteoarthritis, knee pain, knee arthroscopy, meniscal tear, bone marrow lesion

Siwen Liu

BIO

Siwen Liu is a second year Master's student at the Rehabilitation Sciences Institute at the University of Toronto. She is in the Rehabilitation Sciences program doing a Collaborative Specialization in Musculoskeletal Sciences. She is working in Dr. Andy Kin On Wong's Musculoskeletal Imaging & Epidemiology Lab at the Toronto General Hospital Research Institute. Her research interests involve studying knee osteoarthritis and identifying potential predictors of knee pain.

ABSTRACT: Greater fat distribution in the thighs is associated with worse knee outcomes at baseline and at 2-year follow-up: the Osteoarthritis Initiative

Introduction: Body mass index (BMI) has been correlated with the severity of knee osteoarthritis (OA). Fat tissues release pro-inflammatory factors such as cytokines and adipokines, both of which have roles in knee OA pathogenesis. Therefore, it is possible that fat may also play a role in knee OA pathogenesis and contribute to poorer knee outcomes (e.g. knee pain) by exacerbating inflammation. There is fat between and within muscle, known as inter- and intramuscular fat, respectively. The relationship between these fat sources and knee outcomes is unclear. This study aimed to determine the association between fat distribution in the thigh muscles and knee outcomes. It was hypothesized that greater fat distribution is associated with worse knee pain and function.

Methods: Data from the Osteoarthritis Initiative (OAI) was used for this longitudinal study, and included participants (N=4796, 45-70 years old) with or at risk of OA in > 1 knee. Thigh magnetic resonance (MR) images (right thighs only) of 105 participants from a subset of this cohort obtained during the second annual (24-month) follow-up visit (V03) were included for image analysis. There were 15 slices for each participant, each slice being 5 mm thick, with a gap size of 5 mm between slices, for a total 145 mm of coverage. Image analysis was performed using a fully-automated fat segmentation algorithm developed by our lab in Jupyter Notebooks under a Python 3.6.7 environment. Linear regression models determined how total fat volume and total fat percentage of all slices in the thighs related to Knee Injury and Osteoarthritis Outcome Scores (KOOS) at 0, 1-, and 2-years post-MRI from the 24-month visit. Regression coefficients were reported with 95% confidence intervals. Models were adjusted for age, sex, education, income, analgesic use, and physical activity.

Results: Among the 105 thighs analyzed, 2 were excluded due to errors, leaving 103 participants, 55.3% being women, with mean age=67.4+8.1 years, and mean BMI=27.63+4.20 kg/m2. A 1% greater fat percentage in the thighs was associated with worse contemporaneous KOOS knee pain (B=-1.02 (95% CI:-1.91,-0.13)) and with worse KOOS Function (Sport/Rec) 2 years later (B=-2.34(95% CI:-3.97,-0.71)), but not 1 year later.

Conclusion: Greater thigh muscle fat distribution was associated with worse short-term and long-term knee outcomes but not intermediary outcomes at 1 year. Fat distribution in the thigh may contain the source of more immediate pain and could be a target for early intervention before function is affected in the long-term.

KEYWORDS

knee osteoarthritis, knee pain, knee function, intermuscular fat, intramuscular fat

Christina Le

BIO

Christina Le graduated from the Master of Science in Physical Therapy program in 2011 from the University of Alberta in Edmonton, Canada. She is now a PhD candidate in Rehabilitation Sciences in the Faculty of Rehabilitation Medicine at the University of Alberta. As a clinician, she frequently treats athletes with anterior cruciate ligament (ACL) injuries. This experience has motivated her to pursue research to better understand health-related quality of life (HRQoL) following a sport-related knee injury in active youth. Christina is interested in identifying factors that influence youth HRQoL during rehabilitation and developing strategies to improve long-term HRQoL.

ABSTRACT: What does the future hold? Health-related quality of life 3-12 years following a youth sport-related knee injury

Background: Knee trauma is a risk factor for radiographic osteoarthritis. Currently, it is unclear if knee trauma is also associated with features of osteoarthritis illness, including reduced health-related quality of life (HRQoL). This study assessed generic and condition-specific HRQoL in individuals with a 3-12 year history of a youth sport-related knee injury compared to uninjured controls. To further explore the relationship between injury history and HRQoL, the influence of OA disease and HRQoL determinants were also considered.

Methods: Participants included 124 individuals with a 3-12 year history of a youth sport-related, intra-articular, time-loss knee injury and 129 uninjured controls of similar age, sex, and sport. Outcomes included generic (EQ-5D-5L index, EQ-VAS) and condition-specific [Knee injury and Osteoarthritis Outcome Score quality of life subscale (KOOS QOL)] HRQoL. Descriptive statistics were calculated for participant characteristics, outcomes, and covariates. Simple linear regression, accounting for clustering on sex and sport, examined differences in each HRQoL outcome by injury group. Separate multivariable linear regression models (95%CI) explored the influence of sex, time since injury, injury type [anterior cruciate ligament (ACL) tear or other], body mass index (kg/m2), normalized knee extensor and flexor torque (Nm/kg), intermittent pain [Intermittent and Constant Osteoarthritis Pain Score (ICOAP)], and moderate-to-strenuous physical activity [Godin Leisure Time Exercise Questionnaire (GLTEQ)] on the relationship between injury history and each HRQoL outcome.

Results: The median age of participants was 23 years (range 14-29) and 55% were female. Injured participants were a median of 6.7 years (range 2.9-11.6) post-injury and 56% sustained an ACL tear. Simple regression analyses revealed that injury history was associated with poorer KOOS QOL scores [-8.41 (95%CI -10.76,-6.06)] but not with EQ-5D-5L index or EQ-VAS scores. Multivariable models demonstrated that injury history [-5.14 (95%CI -6.90,-3.38)], ICOAP score [-0.40 (95%CI -0.45,-0.36)], and ACL tear [-1.41 (95%CI -2.77,-0.06)] were associated with poorer KOOS QOL scores. Worse ICOAP scores [-0.0024 (95%CI -0.0034,-0.0015)] were associated with poorer EQ-5D-5L index scores and a significant interaction between injury history and sex revealed that injured males scored slightly better than uninjured males [0.0232 (95%CI 0.0042,0.0422)]. Higher GLTEQ scores [0.10 (95%CI 0.03,0.17)] were associated with better EQ-VAS scores.

Discussion: These data suggest that knee injury history is associated with poorer condition-specific but not generic HRQoL 3-12 years post-injury. Intermittent pain, physical activity, and injury type should be considered in future studies to better understand HRQoL, an important feature of osteoarthritis illness, following a youth sport-related knee injury.

KEYWORDS

osteoarthritis, pain, physical activity, and prevention

Samantha Leech

BIO

Samantha is currently pursuing a Master of Science in Biomedical Engineering at the University of Calgary under the supervision of Dr. Sarah Manske and Dr. Ashley Harris. She received her Bachelor of Engineering and Applied Science from Queen's University in 2020. Samantha brings together a unique collaboration that integrates musculoskeletal and brain imaging to study her primary research interest of chronic pain in knee osteoarthritis.

ABSTRACT: Pain outcomes in unilateral vs bilateral total knee arthroplasty patients

Purpose: Total knee arthroplasty (TKA) is the final treatment option for pain relief in end-stage knee osteoarthritis. However, 15-40% of patients have persistent post-surgical pain that is not otherwise explained (e.g., infection, joint loosening). While the majority of patients only have one knee replaced, the prospect of unresolved pain for the substantial fraction of patients who have both knees replaced is unclear. This population-based study used clinically collected data to compare pain outcomes following unilateral and staged-bilateral TKA.

Methods: Demographic and pain outcome data collected by the Alberta Bone and Joint Health Institute was analyzed for all TKAs conducted in Alberta from 2013 to 2020. To be included in this analysis, patients needed to be undergoing primary TKA for knee osteoarthritis and complete Western Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaires prior to surgery and at 3- and 12-months post-surgery. Patients under the age of 30 years and those undergoing TKA for rheumatoid arthritis, trauma, or revisions were excluded.

