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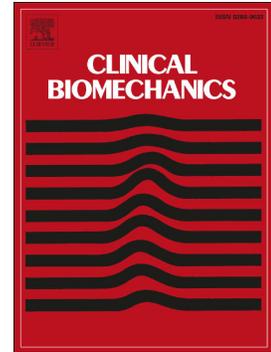
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## Accepted Manuscript

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**Subjects with medial and lateral tibiofemoral articular cartilage defects do not alter compartmental loading during walking**

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None of the authors have any conflict of interest to disclose

### **Author contributions**

- Conception and design - SVR, NK, CH, DVA, IJ
- Analysis and interpretation of the data - SVR, NK
- Drafting of the article - SVR, NK
- Critical revision of the article for important intellectual content - SVR, NK, CH, DVA,IJ
- Final approval of the article – SVR, NK, CH, DVA, IJ
- Provision of study materials or patients – SVR, NK, DVA
- Obtaining of funding – CH, IJ
- Collection and assembly of data – SVR, NK

**Abstract (Word count 241 of 250)**

*Background:* Healthy cartilage is essential for optimal joint function. Although, articular cartilage defects are highly prevalent in the active population and hamper joint function, the effect of articular cartilage defects on knee loading is not yet documented. Therefore, the present study compared knee contact forces and pressures between patients with tibiofemoral cartilage defects and healthy controls. Potentially this provides additional insights in movement adaptations and the role of altered loading in the progression from defect towards OA.

*Methods:* Experimental gait data collected in 15 patients with isolated cartilage defects (8 medial involvement, 7 lateral-involvement) and 19 healthy asymptomatic controls was processed using a musculoskeletal model to calculate contact forces and pressures. Differences between two patient groups and controls were evaluated using Kruskal-Wallis tests and individually compared using Mann-Whitney-U tests ( $\alpha < 0.05$ ).

*Findings:* The patients with lateral involvement walked significantly slower compared to the healthy controls. No movement adaptations to decrease the loading on the injured condyle were observed. Additionally, the location of loading was not significantly affected.

*Interpretation:* The current results suggest that isolated cartilage defects do not induce significant changes in the knee joint loading distribution. Consequently, the involved condyle will capture a physiological loading magnitude that should however be distributed over the cartilage surrounding the defect. This may cause local degenerative changes in the cartilage and in combination with inflammatory responses, might play a key role in the progression from articular cartilage defect to a more severe OA phenotype.

**Keywords:** contact forces – Cartilage defect– Gait – contact pressure – osteoarthritis

## 1. Introduction (Word count: 3468 of 4000)

Healthy knee hyaline cartilage is essential for optimally distributing load over the subchondral bone, reducing friction between the articulating bones and inherent to its physiology optimizing longevity of joint function. However, articular cartilage defects (ACD) following knee injury are highly prevalent in the active population, with approximately 36% of all athletes presenting full-thickness chondral defects(Flanigan et al., 2010). Often articular cartilage defects are accompanied by knee pain, swelling and loss of function, ultimately restricting the quality of life of the patients(Engelhart et al., 2012; Heir et al., 2010; Wondrasch et al., 2013). Due to the limited repair capacity of articular cartilage, the prognosis of full recovery is rather limited(Tetteh et al., 2012). As an articular cartilage defect may hamper joint homeostasis in the long term, the risk for osteoarthritis (OA) development is increased(Tetteh et al., 2012). Indeed, large cohort studies indicated that the majority of isolated cartilage defects in the knee (age >40years) progress to OA within 2 years when left untreated, and 30% of this population require a total knee replacement within 10 years(Davies-Tuck et al., 2008; Spahn and Hofmann, 2014; Wang et al., 2006). Therefore, surgical interventions that aim to restore the articular cartilage surface were developed, however long-term outcome of these interventions is still inadequate and a proportion of surgical interventions should even be discouraged according to some studies(Devitt et al., 2017; Mithoefer et al., 2009; Wondrasch et al., 2013). Therefore, conservative approaches aiming to slow down the progression from defect to OA (e.g. strength training to increase knee stability) are highly relevant(Wondrasch et al., 2013). These interventions focus on regaining joint homeostasis, knee stability and restoring normal load distribution, since aberrant mechanical load distribution is thought to contribute to OA development(Andriacchi and Favre, 2014; Wondrasch et al., 2013).

