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IMPACT OF A PERSONALIZED CARE APPROACH ON 3D GAIT IMPAIRMENTS IN KNEE OSTEOARTHRITIS PATIENTS (A CLUSTER RANDOMIZED CONTROLLED TRIAL)

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Purpose: Knee osteoarthritis (OA) often leads to gait kinematic impairments. The knee kinesiography exam, measuring three-dimensional (3D) knee kinematics during gait on a treadmill, allows to objectively identify gait impairments (GIs) in order to provide recommendations for a personalized care approach (targeted home-based exercises, bracing, etc.) to correct these impairments. A clinical trial showed that this approach can lead to significant improvement in function and pain reduction after 6 months compared to a control group. The aim of this study was to assess the impact of this personalized care approach (PCA) on 3D mechanical GIs in knee OA patients compared to a control group.

Methods: Primary care physicians in this cluster randomized controlled trial in the Province of Quebec (Canada) were asked to recruit patients with a clinical diagnosis of knee OA. Patients were included if 1) knee OA was the main cause of their knee pain, 2) they rated their worst pain in the past 7 days $\geq$ 4 on a 0-10 pain intensity scale, 3) they had a Kellgren-Lawrence grade $\geq$ 2 on radiographs. Eligible patients from a same primary care clinic were randomized to the same group: 1- a control group (usual care), 2- a group with the PCA, and 3- a group with the PCA + an educational program. In all of the three groups, primary care physicians managed their patients according to their individual needs, but only physicians from groups 2- and 3- had access to the recommendations for the PCA. These were treatment recommendations (e.g. bracing, specific activities, etc.) and tailored home exercises targeting the GIs identified with the knee kinesiography results. Patients from group 3- also had a one-hour educational session on knee OA self-management and two follow-up group meetings with a therapist (to answer their questions, regulate the nature and intensity of their exercises, etc.). For all patients, we assessed the presence of 14 known GIs in knee OA at baseline and 6-month follow-up (see Table 1). If a GI changed from "Present" at baseline to "Absent" at 6 months, we considered it as improved. If it changed from "Absent" to "Present", it was considered deteriorated. In order to summarize all GIs' evolution in a single outcome, we calculated for each patient a global evolution ratio (GER) corresponding to the ratio of the sum of improved GIs over the sum of deteriorated GIs. The GER status was defined as "DETERIORATION" ($\leq$0.5), "STABILIZATION" (0.5<GER<1.5), or "IMPROVEMENT" ($\geq$1.5). Chi-square tests were used to assess between-group differences on the GER status.

Results: 221 patients from 55 clinics participated. There were 61.1% women, the mean age was 63 years (95%CI: 62;64), and the mean BMI was 29.5 kg/m^2 (95%CI: 28.7;30.2). There were no differences between groups at baseline on sociodemographic characteristics and patients were equally distributed between the three groups (1-Control: N=71; 2-PCA: N=72; 3-PCA+Education: N=78). There was a significant difference between the three groups on the GER status (p=0.03). Post-hoc analysis showed that both groups who received the PCA significantly differed from the control group (both p<0.05). As shown in Figure 1, the proportion of patients with an improved GER was higher in both groups with the PCA (Group 1: 28.2% vs Group 2: 37.5% and Group 3: 38.5%), and the proportion of patients with a deteriorated GER was lower (Group 1: 50.7% vs Group 2: 26.4% and Group 3: 30.8%) compared to the control group. There was no significant difference between the two groups with the PCA (p=0.75).

Conclusions: Results suggest that a personalized care approach including tailored treatment recommendations (e.g. exercises, orthoses, etc.) to correct GIs can have a positive impact on 3D knee kinematics during gait after 6 months. Patients from both groups who had access to this PCA showed significantly less deterioration, and more stabilization and improvement of their gait impairments compared to the control group. There was no difference between groups 2- and 3-, suggesting that this approach may have an effect on gait impairments even without an additional education program. The proposed global evolution ratio showed interesting results but further analyses are needed to specifically identify which GIs' evolutions have the most impact on patient outcomes.