The minimal clinically important difference (MCID) was defined as a 17-point improvement on the WOMAC transformed pain scale (where 100 indicates no problems and 0 indicates extreme disability). Unpaired t-tests were used to compare outcome pain levels between patients with unilateral and bilateral TKA. Significance was defined as p < 0.05.

Results: In total, 2,571 patients fit the inclusion criteria, 167 of whom had both knees replaced during the assessment period. Pre-surgical pain levels, age, and sex distributions did not differ between uni- and bilateral TKAs. Pre-operative pain was worse prior to the first TKA (45.8, SD 21.4) than the second TKA (60.6, SD 23.0), p < 0.001. Change in pain scores did not differ between unilateral and the first TKA in bilateral patients. Overall, 74% and 77% of unilateral TKA patients reached MCID after 3-months and 12-months respectively. This was similar to the 73% of bilateral patients who reached MCID after 3-months after the first TKA, while 84% reached the MCID after two TKAs at 12-months.

Conclusions: Patients undergoing bilateral TKA have greater improvements in knee pain than patients undergoing unilateral TKA. Nonetheless, 16% of patients do not achieve the MCID 12 months after the second TKA. Notably, there is no consensus definition for important change in pain following TKA as the MCID may differ between bilateral and unilateral TKAs. Future directions will determine whether similar factors predict achievement of MCID after unilateral and bilateral TKAs.

KEYWORDS

Osteoarthritis, total knee arthroplasty, chronic pain

Starlee Lively

BIO

My research focuses on how the cell's environment influences its molecular patterns and what effects these changes have on the cell's function, its residing tissue, and the system on a whole. I am also interested in better understanding the brain-body crosstalk - how the brain influences systemic disease progression; and conversely, how the body can influence brain health. My graduate studies investigated how the plastic nature of the brain's extracellular matrix alters neural cell function during development and after extended seizure activity. For my postgraduate studies, I examined the role of other extracellular cues, such as cytokines, growth factors, and ion channels, in modulating the brain's responses, notably to ischemic and hemorrhagic stroke, and how sex and species influence those responses. My current research aims to better understand inflammatory responses and epigenetic regulation underlying the pathogenesis and progression of spine osteoarthritis with the goal of identifying novel biomarkers and therapeutic targets.

ABSTRACT: Association of Presurgical Circulating MicroRNAs with 1-Year Postsurgical Pain Reduction in Spine Facet Osteoarthritis Patients with Lumbar Spinal Stenosis

Background: Up to 30% of spine facet osteoarthritis patients with lumbar spinal stenosis (S-FOA+LSS) have little to no improvement in their pain after surgery. Lack of meaningful improvement in pain following surgery provides a unique opportunity to identify specific predictive biomarker signatures that might be associated with the outcomes of surgical treatment. The objective of the present study was to determine whether a microRNA (miRNA) signature could be identified in presurgical blood plasma that corresponded with level of S-FOA+LSS patient post-surgical pain intensity one year later.

Methods: RNA was extracted from baseline plasma of S-FOA+LSS patients and prepared for miRNA sequencing. Statistical approaches were performed to identify differentially expressed miRNAs associated with reduced 1-year postsurgical pain (n=56). Local expression was assessed by miRNA in situ hybridization performed in facet joint tissue extracted during surgery (n=3).

Results: We identified a panel of 4 circulating candidate miRNAs (hsa-miR-155-5p, hsa-let-7e-5p, hsa-miR-125a-5p, hsa-miR-99b-5p) with higher levels at presurgical baseline that were associated with greater changes in % NPRS20Φreflecting reduced pain intensity levels at one year. Using integrated computational analyses, we identified putative gene targets and pathways associated with the 4 miRNAs. All 4 miRNAs were observed in locally affected tissue, specifically chondrocytes of facet joint cartilage tissue extracted during surgery.

Conclusions: Taken together, our findings suggest that 4 presurgical baseline circulating miRNAs correlate with 1-year postsurgical S-FOA+LSS patient pain intensity and represent possible candidate biomarker of surgical pain response.

KEYWORDS

lumbar spinal stenosis, pain, surgery, miRNA, spine osteoarthritis, low back pain

Rachael Manion

BIO

Rachael Manion is the Executive Director of the Canadian Association of Psoriasis Patients and the Canadian Skin Patient Alliance. Drawing on her background as a lawyer and consultant, Rachael brings a strategic and creative approach to advocating for better patient care. She is also Chair of the Patient Advisory Council of the Skin Investigation Network of Canada (SkIN Canada).

ABSTRACT: Impacts of COVID-19 on the Psoriasis & Psoriatic Arthritis Community in Canada: Highlights from a National Survey

Introduction: To help us understand the experiences of people with psoriasis and psoriatic arthritis during the pandemic, the Canadian Association of Psoriasis Patients (CAPP), the Canadian Psoriasis Network (CPN) and Unmasking Psoriasis co-developed a survey of the psoriasis (Pso) and psoriatic arthritis (PsA) community across Canada in both English and French. The survey asked about disease experience before and during the COVID-19 pandemic.

Results: Of the 830 survey respondents, 62% lived with PsA and 60% lived with both PsA and Pso. Of the PsA respondents, 88% live with joint pain, 71% with stiffness and 67% with joint swelling.

Only half of PsA respondents (51%) have seen a rheumatologist for treatment. Respondents who were not referred to a rheumatologist were asked why: 56% indicated they hadn't been referred for specialty care; 9% responded that there were no rheumatologists near them, and 7% indicated the wait list was too long.

People living with PsA live with many comorbidities: 36% lived with obesity and 23% with depression. PsA impacted many facets of their lives: their sleep (78%), self-esteem (70%), social lives (70%), work (67%), mental health (66%), intimate lives (60%), and school (11%).

COVID-19 had many impacts on people with PsA and Pso, including access to care, access to treatments, mental health and access to social determinants of health. Almost half of respondents avoided seeking care with a doctor or at a hospital. One-quarter had their rheumatologist appointment cancelled, rescheduled or conducted virtually during COVID-19.

Treatment plans were impacted: 13% had to change their treatment plan to manage new flares, treatment plans of 10% were disrupted because of the pandemic (e.g., supply issues, changes in coverage, etc.), 6% decided to change or stop their treatments because of the impacts of the pandemic, and the physicians of 3% changed their treatment plan because of COVID-19 risks.

The mental health impacts of the pandemic have been significant. Half of respondents noted that their mental health was worse or much worse, 57% experienced anxiety, 56% feelings of isolation, 40% depression and 31% despair.

Patients' access to social determinants of health were compromised during the pandemic: 26% had worse or much worse access to employment – and its benefits; stable income (24%), prescription medication (15%) and over-the-counter medication (13%).

These findings can help healthcare providers, patient groups and policy makers to improve supports for people with Pso and PsA during and after the COVID-19 pandemic.

KEYWORDS

COVID-19, psoriasis, psoriatic arthritis, mental health, social determinants of health, virtual care, access to treatment, comorbidities

Seng Manivong

BIO

I obtained my Pharm.D in 2018 at Université Lyon 1 Claude Bernard (France), while completing a Master degree (equivalent to MSc.) in nanotechnologies and medical devices. I worked in many fields, such as an assurance quality officer in clinical research and in industry, as well as a in formulation and chemical research. I decided to pursue my interest in research and I started my PhD in 2020 under the supervision of Drs F. Moldovan and V.G Roullin. Indeed, I have always been interested in toxicology and biocompatibility. At the same time, nanomedicine, introduced with the concept of "magic bullet", has growing interest. Osteoarthritis affects more and more people worldwide and to date, no pharmacological treatment can cure this disease. Thus, my research goal is to contribute to the development of nanomedicines, by devising an innovative treatment to improve the management of osteoarthritis.