In knee OA and after ACL rupture, gait adaptations to reduce pain and discomfort were documented(Engelhart et al., 2012; Heir et al., 2010; Løken et al., 2009; Wondrasch et al., 2013). However, the role of adaptive movement strategies have only been scarcely studied in patients with isolated articular cartilage defects in the otherwise healthy knee. Gait adaptations following surgical intervention to restore isolated cartilage defects (more specific: matrix-induced autologous chondrocyte implantation (MACI)) were reported and suggested gait adaptations up to 12-months following treatment(Ebert et al., 2010, 2008). On the other hand, one recent study in untreated patients with articular cartilage defects reported no differences in knee reaction forces compared to controls after controlling for gait speed and quadriceps strength before any surgical intervention(Thoma et al., 2017). However, in this study, individual compartmental loading was not reported and the contribution of muscle and ligament forces on knee loading was neglected. Patient-specific gait analysis in combination with musculoskeletal modelling allows the analysis of knee joint loading in terms of compartmental contact forces and might be more sensitive to investigate changes in the knee loading distribution.

Therefore, the present study investigates if patients with an isolated articular cartilage defect in the tibiofemoral joint present movement adaptations that affects the load distribution in the knee. Our hypothesis was that patients with tibiofemoral articular cartilage defects would alter their gait pattern to unload the involved compartment, resulting in a decreased compartmental contact force and contact pressure. By documenting the mechanical joint environment following isolated cartilage defects, this paper furthers the insight in the role of mechanical factors in the progression from isolated articular cartilage defect to OA. This analysis will highlight the need to introduce movement adaptations or unloading bracing in patients with isolated cartilage defects in order to shift weight-bearing loading away from the affected

compartment, as part of conservative approaches to restore normal loading following articular cartilage defects to slow down the progression towards OA.

## **2. Methods**

### *2.1 Participants*

Fifteen patients with an isolated full-thickness articular cartilage defect ( $>1\text{cm}^2$ , ICRS-grade  $\geq 3$  BMI  $<35\text{kg/m}^2$  and age between 18 and 50 years) on the femoral condyle or tibial plateau were included in this study. Patients were subdivided in two groups according to defect location (i.e. medial ( $n = 8$ ) and lateral condyle ( $n = 7$ )). Patients were excluded when on medical imaging (MRI) degeneration of the cartilage, joint space narrowing ( $>50\%$ ), patellofemoral lesion, meniscal defect, or on physical examination uncorrected ligament instability, uncorrected axial malalignment ( $>5^\circ$ ), uncorrected patellar maltracking or instability, retrospective anamnesis tumor, infection, autoimmune inflammatory arthropathy were present or they had surgical intervention within 6 months prior to the study recruitment. To compare patients' data, nineteen healthy asymptomatic adults with no history of knee-injury were included when the absence of cartilage damage was confirmed by an experienced radiologist. All procedures were approved by the university hospital Leuven ethics committee and by the Cardiff & Vale University Health Board ethics committee and informed written consent was obtained from all participants.

### *2.2 Motion analysis*

During a standard motion analysis, three dimensional marker trajectories were recorded along with ground reaction forces (GRF) using ground-embedded force plates. Participants were measured in Leuven (Movements & posture Analysis Laboratory Leuven, KU Leuven) and in

Cardiff (Arthritis Research UK Biomechanics and Bioengineering Centre, Cardiff University). At center 1, marker trajectories were recorded using a 10-camera VICON system (Vicon, Oxford Metrics, UK, 100Hz). GRFs were recorded using three force plates (AMTI, Watertown, USA, 1000Hz). In total, 65 reflective markers were placed according to a full-body Plug-in-Gait marker-set, extended with additional anatomical markers on the sacrum, medial femur epicondyles and the medial malleoli and three marker clusters on the upper and lower arms and legs (Davis et al., 1991). At center 2, marker trajectories were recorded using a 9-camera Qualisys system (Qualisys, Qualisys Medical AB, Sweden, 120Hz). GRFs were recorded using four force plates (Bertec, Columbus, USA, 1080Hz). In total, 54 reflective markers were placed according to a full-body Helen-Hayes marker-set, extended with additional markers on the thigh, shank and foot (Kadaba et al., 1990). After a standing trial, all participants were instructed to walk at self-selected speed across the motion lab until at least three trials with valid force plate contact were captured. Before pooling data of the two different centers, consistency in kinematic and contact force data of control subjects between centers was statistically verified (Supplementary material S1 and S2).