Table 1 - The known gait impairments in knee osteoarthritis patients

Sagittal plane:	Knee flexum at heel strike
	Knee in extension at heel strike
	Limited flexion excursion during loading
	Fixed flexion during stance
	Limited maximum flexion during swing
	Limited sagittal plane range of motion
Frontal plane:	Varus thrust during loading
	Varus alignment at heel strike
	Varus alignment during stance
	Valgus thrust during loading
	Valgus alignment at heel strike
	Valgus alignment during stance
Transversal plane:	External tibial rotation at heel strike
	Internal rotation of the tibia in regards to the femur during loading

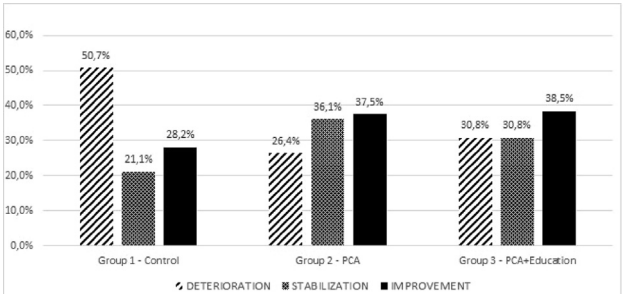

Figure 1 - The proportion of patients with each global evolution ratio' status in each intervention group

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PGC1A IS REQUIRED FOR CHONDROCYTE METABOLISM AND CARTILAGE HOMEOSTASIS

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Purpose: It is widely accepted, that chondrocyte metabolism is restricted by low rates of anaerobic glycolysis due to a limited source of oxygen and nutrient diffusion from the surrounding synovial fluid. Thus, the roles of mitochondria in osteoarthritis (OA) are still not completely understood. However, mitochondria are important regulators for cellular function and survival and their dysfunction may mediate several pathways involved in cartilage degradation including oxidative stress, defective chondrocyte biosynthesis, cartilage matrix calcification and matrix catabolism as well as chondrocyte apoptosis. Peroxisome proliferative-activated receptor gamma coactivator 1 alpha (PGC1 alpha) is known as a "master regulator" of mitochondrial biogenesis. PGC1 alpha is a transcriptional co-regulator involved in the regulation of lipid metabolism and enhancement of mitochondrial volume and activity via its interaction with numerous nuclear transcription factors. Alterations in PGC1 alpha content or activity have been reported in several disorders associated with oxidative stress. Recent studies showed that PGC1-alpha is downregulated in both aging and post-traumatic model of OA in mice. Furthermore, they showed an increased release of nitric oxide and MMPs in response to pro-inflammatory cytokines upon knockdown of PGC1 alpha *in vitro*. However, the effect of chondrocyte-specific PGC1 alpha loss in terms of cartilage development, maintenance and health *in vivo* has not been addressed

Methods: *In vitro*: To examine chondrocyte mitochondrial activity, we isolated immature articular chondrocytes (iMACs) from 5day old *Pgc1α$^{fl/fl}$; Col2-Cre* knockout and control mice and performed MitoStress Tests using a Seahorse XFe-24 analyzer. Chondrocytes were seeded at a density of $0.4*10^5$ per well in a XFe-24 plate and cultured overnight prior to the test. Cells were treated with 1.5μM Oligomycin (ATP synthase inhibitor), 3μM FCCP (disruption of mitochondrial membrane potential) and 0.5μM rotenone-antimycin A (mitochondrial complex III inhibitor) during the test and oxygen consumption rate (OCR) as well as

extracellular acidification rate (ECAR) were recorded. In addition, iMACs were incubated with the cationic dye JC-1 for 10min at 37°C in order to analyze differences in mitochondrial membrane potential between knockout and control cells using fluorescence microscopy. To analyze changes in chondrocyte gene expression and possible downstream targets we isolated RNA from knockout and control iMAC cultures and performed qRT-PCR using specific primers for genes involved in mitochondrial function as well as cartilage marker genes. *In vivo:* Hind limbs of *Pgc1α$^{fl/fl}$; Col2-Cre* knockout and control male mice were harvested at different developmental stages and during aging (P0, P21,6,12 and 18 Months) and processed for histological analysis.