ABSTRACT: Chitosan-based nanogel synthesis and investigation of their biocompatibility: a safe nanoplatorm for future osteoarthritic joint treatment

Background/purpose: Osteoarthritis (OA) is a complex degenerative disease of joints and one of the major causes of disability, without curative treatment to date. Indeed, the avascular nature of the cartilage is a major drawback, leading to the poor control of drug delivery in it.

Hydrogel nanoparticles, or nanogels (NG), combine the characteristics of hydrogels, i.e high water content, a biopolymeric matrix mimicking the extracellular environment of osteo-cartilage tissues, cellular adhesion and a high loading capacity, with the possibility to be nanoengineered. Nanosized materials are tunable nanocarrier systems affording both controlled delivery and sustained release of active components to target tissues. However, despite the various nanosystems that are being developed, their safety and toxicity profiles must be investigated since they are destinated to be administrated for long-term periods to OA patient.
Hence, our goal is to develop biocompatible and biodegradable biopolymeric nanogels for the local and long-term administration of active components, increasing their effectiveness for OA treatment.

Methods: Two formulas of blank NG (i.e. without component) were synthesized by ionic gelation from a negatively-charged hyaluronic acid (HA) and a positively-charged chitosan (CS) solution. To be positively-charged, CS is solubilized either in citric acid 10% (CS/CA10) or in acetic acid 2% (CS/AA2).
In vitro toxicity of these NG was evaluated on human primary chondrocytes and synoviocytes by MTS/LDH tests, DNA degradation and NO dosage.
Embryotoxicity was followed in terms of survival, hatching and malformations by exposure of zebrafish embryos (Danio rerio) to increasing concentrations of NGs (up to 100 µg/mL) for 4 days.

Results: Low molecular weight CS and 60 kDa-HA were determined to be the optimal reagents for NG synthesis. NG size (268 +/- 21 nm and 382 +/- 92 nm; CS/CA10 and CS/AA2) and surface charge (27 +/- 8 mV and 40 +/- 10 mV; CS/CA10 and CS/AA2) were characterized by dynamic and electrophoretic light scattering. Cationic NG (provided by chitosan) will target the surface of the negatively charged cartilage, thus ensuring a local deposition, a reduction in systemic exposure and the elimination of peptides.
The two studied formulas did not show in vitro toxicity up to 400 µg/mL after 72 hours. Interestingly, NG seemed to induce premature hatching of embryos in a dose-dependent manner for both formulas.

Conclusion: Our preliminary results of cytotoxicity and embryotoxicity of blank NG allowed us to select the optimal formula for peptide grafting and the safest for its application for the treatment of OA.

KEYWORDS

nanoparticles, nanogel, osteoarthritis, biocompatibility

Darren Mazzei

BIO

Darren's clinical experience as a physiotherapist inspired him to undertake a PhD in Health Economics under the supervision of Dr. Deborah Marshall at the University of Calgary. Darren wants to investigate the socioeconomic impacts of osteoarthritis management with the goal of improving patients' access to evidence-based services. Darren's doctoral thesis is centered around the need, value and affordability of first-line therapies for hip and knee osteoarthritis in Alberta. He is undertaking an economic evaluation of the Good Life with Osteoarthritis Denmark (GLA:DTM) program to inform resource decisions in Alberta.

ABSTRACT: Patterns of Usual Care for Nonsurgical People with Knee Osteoarthritis – A Descriptive Survey

Background: Approximately one-third of people with knee osteoarthritis(OA) referred for total knee replacement (TKR) consultation in Alberta do not meet surgical criteria. International clinical guidelines recommend people with knee OA receive education, exercise, weight management (if appropriate) and pain medication (as needed) to help manage their nonsurgical knee pain. There is limited information about how individuals with OA who are not eligible for surgery manage their OA.

Objectives: Describe 'usual care' patterns for nonsurgical OA treatments in a cohort who were not surgical candidates during TKR consultation at Edmonton, Alberta's centralized intake clinic.

Methods: People diagnosed with nonsurgical knee OA by an orthopedic surgeon were invited to take a standardized, telephone-administered questionnaire to capture key socio-demographics and OA treatments used over 4-6 years since TKR consultation. Descriptive statistics (frequencies, means and standard deviations) summarised key variables. The primary outcome, recommended nonsurgical treatments, was defined as using education, exercise and weight loss (if body mass index ⇢ 25 kg/m2) and at least 1 recommended medication (oral or topical anti-inflammatory, acetaminophen or corticosteroid injection). Secondary outcome, not recommended treatments, was defined as use of opioids, hyaluronic acid, platelet rich plasma and stem cell therapy.

Results: 563 people were invited and 250 participated (44%). Participants were 61% female, mean age 66.3 (SD 8.33), mean body mass index 33.5 (SD 6.7), 91% Caucasian, 71% retired, 69% married, 66% living with a spouse or relative, 58% post-secondary education and 47% had >=3 co-morbidities. The most common reason for nonsurgical recommendation during the initial TKR consultation was symptoms were not severe enough (58%). Recommended nonsurgical treatments were used by 20% of participants following their initial TKR consultation. Among these participants, 64% received education by a health professional, 74% exercised regularly, 38% attempted weight loss, and 91% used recommended pain medications. 42% of participants used treatments that were not recommended. Over 6 years, 34% of participants proceeded to surgery.

Conclusions: One in five participants used recommended nonsurgical treatments to manage knee OA within 6 years of orthopedic surgeon consultation. Future work will assess the association of participant characteristics with use of recommended treatments. Findings will help provincial decision-makers plan future OA service delivery to optimize nonsurgical care.

KEYWORDS

Osteoarthritis, Education, Exercise, Weight Management, Pharmacological, Health Services Research, Utilization, Nonsurgical

Samaneh Mehri

BIO

Samaneh Mehri is a graduate student at the University of Windsor under the supervision of Dr.Lisa Porter & Dr. John Trant. She joined the biomedical research group working on the development of therapies for cancer and autoimmune disease in fall 2019. Her research focuses on funded research into developing a treatment for autoimmune diseases.

ABSTRACT: HLA Blockers for potentially treating Rheumatoid arthritis

Individuals with Autoimmune Diseases such as Rheumatoid Arthritis (RA) experience a slightly increased risk for developing certain types of cancers, including hematological disorders and some solid tumors. RA is an autoimmune disease, caused by improper recognition of self-peptides, particularly human cartilage glycoprotein and type II collagen, by the human leukocyte antigen (HLA) receptors. Normally T-cell specific for these peptides are destroyed in the thymus before they are released, preventing autoimmunity. However, certain post-translational modifications, especially citrullination, can lead to “self-peptide” recognition by non-self T cells.

HLA, also called Major Histocompatibility Complex II (MHC-II), is a heterodimer formed by glycosylated proteins (ΦΦchains), and presents 3 isotypes: HLA-DR, HLA-DP, HLA-DQ. While the DNA sequences for Φchain are conserved in each class, those for Φchain present polymorphism, resulting in the diversity and specificity of peptide binding. In the (HLA-DR), the Φchain is exclusively coded by DRA*01:01 allele whereas allelic variants of the Φchain (DRB) are encoded by 1700 alleles. HLA allele DR4 is the strongest genetic risk factor for RA (>65% prevalence in RA patients). Blocking the HLA-antigen interaction as a potential target intervention for RA patients. Our work consists in the expression and purification of the HLA chain proteins using HEK293 cells as a mammalian cells protein expression system. These proteins will be used in vitro to test the efficacy of HLA blockers synthetic peptides designed and constructed in our lab using cyclic peptides. To be effective these synthetic peptides should be able to competitively displace and prevent the binding of disease causing peptides in the HLA.

There is not any cure for RA. Current and emerging therapeutics can treat the symptoms non-specifically, which makes immunocompromised patients more susceptible to infection and/or cancer. Immunosuppressive drugs make the immune system less able to detect and destroy cancer cells or fight with infections that cause cancer. HLA blockers peptides present a promising form of therapy/treatment for individuals affected by RA.