Data from both centers was analyzed with an identical musculoskeletal modeling workflow: Tibiofemoral contact forces and pressures were calculated using a scaled musculoskeletal model, that was previously presented (Lenhart et al., 2015). It integrates an extended knee model, that allows 6 degrees of freedom (DoF) patellofemoral and 6 DoF tibiofemoral movement, in a generic full-body model (Arnold et al., 2010). Each leg included 44 musculotendon actuators spanning the hip, knee and ankle and 14 bundles of non-linear springs that represent the major knee ligaments and posterior capsule. A non-linear elastic foundation formulation was used to calculate the cartilage contact pressures, based on the penetration depth of the overlapping surface meshes of the contact model (Smith et al., 2016). The cartilage was modelled with a uniformly distributed thickness of 4mm tibiofemoral and

7mm patellofemoral(Draper et al., 2006; Eckstein et al., 2001; Hudelmaier et al., 2003). The elastic modulus and Poisson's ratio were assumed as 10MPa and 0.45, respectively(Adouni and Shirazi-Adl, 2014; Blankevoort et al., 1991; Li et al., 2001). This model was implemented in SIMM with the Dynamics Pipeline (Musculographics Inc., Santa Rosa, CA) and SD/Fast (Parametric Technology Corp., Needham, MA) to generate the multibody equations of motion.

At first, the generic model was scaled to the subjects' anthropometry. Next, joint angles (pelvic translations and rotations, hip flexion, hip adduction, hip rotation, knee flexion and ankle flexion) were calculated using inverse kinematics(Lu and O'Connor, 1999). Subsequently, the muscle forces and secondary knee kinematics (11 DoF, i.e. all except knee flexion) required to generate the measured primary hip, knee and ankle accelerations were estimated using the concurrent optimization of muscle activations and kinematics algorithm. In the optimization the weighted sum of squared muscle activations and contact energy were minimized(Smith et al., 2016). As only the knee flexion angle was used in the optimization, joint kinematics in the secondary knee DoF evolved as a function of muscle, ligament and contact forces(Lenhardt et al., 2015; Smith et al., 2016; Thelen et al., 2014).

### *2.3 Patient reported outcome measures*

The Knee Osteoarthritis Outcome Score (KOOS) was completed by all patients and control subjects prior to being assessed in the experimental motion analysis(Roos et al., 1998). Subscores included in the analysis were pain, symptoms, activities of daily living and quality of life.

### *2.4 Statistics*

For each trial, the stance phase was identified as the period in which the GRF exceeded 20N. Next, the magnitude and timing of the first and second peak (FP and SP) of the resultant total

tibiofemoral contact force was determined during the first and second half of the stance phase, respectively as well as the minimum force during single leg support (MS). Furthermore, the concomitant average and maximum pressure over the contact surface was analyzed. Each variable was determined for the total knee as well as for the medial and lateral condyle separately and were averaged over three trials. Additionally, the joint angles in the trunk, hip, knee and ankle at FP, SP and MS as well as their respective range of motion (RoM) and the joint moments in the hip, knee and ankle at FP, SP and MS were analyzed. Furthermore, the point of application of the total knee, medial and lateral contact force expressed in the local reference frame of the femur as well as the contact area at FP, SP and MS were analyzed. Joint moments were scaled to body mass, contact forces were scaled to bodyweight (BW). Between group differences were examined using a Kruskal-wallis test. When significant ( $p < 0.05$ ) differences were found, pairwise comparisons using Mann-Whitney U-tests with Bonferroni-corrected alpha levels were performed to determine if the patient groups were significantly different from the control group ( $\alpha_{BC} = 0.025$ ). All test were conducted in MATLAB (MATLAB 2016b, The Math Works, Inc., Natick, Massachusetts, USA). Finally, the difference in pressure distribution at FP, SP and MS between patients and healthy controls was determined (figure 2).

