9
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

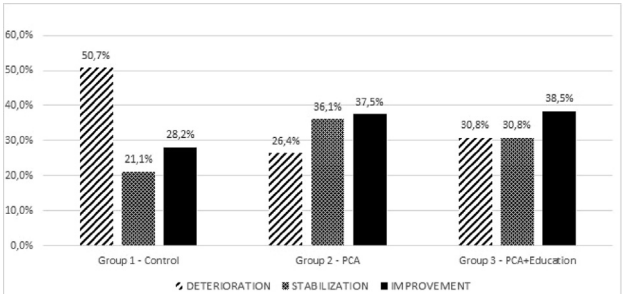

Figure 1 - The proportion of patients with each global evolution ratio' status in each intervention group

10
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