Mohammad Movahedi

BIO

Dr Mohammad Movahedi is an assistant professor (status) in Institute of Health Policy, Management and Evaluation, University of Toronto. He graduated from medical school at the University of Tehran in 1992. He has since developed an interest in epidemiology and public health and received his PhD in clinical epidemiology from the University of Leeds in 2005. Between 2005 and 2011, he held an Assistant Professor faculty position at Iran universities where he taught "Principles of Epidemiology, "Research Methods", and "Systematic Review" courses for MSc and PhD programs. He worked as a post-doc researcher in pharmacoepidemiology at Arthritis Research UK Centre for Epidemiology, the University of Manchester by 2015. Since then he has been conducting epidemiologic and statistical data analyses on clinical data of Rheumatoid Arthritis (RA) patients collected by the Ontario Best Practice Research Initiative (OBRI) registry at University Health Network.

ABSTRACT: Physician and Patient Reported Effectiveness Outcomes are similar in Tofacitinib and TNF Inhibitors in Rheumatoid Arthritis Patients: Data from a Rheumatoid Arthritis Registry in Canada

Background: Tofacitinib (TOFA) is an oral, small molecule drug used for rheumatoid arthritis (RA) treatment as an alternative option to biologic disease modifying antirheumatic drugs (bDMARDs) including tumor necrosis factor inhibitors (TNFi). Objectives: We aimed to evaluate physician and patient reported efectivness outcomes in TNFi compared to TOFA, using real-world data from the Ontario Best Practices Research Initiative (OBRI).

Methods: RA patients enrolled in the OBRI initiating their TOFA or TNFi (Adalimumab, Certolizumab, Etanercept, Golimumab, Infliximab, and Biosimilars) between 1st June 2014 (TOFA approval date in Canada) and 31st Dec 2019 were included. Patients were required to have physician and patient reported effectivness outcomes data available at treatment initiation and 6-month (± 2 months) follow-up. These included clinical disease activity index (CDAI), rheumatoid arthritis disease activity index (RADAI), HAQ-DI, sleep problem, and anxiety/depression scores. Multiple imputation (Imputation Chained Equation, N=20) was used to deal with missing data for covaraites at treatment initiation. To deal with confounding by indication, we estimated propensity scores for covariates with an absolute standard difference greater than 0.1 between the two treatment groups.

Results: A total of 419 patients were included. Of those, 226 were initiating a TNFi and 193 TOFA, and had a mean (SD) disease duration of 8.0 (8.7) and 12.6 (9.6) years, respectively. In the TNFi group, 81.9% were female and mean age (SD) at treatment initiation was 56.6 (13.4) years. In the TOFA group, 85% were female and mean (SD) age at treatment initiation was 60.3 (11.2) years. The TNFi group was less likely to have prior biologic use (21.7%) compared to the TOFA group (67.9%). At treatment initiation, physical function measured by HAQ-DI was significantly lower in TNFi compared to the TOFA group (1.2 vs.1.4).

The rate of CDAI LDA/remission at 6 months was 33.6% and 26.4% in TNFi and TOFA group, respectively. The generalized linear mixed models (GLMM) adjusting for propensity score quantile, showed that there was no significant difference in CDAI LDA/remission (ORs: 0.85, 95% CI: 0.51, 1.43), RADAI (Φcoefficient: 0.48, 95% CI: -0.18, 1.14), HAQ-DI (Φcoefficient: -0.01, 95% CI: -0.18, 0.16), sleep problems (Φcoefficient: -0.25, 95% CI: -0.95, 0.45), and anxiety/depression scores (Φcoefficient: 0.12, 95% CI: -0.35, 0.58) between the two treatment groups (TOFA used as reference).

Conclusions: In this real-world data study, we found that, physician and patient reported effectivness outcomes are similar in the TNFi and TOFA groups 6 months after treatment initiation in patients with RA.

KEYWORDS

rheumatoid arthritis, TNF inhibitors, tofacitinib, patient reported effectiveness outcome, physician reported effectiveness outcome, real world data

Akihiro Nakamura

BIO

Dr. Akihiro Nakamura, a clinical fellow and a PhD candidate supervised by Dr. Nigil Haroon at Toronto Western Hospital, is working on spondyloarthritis to unveil the mechanism and find a novel therapeutic target.

ABSTRACT: Macrophage migration inhibitory factor is necessary and sufficient for the immunopathology of Spondyloarthritis

Background: Spondyloarthritis (SpA) is a systemic rheumatic disease that primarily affects the joints, spine, gut, skin and eyes. Current therapeutic modalities inhibiting TNF and IL-17A control symptoms in only 60% of SpA patients. Thus, there is an urgent unmet need for novel disease-modifying drugs in SpA. Macrophage migration inhibitory factor (MIF) is a pro-inflammatory cytokine, yet the specific role in the pathogenesis of SpA remains elusive.

Methods: Curdlan (Φglucan) or MIF-plasmid (mini-circle) was injected into SKG mice (8-10 weeks) to induce a SpA phenotype in vivo. The expression of MIF in serum or tissues was measured by ELISA, qPCR, immune-blotting, IHC and/ IF. Mif knockout (KO) SKG mice was also generated. A MIF antagonist (MIF098) was used to block the function of MIF in curdlan-treated SKG mice. Proportion or frequency of immune cells was assessed by flow cytometry. Anti-Gr-1 monoclonal antibody (mAb) or isotype control mAb was used to block the function of neutrophils. Human regulatory T cells (Tregs) in peripheral blood and synovial fluids were isolated and cultured with or without recombinant MIF protein. A total RNA-seq for neutrophils isolated from SKG or Mif KO SKG mice was performed.

Results: The expression of MIF and its receptor CD74 were increased in blood, spleen, gut, sacroiliac and ankle joints of curdlan-treated SKG mice. We found that MIF overexpression is sufficient to induce SpA-like clinical features in SKG mice including expanded populations of T helper 17 (Th17) cells, group 3 innate lymphoid cells and inflammatory macrophages, with decreased Tregs in the inflamed joints. In contrast, Mif KO SKG mice and SKG mice treated with MIF098 prevents or attenuates these manifestations with substantial reduction of type 3 immunity. We determined that inflammatory neutrophils expand and produce MIF in the disease. Cell adoptive transplantation of inflammatory neutrophils into Mif KO SKG mice induces a SpA-like phenotype with enhanced type 3 immunity, while blocking the function of neutrophils with anti-Gr-1 antibody suppresses the induced SpA-like phenotype. We also confirmed the pathogenic role of MIF in neutrophils by a total RNA-seq study. Strikingly, we identified that MIF boosts both human and mouse Treg acquisition of a Th17 cell-like phenotype, including the upregulation of RORΦ, IL-17 and IL-22 in vitro. Tregs in blood and synovial fluids with increased MIF concentrations from SpA patients possess the pathologic Th17-like phenotype.

Conclusion: These results indicate that MIF is a crucial regulator and a potential new therapeutic target in SpA.

KEYWORDS

macrophage migration inhibitory factor (MIF), CD74, spondyloarthritis, SKG mouse, type 3 immunity

Razieh Rabani

BIO

I am a senior post-doctoral fellow at university health network (UHN), Toronto. My research interest focuses on cell therapy approaches for treatment of osteoarthritis and other inflammatory diseases.
I did my PhD in experimental medicine at McGill university working on signal transductions in neutrophils. My first postdoc at Saint Michael's hospital, Toronto involved investigation of mechanism of action of mesenchymal stromal cells in pre-clinical model of sepsis. This sparked my interest and enthusiasm in building a career in clinical and translational research. So, in 2018, I started my second post-doc at arthritis program at UHN, Toronto to elucidate the pathology of osteoarthritis as well as therapeutic efficacy of mesenchymal stromal cells in treatment of osteoarthritis.