### **3. Results**

#### *3.1 Patient characteristics*

Both patient groups scored significantly worse self-reported subjective outcomes than the controls. Patients with lateral compartment involvement were significantly heavier, had higher BMI and walked slower than the healthy controls. A more detailed overview of group characteristics is presented in table 1.

### *3.2 Joint kinematics and kinetics*

Joint kinematics during walking were not significantly different between the healthy controls and patients presenting medial compartment involvement. Patients with lateral compartment involvement presented reduced hip adduction range of motion ( $9.83^\circ$  (SD  $1.94^\circ$ ) vs  $12.21^\circ$  (SD  $1.84^\circ$ ) in the control group,  $p = 0.013$ ), increased plantarflexion at the first peak ( $-8.25^\circ$  (SD  $3.35^\circ$ ) vs  $-1.74^\circ$  (SD  $5.86^\circ$ ) in the control group). Patients with medial compartment involvement presented an increased knee adduction moment at midstance ( $-0.19\text{Nm/kg}$  (SD  $0.07\text{Nm/kg}$ ) vs  $-0.11\text{Nm/kg}$  (SD  $0.04\text{Nm/kg}$ ) in the control group,  $p = 0.018$ ). The remainder of the joint moments were not significantly different between groups (figure 1). Figures of the joint angles and moments are provided in supplementary material S3 and S4.

### *3.3 Knee loading*

In patients with medial involvement, mean medial condyle pressure during midstance was significantly increased compared to healthy controls ( $4.38\text{MPa}$  (SD  $0.88\text{MPa}$ ) vs  $3.59\text{MPa}$  (SD  $0.51\text{MPa}$ ) in the control group,  $p = 0.01$ ). The remainder of the knee joint loading variables were not significantly different between patients with medial involvement and healthy controls (table 2). In patients with lateral compartment involvement, peak medial condyle contact force during loading response was significantly lower compared to healthy controls ( $1.54\text{BW}$  (SD  $0.18\text{BW}$ ) vs  $1.84\text{BW}$  (SD  $0.23\text{BW}$ ) in the control group,  $p = 0.008$ ). The remainder of the knee joint loading variables were not significantly different between patients with lateral involvement and healthy controls (table 2).

### *3.4 Loading location*

Point of application of the total knee, medial and lateral contact forces as well as the contact area were not significantly different between groups (supplementary material, S5 and S6).

Additionally, the contact pressure distribution on the femur was not significantly different compared to the contact pressure distribution observed in healthy controls (figure 2).

#### 4. Discussion

The current study evaluated cartilage loading during walking at self-selected speeds in patients suffering from isolated articular cartilage defects in an otherwise healthy joint and compared to a cohort of healthy controls with no joint symptoms. Cartilage loading was evaluated in terms of contact forces and pressures using musculoskeletal modeling and using patient-specific gait patterns. This allowed to evaluate if patient-specific gait adaptations, in response to articular cartilage defects alter the compartmental loading magnitude and location. This can provide further insight in the role of aberrant mechanical loading on the long-term increased incidence of OA in patients with an articular cartilage defect.

In line with previous observations, both cartilage defect patient groups in the present study reported significantly worse subjective feeling (Engelhart et al., 2012; Heir et al., 2010; Wondrasch et al., 2013). Gait adaptations, related to a pain-avoidance strategy were previously reported in OA-patients and patients following MACI to reconstruct articular cartilage defects (Ebert et al., 2010, 2008, Turcot et al., 2013, 2012). It was therefore expected that during walking similar adaptive strategies could be identified in patients with untreated articular cartilage defects to reduce loading on the involved compartment (Løken et al., 2010). In contrast, limited gait adaptations in the movement pattern were observed compared to asymptomatic controls. Comparable to OA patients, the knee adduction moment at midstance was increased in patients with medial compartment involvement (Landry et al., 2007; Meireles et al., 2016; Zeni and Higginson, 2009). However, and in contrast to early OA subjects, this increase in knee adduction moment did not result in significantly increased medial compartment contact forces and may therefore not play a key role in further cartilage