Results: Pgc1α$^{fl/fl}$; Col2-Cre knockout chondrocytes show a significant decrease in spare respiratory capacity and reduced mitochondrial membrane potential compared to control cells. qPCR analysis confirms reduced PGC1alpha mRNA expression (more than 90%) in KO cells and showed no apparent compensatory effect by the highly homologous family member PGC1beta. Cartilage markers Sox9, Col2, ColX and PRG4 are expressed at reduced levels in KO cells. Interestingly, the expression of RORalpha is strongly increased in mutant cells. *Pgc1α$^{fl/fl}$; Col2-Cre* mice develop mild developmental phenotypes including delayed secondary ossification and growth plate disorganization. At 18 months knockout mice develop end stage OA with complete loss of cartilage and severe subchondral sclerosis and osteophyte formation, while control mice show moderate OA.

Conclusions: PGC1alpha is important to maintain chondrocyte metabolic flexibility and regulates tissue maintenance. The decrease in chondrocyte mitochondrial spare respiratory capacity as well as the reduced mitochondrial membrane potential in the absence of PGC1 alpha makes cells less resistant to stress, including oxidative stress, resulting in a more severe OA phenotype during ageing. In general, our study illustrates the importance of chondrocyte metabolic activity during cartilage development and maintenance and suggest that the activation of PGC1alpha is a potential strategy to delay or prevent the development of OA.

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MICRORNA-29A PROTECTS AGAINST CHONDROCYTE SENESCENCE AND OSTEOARTHRITIS DEVELOPMENT THROUGH REPRESSING FOXO3 METHYLATION

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Purpose: Osteoarthritis (OA) of the knee accounts for a leading cause of disability of the elderly. Chondrocyte loss is a prominent feature of articular cartilage damage in the development of OA. Dysregulated epigenetic pathways, like microRNA and DNA methylation, are shown to repress extracellular matrix synthesis and survival of chondrocytes. This study is aimed to characterize what the role microRNA-29a (miR-29a) may play in chondrocyte senescence and OA development.

Methods: OA and non-OA cartilage specimens were harvested from patients who required total knee arthroplasty. Mice deficient in miR-29a and mice overexpressing miR-29a were subjected to collagenase- and destabilized medial meniscus (DMM)-mediated OA. Articular injury and osteophyte formation were quantified using OARSI grading system and μCT imaging. miR-29a transcripts, senescence markers p16^{INK4a} and p21$^{Waf/cipl}$, along with anti-aging regulator forkhead box class 3 (FOXO3) and DNA methylation marker 5-methylcytosine (5mC) in specimens and chondrocyte cultures were probed using in situ hybridization and RT-quantitative PCR. The methylation status of FOXO3 promoter was quantified using methylation-specific PCR.

Results: Chondrocytes in human OA specimens showed increased cell senescence markers p16^{INK4a} and p21$^{Waf/cipl}$ immunostaining and DNA methylation marker 5mC immunostaining, whereas anti-aging maker FOXO3 and miR-29a signaling were decreased as compared to non-OA specimens. Serum miR-29a levels were decreased with age of patients with knee OA. Aged miR-29a knockout mice showed severe OA signs, like articular cartilage damage along with osteophyte formation and subchondral bone loss. Of note, miR-29a transgenic mice exhibited mild OA development in collagenase and DMM-injured knee joints as compared to severe cartilage damage in wild-type mice. In vitro, forced miR-29a expression attenuated senescence marker expression and extracellular matrix loss in inflamed chondrocytes, whereas miR-29a knockdown accelerated chondrocyte aging. Mechanistically, miR-29a targeted DNA methyltransferase (DNMT3a) expression, downregulating FOXO3 promoter methylation to maintain FOXO3 signaling.