ABSTRACT: Differential microRNA profile of mesenchymal stromal cells underlies their therapeutic efficacy in the context of osteoarthritis

Background: Osteoarthritis (OA) is a joint disease affecting > 5 million Canadians. Patients have limited palliative and joint-replacement surgical options, emphasizing the need for new curative therapies. Stromal cell therapy is emerging as a compelling treatment for OA. Our first-in-Canada Ph1/2 trial with bone marrow mesenchymal stromal cells (MSC(M)) in OA patients showed significant improvement in patients reported outcomes. Furthermore, pro-inflammatory monocytes/macrophages were reduced in the synovial fluid (SF), suggestive of a clinical MSC anti-inflammatory action. Although, beneficial effect of MSCs was observed in all the patients, MSCs efficacy varied among participants. Following OMERTI-OARSI guidelines, we categorised the participants into two groups of completes responder vs partial responder patients. The goal of this study is to identify novel microRNAs (miRs) and their gene targets that correlate with therapeutic efficacy of MSCs in the context of osteoarthritis.

Methods: We conducted an unbiased microRNA (miR) sequencing on MSCs from partial responder and complete responder participants of our clinical trial. miRs differential expression (DE) analysis is done using DESeq2 algorithm, followed with mirDIP and pathDIP analysis to identify DE-miR gene targets and pathways. Finally, biological relevance of DE-miRs with MSCs immunomodulatory action and patient reported outcomes are correlated.

Results: Analysis of miR profile of MSCs from complete responders vs partial responders revealed that 34 miRs are expressed differentially with a fold change greater than 1.5. Interestingly, we found that the identified DE-miRs are associated with TGFb, VEGF/VEGF receptor and growth factors pathways as well as immune response signaling; thereby contributing to immunomodulatory action and proliferation capacity of MSCs; and OA pathology. Based on pathways analysis results, we selected the top three DE-miRs for further investigation. Currently, we are manipulating MSCs with mimics and inhibitors for the miRs of interest and therapeutic effect of the engineered-MSCs will be validated through in vitro functional assays (i.e. co-culture with monocyte/macrophages and synovial fibroblasts) as well as animal model of OA.

Conclusions: microRNA profile of MSCs contributes to therapeutic efficacy of MSCs. Understanding therapeutically relevant mechanism of action of MSCs will help to develop enhanced MSCs; and define potency criterion for screening effective MSCs in OA patients. This in turn will enable a successful MSC pivotal clinical trial in OA.

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KEYWORDS

Osteoarthritis, Mesenchymal Stromal Cells, Therapeutic efficacy , microRNA, Inflammation , Immunomodulation

Shawn Robbins

BIO

Dr. Shawn Robbins is an Associate Professor in the School of Physical and Occupational Therapy at McGill University. He completed his BScPT and PhD at the University of Western Ontario in 2001 and 2010 respectively, and he completed a post-doctoral fellowship at Dalhousie University. His research focuses on the neuromuscular and biomechanical factors underlying mobility in patients with orthopaedic health conditions, particularly osteoarthritis. Specifically, he is examining biomechanical mechanisms that underline knee osteoarthritis progression, and the effectiveness of treatments for these patients.

ABSTRACT: Muscle Activation and Knee Moments during Gait Predict Cartilage Volume Loss in Patients with Non-Traumatic and Post-Traumatic Knee Osteoarthritis

Background/Purpose: Knee moments measured during gait relate to disease progression in patients with knee osteoarthritis (OA). Knee OA can be classified as non-traumatic (patients with no history of knee trauma but developed OA) and post-traumatic (patients having a knee trauma and subsequently developed OA). Risk factors for progression may differ between patients with non-traumatic and post-traumatic knee OA. The purpose of this study was to examine if relationships between knee osteoarthritis (OA) progression with knee moments and muscle activation during gait vary between non-traumatic and post-traumatic knee OA.

Methods: Participants with non-traumatic (n=17) and post-traumatic (n=18) knee OA were recruited. The latter group had a previous anterior cruciate ligament rupture. External knee adduction (KAM), flexion (KFM), and rotation (KRM) moments were measured using motion capture and force plates as participants completed five walking trials. Surface electrodes measured muscle activation of the quadriceps, hamstrings, and gastrocnemius. Cartilage volume change over 2 years was measured with magnetic resonance imaging and an automatic cartilage segmentation process in the medial and lateral condyle, and medial and lateral plateau. Regression analyses examined relationships between cartilage volume change with knee moments/muscle activation, OA group, and their interaction.

Results: Greater KAM values (ß=554.59, p=0.020) and greater differences in KRM internal-external rotation values (ß=1615.19, p=0.021) were related to lateral condyle cartilage loss in both groups. Greater KAM values (interaction ß=-1037.27, p=0.047) were associated to lateral plateau cartilage loss in the non-traumatic group only. There were no relationships between knee moments and cartilage loss in the medial compartment. Lower vastus lateralis (ß=3.88, p=0.003) was related to greater lateral plateau cartilage loss in both groups, while lower lateral hamstring activation (interaction ß=4.30, p=0.044) was associated with greater lateral condyle cartilage loss in the post-traumatic group only. Lower medial hamstring activation (interaction ß=-1.65, p=0.044) was related to medial plateau cartilage loss in the non-traumatic group, and cartilage maintenance in the post-traumatic group.

Conclusions: These findings demonstrate that gait risk factors for OA progression vary between patients with non- and post-traumatic knee OA. Future studies should evaluate if the effectiveness of interventions that aim to slow OA progression vary between non-traumatic and post-traumatic knee OA. Understanding if factors in OA progression differ between OA subtypes will help direct treatment.

KEYWORDS

osteoarthritis, gait, anterior cruciate ligament, trauma, magnetic resonance imaging, motion analysis

Naym Uddin Roby

BIO

Naym Uddin Roby is a master's student at the School of Rehabilitation Science, McMaster University. His academic background is in physical therapy and public health. He has worked as a physiotherapist and health researcher in Dhaka, Bangladesh. He has a keen research interest in the areas of musculoskeletal problems, epidemiology, injury prevention, e-health and health policy. His master's thesis is focused on improving the assessment and understanding of chronic pain and sensitization in people with knee osteoarthritis.

ABSTRACT: Validity of the Central Sensitization Inventory through Rasch analysis in patients with Knee OA

Background/purpose: The experience of pain in persons with knee osteoarthritis (KOA) is well-recognized, persistent and chronic in nature. Central sensitization (CS) is one of the responsible factors for chronic pain and exemplifies the fundamental contribution of the central nervous system to the generation of pain hypersensitivity. Persons with KOA have shown evidence of CS by demonstrating hyperalgesia at local and remote sites. CS is measured by psychophysical testing and by patient reported methods such as the Central Sensitization Inventory (CSI). However, values from psychophysical tests indicating sensitization and the recommended cut scores from the CSI have poor agreement in people with KOA. The CSI was developed using subgroups of people with chronic pain but not KOA. The purpose of this study was to evaluate the validity of the CSI through Rasch analysis in patients with KOA.

Methods: We performed a secondary analysis of a cohort study (n=293) with patients (age =>40) diagnosed with KOA consulting orthopaedic surgeons at 3 Montreal hospitals. Rasch analysis was conducted to assess how the CSI fit to the Rasch Model (supporting validity) using RUMM2030 software, making adjustment as required to achieve model fit.

Results: Our sample included 58.7% female patients, with a mean age of 63.6 (±9.5) and almost half (49.1%) of the participants were obese. The mean CSI score was 30.8. Initial evaluation with Rasch modelling indicated misfit. Eleven of the twenty-five items on the CSI displayed disordered thresholds which were re-scored by collapsing response categories until the thresholds demonstrated sequential levels. Re-analysis demonstrated persistent model misfit so we developed a subtest to address local dependency of 4 items. After this correction, we achieved model fit (P=0.08, indicating not differing from Rasch model) and unidimensionality (P=0.068 with 95%CI 0.043-0.093). Only one item (item 21- frequent urination) from the CSI showed a pattern of uniform DIF by age which was statistically significant (p<0.001).