degeneration. This finding might be the result of the low sample size as well as the dependency of medial compartment loading to other kinematic and kinetic parameters (Adouni and Shirazi-Adl, 2014; Meireles et al., 2016; Walter et al., 2010). Therefore, it should be investigated if the previously reported kinematic and kinetic changes after cartilage reparative surgeries are merely a consequence of the open knee surgery or of the post-operative period without weight-bearing and with rehabilitation and if this might be indicative of an incomplete restoration of normal joint function 12 months after surgery (Ebert et al., 2010, 2008; Van Assche et al., 2010).

Walking speed of the patient group with lateral compartment involvement was significantly slower compared to the healthy asymptomatic controls. This decrease in walking speed can presumably explain the decreased peak medial contact force, observed in patients with lateral compartment involvement. In previous literature, patients with articular cartilage defects and after cartilage repair were found to decrease their self-selected walking speed presumably to avoid pain and symptoms, as well as to reduce loading in the knee induced by the momentum of gait, as increased walking speed was previously found to result in increased joint loading (Ebert et al., 2010, 2008; Thoma et al., 2017). During gait at self-selected speed, for patients with medial compartment involvement contact forces were indeed not different from the contact forces in healthy asymptomatic controls and modified movement patterns to unload the injured condyle could not be confirmed. Recently, no differences in joint reaction forces were observed between patients with articular cartilage defects and asymptomatic controls after controlling for walking speed and could further confirm the present findings (Thoma et al., 2017).

Therefore, we need to conclude that in the studied patient cohort with medial and lateral compartment involvement no significant differences in magnitude and loading location were found in the involved nor the uninvolved compartment. As loading magnitude was not

different, a comparable force magnitude needs to be distributed over the remaining cartilage surrounding the articular cartilage defect. This is of concern as in-vitro studies previously observed increased pressure at the defect rim posing additional stress on the remaining healthy cartilage(Kock et al., 2008; Raimondi and Pietrabissa, 2005). Furthermore, isolated cartilage lesions do not affect the loading location in the joint since neither the contact pressure distribution, nor the point of application of the contact forces was significantly changed between groups. In ACL-deficient knees altered contact locations were previously observed and were hypothesized to result in excessive loading of cartilage that is not adapted to the normal loading experienced during walking(Chaudhari et al., 2008; Van De Velde et al., 2009). This local increase in loading may disrupt cartilage homeostasis and consequently initiate degenerative changes.

Interestingly, in this population with isolated cartilage defects loading magnitude and location were not altered at the time of evaluation. Nevertheless, a portion of these patients will progress towards (early) OA(Davies-Tuck et al., 2008; Spahn and Hofmann, 2014; Wang et al., 2006). Altered loading is accepted to contribute to OA progression, since in patients with established OA altered joint moments and contact forces are suggested to contribute to further degeneration of the cartilage(Meireles et al., 2016). In contrast, in early OA patients knee moments and total knee loading were not significantly different(Meireles et al., 2016). Recently, it was shown that also in early OA patients small differences in joint kinematics resulted in altered medial-lateral load distribution and contact location(Meireles et al., 2017). Since the loading magnitude and location are not significantly altered in this population with isolated cartilage defects in an otherwise healthy joint included in this study, it may be important to investigate further and identify additional factors that may induce altered loading magnitude and location that will induce the altered loading conditions associated with early OA. Regarding this, the role of altered transverse plane kinematics and kinetics in the

presence of ligamentous laxity have previously been suggested as major contributing factors(Andriacchi et al., 2004; Meireles et al., 2017). However, in the present cohort, transverse plane kinematics and kinetics were still unaffected.