Conclusions: miR-29a loss is relevant to DNA hypermethylation and chondrocyte senescence in human knee OA and accelerates OA development in mice. miR-29a is indispensable in slowing down senescence program in chondrocytes through downregulating DNMT3a hypermethylation of FOXO3 promoter. Collective analysis offers a productive insight into how microRNA regulates DNA methylation to maintain chondrocyte function. This study also sheds new light onto the epigenetic protection against chondrocyte senescence in the development of OA.

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COMPARISON OF RADIOGRAPHIC AND MRI OSTEOARTHRITIS DEFINITIONS AND THEIR COMBINATION FOR PREDICTION OF TIBIAL CARTILAGE LOSS, KNEE SYMPTOMS AND TOTAL KNEE REPLACEMENT - A LONGITUDINAL STUDY

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Purpose: In the absence of a clear definition of osteoarthritis (OA) using magnetic resonance imaging (MRI) features, the Osteoarthritis Research Society International (OARSI) OA Imaging Working Group developed a definition of MRI-defined structural OA (MRI-OA) by incorporating MRI changes using a Delphi approach, but this needs validation. This study aimed to assess whether MRI-OA is superior to the radiographic definition of OA (ROA) by describing their value for predicting tibial cartilage loss, knee pain and disability and total knee replacement (TKR) in a population-based cohort.

Methods: In a prospective, population-based older adult cohort, 574 participants (mean 62 years, 49% female) with baseline data on both MRI and x-ray scans of the right knee were included in this study. ROA and MRI-OA at baseline were defined according to the OARSI atlas and a published Delphi exercise, respectively. A 1.5T MRI of the right knee was also performed at 2.6 and 10.7 years. Tibial cartilage volume was measured over 2.6 and 10.7 years. Knee pain and disability were assessed using the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at baseline, 2.6, 5.1 and 10.7 years. TKR of the right knee over 13.5 years was identified with linkage to the Australian Orthopaedic Association National Joint Replacement Registry. The value of ROA (vs. no ROA), MRI-OA (vs. no MRI-OA) and the combination of them (vs. those with neither) for predicting tibial cartilage loss, the onset and progression of knee symptoms and risk of TKR was evaluated using multivariable linear regression or log-binomial regression models.

Results: Of participants included, 8% had ROA alone, 15% had MRI-OA alone, 13% had both ROA and MRI-OA. Having ROA (vs. no ROA) and MRI-OA (vs. no MRI-OA) predicted greater tibial cartilage loss over 2.6 years (-75.9 and -86.4 mm^3/year, respectively) and higher risk of TKR over 13.5 years (Risk Ratio [RR]: 15.0 and 10.9, respectively). However, only MRI-OA predicted tibial cartilage loss over 10.7 years (-7.1 mm^3/year) and only ROA predicted the onset and progression of knee symptoms (RR: 1.32-1.88). Compared to participants with neither MRI-OA nor ROA, those with ROA alone showed an increased risk of knee symptom progression over 10.7 but not 2.6 or 5.1 years (RR: 1.32-1.88) and those with MRI-OA alone had greater loss of tibial cartilage volume over 2.6 but not 10.7 years (-81.7 mm^3). Participants with either ROA or MRI-OA alone had an increased risk of TKR (6.4% and 3.6%, respectively; RR: 11.5 and 6.8, respectively) compared to those with neither (0.5%). In contrast, participants with both MRI-OA and ROA had the greatest loss of tibial cartilage volume (over 2.6 years: -116.1 mm^3/year; over 10.7 years: -11.2 mm^3/year) and the highest onset and progression of knee symptoms (RR: 1.75-2.89) and risk of TKR (25%, RR: 50.9).

Conclusions: The findings of this study suggest that the present MRI-defined OA using Delphi exercise is not superior to ROA for predicting structural or symptomatic OA progression but, its combination with ROA has much stronger predictive validity.