Discussion/Conclusion: The CSI was able to be fit to the Rasch model after rescoring while retaining all 25 items. Floor effects were seen, potentially due to a lower prevalence of CS in this population. Users of the CSI should be aware of the potential for differences in scoring across age groups for the frequent urination item. The unidimensionality validates CS as measured by the CSI as a singular construct.

KEYWORDS

Knee Osteoarthritis, Central Sensitization Inventory, Rasch Analysis.

Jason Rockel

BIO

During my PhD at Western University, I investigated inflammatory signalling mechanisms regulating gene expression in cartilage cells. Following this, I garnered expertise in transgenic and surgical mouse models of osteoarthritis at Sick Kids to determine molecular signals important during joint development that could be exploited to alter the pathogenesis of osteoarthritis. My current research focuses on identification of novel biomarkers and therapies for OA. In particular, I am investigating: The relationship between molecular signals in the local joint environment and changes to the systemic metabolome, including their contribution to the pathogenesis of osteoarthritis, Novel biomarkers of osteoarthritis disease state, pain or prognosis related to patient characteristics including age, sex, BMI and ethnicity, and The use of small molecule, biologics and cell therapies for treatment of osteoarthritis.

ABSTRACT: Identification of Two Metabolite-Based Phenotypes in Patients with Late-Stage Knee Osteoarthritis

Purpose: Osteoarthritis (OA) is a heterogeneous disease with a variety of factors contributing to different OA phenotypes. There remains unexplained heterogeneity in patients with OA. Systemic metabolites may help to explain some of the underlying heterogeneity between OA patients. Contributions of systemic metabolites in helping define patient phenotypes are not well understood. Using a cross-sectional population of patients with late-stage knee OA, we sought to determine whether distinct clusters of patients with OA could be identified by plasma metabolomes. Non-diabetic and non-obese patients were selected to limit the impact of metabolic disorders.

Methods: Metabolite levels were analyzed by metabolomics in plasma of 214 non-diabetic, non-obese (BMI < 30) late-stage knee OA patients collected prior to knee replacement surgery. Metabolite level-based patient clusters were determined by hierarchical clustering. Thirty-five anthropometric, sociodemographic, patient reported comorbidities and drug use characteristics were compared to determine significant deviations (p < 0.05) in patient distributions. Where significant deviations were identified, metabolites with FDR-adjusted t-test p < 0.05 were determined. A refined metabolite signature differentiating patient clusters was identified by selecting metabolites with ⇢ 10% fold-difference, significant by FDR-adjusted t-test (p < 0.05), and random forests importance scores > 1. AUROC analysis confirmed cluster discriminatory ability of the refined metabolite signature. Bioinformatics analysis identified genes linked to ⇢ 2 Kyoto Encyclopedia of Genes and Genomes (KEGG) annotated signature metabolites. Gene-associated enriched pathways (FDR p-value < 0.05) were determined using pathDip (http://ophid.utoronto.ca/pathDIP/).

Results: From 188 metabolites measured, 151 were identified. Two patient phenotypes emerged by hierarchical clustering. The distribution of patients with daily narcotic use was significantly different between the two clusters (p = 0.0041 by Fisher's exact test). No metabolites were significantly modified in daily narcotic users suggesting minimal influence of these patients on metabolite levels between clusters. After signature refinement, 24 metabolites accurately predicted patient cluster classification with outstanding discrimination. Finally, 56 genes were linked to at least 2 KEGG annotated metabolites. Pathway analysis identified 26 of the 56 genes were linked to various enriched pathways including tRNA acylation and B-vitamin metabolism.

Conclusions: A signature consisting of 24 metabolites was able to distinguish two clusters of late-stage knee OA patients. This signature was linked to distinct genes and pathways that may contribute to disease processes including OA symptoms and joint degeneration. We next aim to understand the relevance of this metabolite signature in prognostication and explore the importance of these biologically-relevant OA patient phenotypes.

KEYWORDS

osteoarthritis, metabolomics, patient clusters, bioinformatics

Hamed Alizadeh Sardroud

BIO

My name is Hamed Alizadeh Sardroud, and I am a 3rd year PhD student in Biomedical Engineering at the University of Saskatchewan. My supervisors are Dr. Eames and Dr. Chen, and my thesis is on cartilage tissue engineering. I study use of 3D-bioprinted hybrid constructs to shield the stress applied on the embedded-cells. To this end, I fabricated cell-embedded 3D-bioprinted hybrid and hydrogel constructs and implanted them in the joints of pigs. I am studying effects of applied in vivo loadings on two type of the aforementioned constructs to see if hybrid constructs can shield the stress and lead to lower collagen type I deposition and better hyaline cartilage formation. As my other side of thesis, I also do similar experiment of loadings on the constructs in an in vitro condition using a biodynamic machine. For this part, I apply various amount of forces on hydrogel and hybrid constructs and analyze the output in terms of collagen type I and II deposition to see how loading can affect hyaline cartilage formation in different constructs.

ABSTRACT: Study of hyaline cartilage formation in 3D-bioprinted hybrid and hydrogel constructs implanted in pig joints

Background/purpose:Efforts in hyaline cartilage regeneration have focused on using hydrogels as biomaterials. Cells embedded within hydrogel feel high mechanical loadings when implanted into joints, and this leads to the upregulation of collagen type I and fibrocartilage formation instead of hyaline cartilage. Here, we investigate using 3D-bioprinted alginate/polycaprolactone hybrid constructs to shield cells from high mechanical loading, and this can lead to lower collagen type I and higher collagen type II deposition.

Methods: Potential force-shielding can be investigated by implanting hybrid and hydrogel constructs into joints and observing cellular responses to loading forces. We hypothesize that less collagen type I would be deposited in the hybrid compared to the hydrogel constructs. To this end, 3D-bioprinted hybrid and alginate hydrogel (control group) constructs containing cells from the chondrogenic line ATDC5 were implanted into punched defects in the joints of 10 pigs. The pigs were euthanized after 1 or 3 months for further imaging, histological, and immunostaining analyses. Samples from the joints were imaged at Canadian Light Source (CLS) in Saskatoon. This imaging tool is capable of visualizing different materials and tissues and helps to analyze the changes within the defect in terms of newly formed tissue and degradation of materials.

Results: Gross observation of the defects showed the formation of cartilage-like tissue within the defects. There was an increase in filling the defects with the new tissue after 3 months compared to 1 month period. Covering of the defects' surface was better and less distinguishable from the surrounding tissue in hybrid implanted defects compared to hydrogel implanted ones. Synchrotron imaging could visualize the implanted constructs and surrounding tissues together. Implanted PCL strands were visible, though hydrogels strands were not. The reason could be hydrogel strands either couldn't be detected by the beam or degeraded within that period. Further 3D volume rendering will allow us to analyze biomaterial and cartilage changes qualitatively and quantitatively.

Discussion/Conclusion: So far, gross observations have shown cartilage-like tissue formation within the defects, although immunostainings for collagen type I and II must be carried out to determine the type of the cartilage. Also, imaging results have shown that synchrotron imaging could visualize both the implanted construct and the surrounding tissue, whereas other imaging techniques such as desktop CT imaging is not capable of. The imaging results will also be quantitively analyzed for degradation of implanted PCL and formation of new tissue.

KEYWORDS

Cartilage, 3D-bioprinted, hybrid construct, collagen type I, collagen type II, in vivo

Michael Tang

BIO

Dr. Michael Tang is a postdoctoral fellow at the Schroeder Arthritis Institute, University Health Network, Toronto. Under the supervision of Dr. Robert Inman, Michael is investigating the emerging role CD8 cytotoxic T cells in Ankylosing Spondylitis (AS) by studying their molecular profile in the blood and synovial joint fluid of patients living with AS. This detailed immune profiling study will be the first of its kind, and its findings could shed light on new opportunities to diagnose AS early and develop new treatment. Michael is a recipient of the training postdoctoral fellowship (TPF) award from the Arthritis Society.