The results of the current study indicate that localized degenerative changes in the cartilage following isolated cartilage defects are not induced by altered compartmental loading or by altered contact locations. Since no gait modifications that unload the involved compartment were identified, it is likely that strain-induced local degenerative changes at the defect rim contribute to the progression from articular cartilage defect to a more severe OA phenotype. In support of this, a decrease in proteoglycans in the cartilage of the lesion rim and an increased amount of osteophytes were found 20 weeks after experimentally creating a femoral articular cartilage defect in rabbits(Lefkoe et al., 1993). Additionally to this, local degenerative changes in the cartilage surrounding the defect and cartilage degeneration will be further accelerated by the presence of inflammatory cytokines, proteases and deregulation of growth factors that will trigger catabolic responses of the chondrocytes and the surrounding musculoskeletal tissue(Hedbom and Häuselmann, 2002; Schulze-Tanzil, 2009). Therefore, the role of gait retraining and bracing should be further evaluated as part of conservative treatments to reduce the stress on the cartilage surrounding the defect to slow down the progression towards OA, especially in case patients do not present a voluntary strategy to unload the involved compartment.

Some limitations need to be considered when interpreting the results of this study. First, sample size of the patient cohort was limited. Given the heterogeneity of the patient group, in terms of sample characteristics, exact chondral defect locations and duration of defect presence, our results need to be confirmed by a larger sample. Secondly, despite careful selection, some patients received previous surgeries to the involved knee (on average 5.5 years before inclusion) and it is possible that, less-severe comorbidity might be present, which

may affect the variability of our findings. Thirdly, the unbalanced recruitment of patients between centers in combination with the small differences observed in joint kinematics between the asymptomatic control subjects of the two centers, have minimally biased the reported differences. In terms of the methodology, the model that was used in the current study comprises a generic knee model, with a uniformly distributed cartilage thickness. Consequently, the effect of a cartilage defect on the calculated contact pressure distribution is neglected. Lastly, the optimization algorithm used in the current study did not account for subject-specific muscle contractions. This would require the use of an EMG-driven modelling approach. Therefore, the observed deviations are mostly determined by deviations in joint kinematics and external forces. However, since co-contraction of the lower-limb muscles was not altered in patients with a cartilage defect, this effect is considered to be minimal (Coats-Thomas et al., 2013; Heiden et al., 2009; Hubley-Kozey et al., 2009; Thoma et al., 2016).

## **5. Conclusions**

Contrary to our expectations, patients with articular cartilage defects did not adapt their movement pattern to unload the injured femoral condyle during walking at self-selected speed. This indicates that the remaining healthy cartilage surrounding the defect should capture and distribute the loading. This may cause local degenerative changes in the cartilage, which in combination with inflammatory responses might play a key role in the progression from an articular cartilage defect to a more severe OA phenotype.

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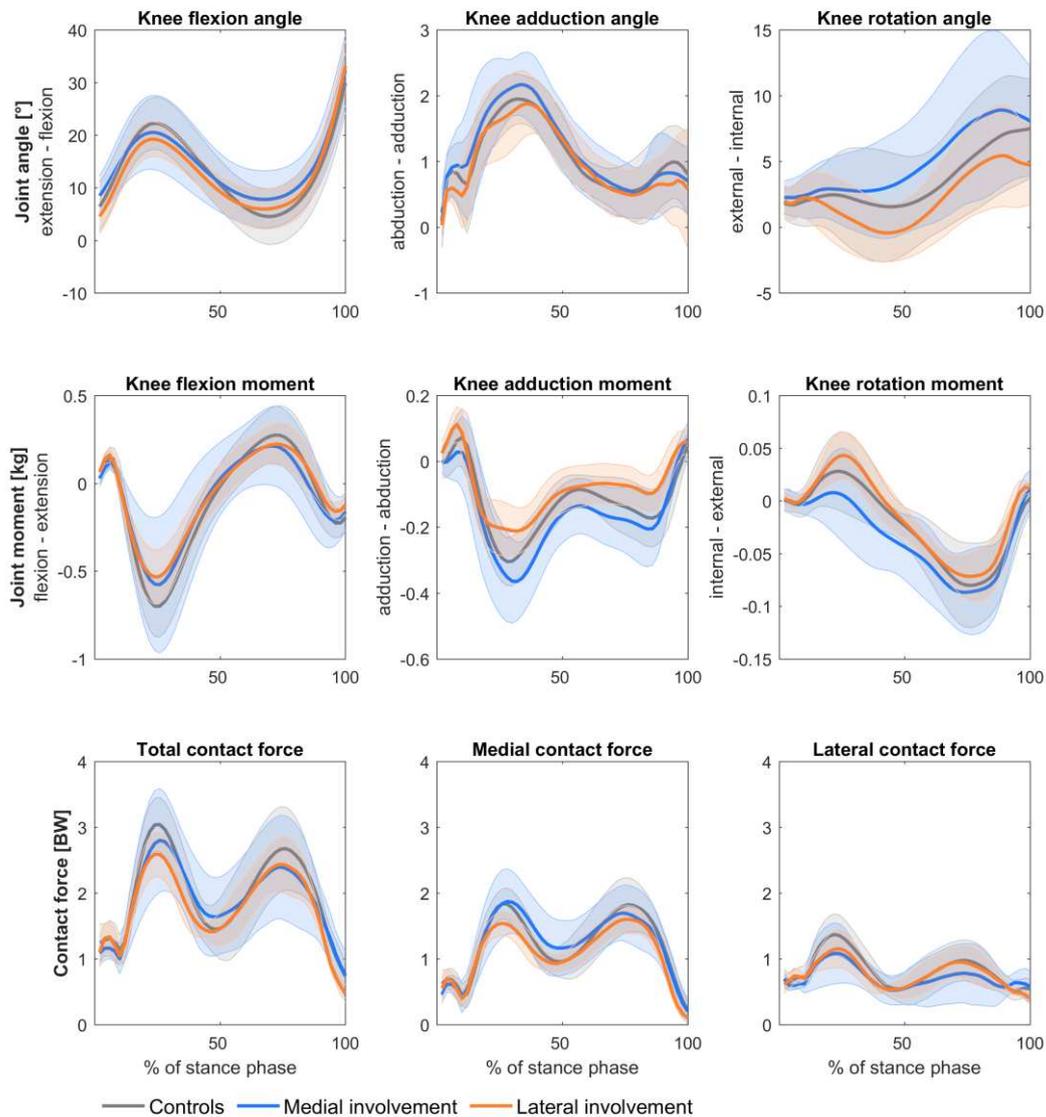
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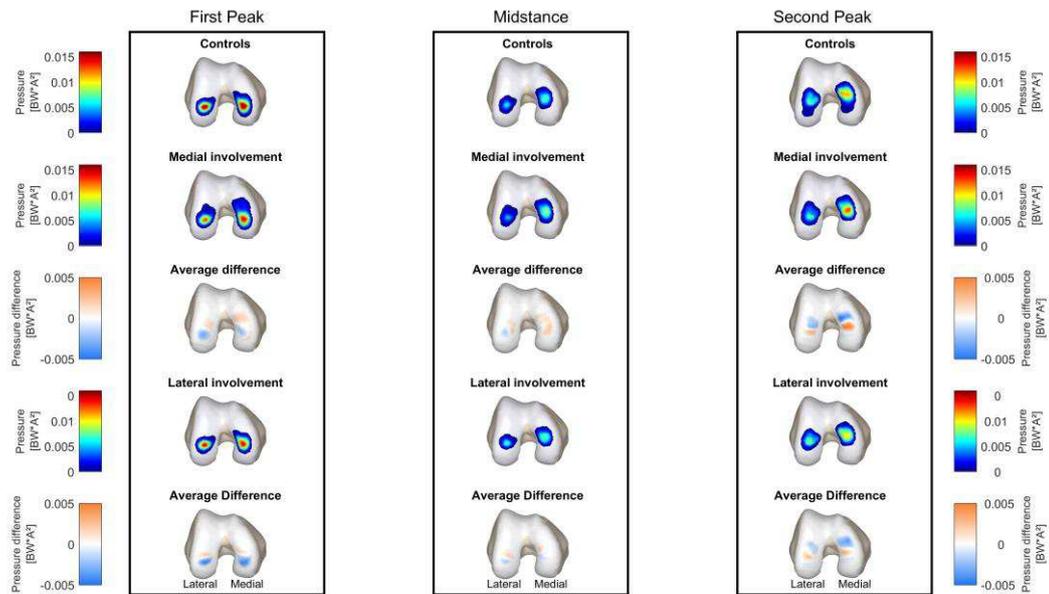
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## 7. Figures



**Figure 1. Average curves of the knee kinematics, kinetics and contact forces.**

Average patterns of the knee joint angles, knee moments and knee contact force. Gray area represents the healthy controls, blue the patients with medial compartment involvement and orange the patients with lateral compartment involvement.