ABSTRACT: CD8+ T Cell Subsets and Immune Checkpoint Profiles in Ankylosing Spondylitis Implicate Dysregulation of Cytotoxic T Lymphocytes (CTL)

Background: Ankylosing Spondylitis (AS) is characterized by chronic inflammation which underlies the pain and precedes spinal ankylosis. The strongest genetic association with AS is the HLA-B27, implicating involvement of CD8+ cytotoxic T cells (CTL) in AS pathogenesis. To date, the CTL compartment that underlies AS inflammation has yet to be fully defined. Our lab recently reported altered cytotoxicity profiles in CTL from AS patients, suggesting that dysregulated CTL with a cytotoxic phenotype are recruited to the joints. These findings suggest a central role of dysregulated CTLs in AS pathogenesis, warranting further investigation. Here we sought to characterize CTL subsets and immune checkpoint (IC) expression on CTL from patients with AS.

Hypothesis: We hypothesized that effector memory subsets of CTL are enriched in the periphery and targeted sites of the inflamed joints from patients with AS. These effector subsets of CTLs contribute to uncontrolled inflammation through aberrant expression of IC molecules and sustained release of proinflammatory cytokines and cytotoxic mediators.

Methodology: We performed immunophenotyping of peripheral blood mononuclear cells (PBMCs) and synovial fluid mononuclear cells (SFMCs) by flow cytometry. A 21- plus marker mass cytometry time-of-flight (CyTOF) panel is currently being developed to comprehensively assess the CTL compartment in AS patients.

Results: We identified a sub-cohort of AS patients with an enriched population of terminally differentiated memory CTL (up to 46.2% of all CD8+, expressing CD45RA+CCR7-) in the periphery and elevated expression of the IC molecules PD-1 (18.3% vs 10.2% of total CD8+ T cells) & TIGIT (17.3% vs. 4.4% of total CD8+ T cells) on AS CTL compared to healthy controls. Effector memory CTL (CD45RA- CCR7-) were highly enriched in the SF. PD-1 expression is also highly upregulated in the synovial CTL (up to 75% of CD8+ T cells), suggesting local immune activation. Despite PD-1 upregulation in these CTL subsets, evidence of immune exhaustion, as assessed by EOMES expression, was not found. Immune profiling of PBMC and SFMC by mass cytometry revealed a subset of activated tissue-resident memory like CD103+ CD69+ CTLs residing in the synovial fluids that express the immune checkpoints PD-1, TIGIT, and LAG-3.

Conclusions: We demonstrate that CTL from AS patients are highly activated, and are characterized by a distinct immune phenotype which implicates an intrinsic CTL dysregulation in AS pathogenesis.

KEYWORDS

Ankylosing spondylitis, immune regulation, cytotoxic T cells, single-cell analyses

Ghazaleh Tavallaee

BIO

I am a cell and molecular biologist with research experience in different fields including diabetes type II, obesity and lipid metabolism. I am interested in developmental biology and molecular mechanisms of cell and organ differentiation, as my master's project was focused on the molecular mechanisms of sextual differentiation in mammals.

ABSTRACT: MicroRNA-27b-3p is involved in the regulation of synovial extracellular matrix and fibrosis in osteoarthritis

Purpose: Synovial fibrosis, characterized by excessive extracellular matrix (ECM) deposition, is a hallmark of osteoarthritis (OA) pathology. However, the underlying mechanisms of uncontrolled ECM production in the synovium are largely unknown. We have previously shown that the expression of microRNA (miR)-27b-3p is increased in the synovial fluid of late-stage radiographic knee OA patients. Here, we investigated the potential contributions of miR-27b-3p to synovial ECM production and OA-related synovitis.

Methods: In situ hybridization was used to visualize miR-27b-3p distribution in the human and mouse synovium. Expression of type I collagen (COL1A1, major ECM marker) was measured by RT-qPCR, western blot and immunofluorescence. Primary fibroblast-like synoviocytes (FLS), were transfected with miR-27b-3p mimic and subjected to ECM-specific qPCR array and RT-qPCR validation to examine the effect of miR-27b-3p on ECM expression. Transwell was used to assess the effect of miR-27b-3p on OA FLS migration. Immunohistochemistry was used to localize ECM proteins in mouse knee joints. In vivo grade miR-27b-3p mimic was intra-articularly injected into mouse knee joints. RNA sequencing and integrative computational analysis were performed in miR-27b-3p mimic-treated OA FLS, followed by rescue assays and siRNA transfection, to identify miR-27b-3p signaling mechanisms.

Results: miR-27b-3p expression is increased in the synovial lining of late-stage knee OA patients and knee OA mouse model. MiR-27b-3p mimic transfection of human OA FLS enhanced their migration and increased COL1A1 expression. Array screening of ECM-related genes and RT-qPCR validation identified six key ECM genes [COL1A1, collagen type V alpha 1 (COL5A1), collagen type XIV alpha 1 (COL14A1), fibronectin (FN1), thrombospondin 1 (THBS1) and a disintegrin and metalloproteinase with thrombospondin motifs-8 (ADAMTS8)] that were markedly elevated in miR-27b-3p mimic-treated OA FLS. COL5A1, COL14A1, and ADAMTS8 showed similar localization patterns to that of miR-27b-3p in the OA mouse knee joints. Intra-articular injections of miR-27b-3p mimic induced an OA-like synovitis in mouse knee joints in vivo. RNA sequencing and computational analysis revealed that miR-27b-3p regulates numerous ECM-related genes expression, highlighting PPAR-ΦADAMTS8 as a potential signaling axis through which miR-27b-3p may impart its signaling in OA FLS. We showed that miR-27b-3p negatively regulates PPAR-Φand employed rosiglitazone to promote PPAR-Φunction which inhibited miR-27b-3p-induced overexpression of key ECM genes. Furthermore, siRNA-knockdown of ADAMTS8 in OA FLS attenuated miR-27b-3p-induced increase in expression of COL14A1, COL5A1 and FN1, indicating partial contribution of ADAMTS8 to the regulation of miR-27b-3p-modulated ECM genes.

Conclusions: miR-27b-3p plays essential roles in regulation of synovial ECM and fibrosis during OA.

KEYWORDS

Osteoarthritis, miRNAs, synovial fibrosis, extracellular matrix

Anthony Teoli

BIO

My name is Nada Abughazaleh. I am a Ph.D. student from the University of Calgary Department of Biomedical engineering. I have a bachelor's degree in biomedical engineering from The Hashemite University in Jordan. I came to Canada in 2010 and earned a master's degree in biomedical engineering. During my master's, my research focused on determining the effect of different types of exercise on chondrocyte viability and cartilage degeneration and Osteoarthritis. My work has been published in Clinical biomechanics journal. Currently, I am working in the Human performance lab at the University of Calgary under Dr. Walter Herzog's supervision to identify the effect of obesity and the associated systemic inflammation and imbalance in the microbial community with musculoskeletal degeneration and a specific phenotype of osteoarthritis.

ABSTRACT: The relationship between baseline sensitivity to physical activity with clinical outcomes following an 8-week rehabilitation program in patients with knee osteoarthritis

Background/Purpose: Sensitivity to physical activity (SPA) is a novel measure quantifying the pain response to standardized physical activities or tasks. However, it is unclear which tasks are most appropriate to assess SPA in patients with knee osteoarthritis (OA) and the prospective value of SPA remains unexplored. This study aimed to compare baseline evoked pain responses across physical tasks and determine whether baseline task-specific SPA is associated with pain and physical function following an 8-week rehabilitation program in patients with knee OA.

Methods: Fifty-two participants with knee OA (mean age=61 years, 36 females) underwent an 8-week rehabilitation program. Participants received one 1.5-hour treatment per week by a physiotherapist, focusing on patient education, range of motion, flexibility, strengthening and aerobic exercises. Outcomes were assessed at baseline and following the 8-week rehabilitation program. Pain and physical function were assessed using the Knee Injury & Osteoarthritis Outcome Score (KOOS) pain and function in daily activities subscales. To determine SPA, participants verbally rated their pain severity using a 0-100 numeric rating scale before and after five tasks: 30-Second Chair Stand (30CST), 40-Meter Fast-Paced Walk (40FPW), Timed-Up-and-Go (TUG), 6-Minute Walk Test (6MWT) and Step Test (ST). Task-specific SPA indices were generated by subtracting the pre-task pain from the post-task pain. Paired samples t-tests evaluated whether the post-task pain was significantly greater than the pre-task pain for tasks at baseline, and compared task-specific SPA, pain and physical function at baseline and 8 weeks. Pearson correlations examined associations between baseline task-specific SPA with pain and physical function following the 8-week rehabilitation program.

Results: The 30CST (6-point increase, p<0.001), 40FPW (9-point increase, p<0.001), 6MWT (14-point increase, p<0.001) and ST (20-point increase, p<0.001) elicited a significant increase in pain at baseline. There was a significant reduction in pain (mean difference:-9.3, p=0.001) and physical function (mean difference:-5.9, p=0.015) following the 8-week rehabilitation program. Task-specific SPA did not significantly differ from baseline to 8 weeks (p>0.05). Baseline task-specific SPA was not associated with pain and physical function following the 8-week rehabilitation program (r=-0.230 to 0.251, p>0.05).

Discussion/Conclusion: All tasks except for the TUG elicited a significant increase in pain in patients with knee OA at baseline. Baseline task-specific SPA was not associated with pain and physical function following the 8-week rehabilitation program. The majority of patients did not experience a clinically important increase in pain (⇢20-point increase) following the tasks at baseline, which may have influenced the prospective relationship with clinical outcomes.

KEYWORDS

Knee osteoarthritis, rehabilitation, sensitivity to physical activity

Salem Werdyani

BIO

Salem Werdyani obtained his B. Sc. in 1998 from the United Arab Emirates University, UAE. Then he moved to Canada and completed a bioinformatics graduate certificate program at Centennial College, Toronto, Canada. After graduation in 2010, he joined The Ozcelik cancer genetics Lab, Mount Sinai Hospital, University of Toronto, Canada. In 2012, Salem moved to Newfoundland where he accomplished his Master of Science in Medicine and started his PhD. at the Discipline of Genetics, Faculty of Medicine, Memorial University of Newfoundland, Canada. His PhD. project at the Zhai Lab aims to apply genomics and metabolomics approaches to identify novel biomarkers for osteoarthritis, which can improve our understanding of the pathogenesis of the disease and suggest novel targets for developing disease-modifying therapies.

ABSTRACT: Metabolomic Signatures For The Longitudinal Reduction Of Muscle Strength Over 10 Years

Background: Osteoarthritis (OA) is the most common type of arthritis that affects about 10% of world population aged 60 years and older. Since skeletal muscles have an integral role in synovial joints, this study was performed to investigate the metabolomic signatures for the longitudinal reduction of muscle strength over 10 years in a well-established community-based older adult cohort.

Methods: Study participants were 50-79 years old from the Tasmanian Older Adult Cohort (TASOAC) Study. Hand grip, knee extension, and leg muscle strength were conducted at baseline, 2.5-, 5-, and 10-year follow-up points. Blood samples were collected at the 2.5-year follow-up after at least 8 hours fasting, and the metabolomic profiling was performed using the TMIC Prime Metabolomics Profiling Assay. Generalized linear mixed effects model was used to identify the metabolites that were associated with the longitudinal reduction of muscle strength over 10 years with adjustment for age, sex, and BMI. Further, a GWAS analysis in 77 individuals from the Newfoundland Osteoarthritis study (NFOAS) was performed to explore the potential mechanisms of the association between the identified metabolomic markers and the longitudinal reduction of muscle strength over 10 years.

Results: A total of 409 older adults (50% of them were females) were included in this study. Study participants had a mean age of 60.93±6.50 years, and mean BMI of 27.12±4.18 kg/m2 at baseline. Among the 143 metabolites measured, 129 passed the quality control filtering and were included in the subsequence analysis. We found that the elevated level of asymmetric dimethylarginine (ADMA) was significantly associated with the reduction of average hand grip strength (p=0.0003) and knee extension strength (p=0.008) over 10 years. GWAS analysis detected that SNP rs1125718 on chromosome 8 was significantly associated with ADMA levels (p=4.394*10-08). This SNP is adjacent to WISP1genes that plays a central role in the muscle stem cells regeneration following to muscle injury or pathogenesis. Further, we found that the increased concentration of uric acid was significantly associated with the decline of leg strength over 10 years (p = 0.0001) but not with hand grip or knee extension strength.

Conclusion: Our results demonstrated that elevated serum concentrations of ADMA, and uric acid were significantly associated with age-dependent muscle strength reduction which may make study participants susceptible for the development of OA. These findings provided new insights into the pathogenesis of age-related muscle strength decline and novel targets for developing strategies to prevent muscle strength loss over time.

KEYWORDS

Skeletal muscle strength; Muscle Strength reduction; Metabolomics; Biomarkers; Asymmetric dimethylarginine; Uric acid

Nima Yazdankhah

BIO

Hello! My name is Nima Yazdankhah and I am a Research Analyst at UHN in Toronto. I completed my undergraduate degree in Biomedical Science at York University and have been doing research in Dr. Andy Kin On Wong's MSK imaging & epidemiology lab.

ABSTRACT: The association between infrapatellar fat pad volume and knee pain scores in non-overweight postmenopausal women

The infrapatellar fat pad (IPFP) in the knee joint is known to be a significant source of pro-inflammatory cytokines. Little is known about its relation to pain and knee function in non-overweight postmenopausal women at risk for osteoarthritis who may lack adiposity compared to the overweight. While inflammatory activity is difficult to assess from images, IPFP volume can be determined by segmentation using magnetic resonance (MR) and computer tomography (CT) images. We hypothesize that there is a relationship between IPFP volume and pain scores and/or physical functioning in non-overweight postmenopausal women with knee symptoms.

Postmenopausal women aged 50-85 (N=49) with a BMI < 25 kg/m2 with variable knee pain were recruited as a convenience sample from the University Health Network. Those with rheumatoid arthritis, joint replacements, and/or contraindications to MR/CT imaging were excluded. Participants completed proton-density-weighted MRI scans in sagittal view which provided ten contiguous 3mm-thick slices. The IPFP was manually segmented using Slice-o-matic and volume was generated. Participants completed a peripheral CT scan in which four transaxial 2.3 mm thick slices were prescribed at each knee compartment and IPFP areas were manually contoured. Knee pain was evaluated using the Intermittent and Constant Osteoarthritis Pain (ICOAP) and the Knee Osteoarthritis and Outcome Score (KOOS) questionnaires (pain, functionality, and quality of life). Participants completed a 30-sec chair stand test, a 40m walk test, and a 9-step stair climb test. General linear models examined the relationship between ICOAP/KOOS scores or physical function tests and each of the CT IPFP areas in each compartment, and MR IPFP volume. Age, BMI, and pain medication were used as covariates.

A 1cm2 larger pQCT IPFP area in the medial tibial condyle was associated with a 4.7 point lower KOOS score in knee-specific pain, 3.6 lower daily activity, and 7.3 lower quality of life (P-values 0.034, 0.039, 0.029, respectively) while a 1cm3 higher MR IPFP volume related to a 1.79 and 1.50 point higher score for intermittent knee pain meaning more pain, respectively. There was no association between IPFP volume and physical function tests.

A possible explanation for higher IPFP volume correlating with higher pain scores is that a higher volume may in fact contribute more inflammation to the knee joint causing more pain. As no association was found with physical functioning, IPFP may be more involved in the inflammatory pathway rather than mechanically.

KEYWORDS

Infrapatellar fat pad (IPFP), segmentation, MRI, CT, pain scores, physical functioning