**Figure 2. Contact pressure distribution**

Average contact pressure patterns at first peak, midstance and second peak for the healthy control group and the patients with medial and lateral compartment involvement. Furthermore, the average difference between the pressure pattern in patients and the healthy control pressure pattern is shown. Orange indicates more loading in the patient on that specific location, blue indicates decreased loading compared to the controls.

## 8. Tables

Table 1: Patient characteristics mean (SD)

	Controls	Medial- affected	Main effect	C vs Med	Lateral- affected	C vs Lat
<b>Mass (kg)</b>	71.1 (7.85)	74.33 (5.36)	0.022*	0.3	88.8 (16.67)	0.011*
<b>Height (cm)</b>	175.95 (7.33)	174.94 (4.16)	0.875	-	174.59 (6.12)	-
<b>BMI (kg/m<sup>2</sup>)</b>	22.95 (2.03)	24.29 (1.68)	< 0.001*	0.075	29.07 (4.82)	0.001*
<b>Age (Years)</b>	29.95 (5.9)	34.63 (8.62)	0.257	-	36.86 (12.23)	-
<b>Gender (M/F)</b>	10/9	6/2			6/1	
<b>Stance time (s)</b>	0.65 (0.04)	0.65 (0.05)	0.264	-	0.69 (0.05)	-
<b>Gait speed (m/s)</b>	1.36 (0.15)	1.33 (0.21)	0.072	-	1.18 (0.12)	0.021*
<b>KOOS</b>						
<i>Quality of life</i>	96.4 (4.63)	52.5 (32.59)	< 0.001*	< 0.001*	64.57 (20.57)	0.002*
<i>Activies of daily life</i>	99.24 (1.79)	71.94 (21.64)	< 0.001*	< 0.001*	73.71 (23.15)	< 0.001*
<i>Symptoms</i>	98.98 (2.27)	56.02 (29.23)	< 0.001*	< 0.001*	61.14 (26.61)	< 0.001*
<i>Pain</i>	97.94 (4.26)	57.54 (30.19)	< 0.001*	< 0.001*	67.57 (21.24)	< 0.001*
<b>Measurement location</b>						
<i>Center 1</i>	15	5			0	
<i>Center 2</i>	4	3			7	
<b>Symptom duration (years)</b>						
	-	2.4			3.5	
<b>Previous surgery (n)</b>						
<i>Involved knee</i>	-	3			4	
<i>Non-involved knee</i>	-	1			0	
<b>Defect location (n)</b>						

<i>Anterior</i>	-	4	2
<i>Middle</i>	-	3	1
<i>Posterior</i>	-	0	2
<i>Not specified</i>		1	2

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Table 2: Mean (SD) of the loading variables.

<b>First peak</b>	Controls	Medial-affected	Main effect	C vs		C vs Lat
				Med	Lateral-affected	
<b>Total knee</b>	Average (SD)	Average (SD)	p-value	p-value	Average (SD)	p-value
<i>Contact force [BW]</i>	3.09 (0.39)	2.97 (0.7)	0.063	-	2.62 (0.33)	-
<i>Mean pressure [MPa]</i>	6.096 (0.492)	6.056 (1.187)	0.957	-	6.118 (1.086)	-
<i>Max pressure [MPa]</i>	14.371 (1.511)	13.795 (2.412)	0.824	-	14.607 (3.465)	-
<b>Medial Condyle</b>						
<i>Contact force [BW]</i>	1.84 (0.23)	1.92 (0.49)	0.039*	0.614	1.54 (0.18)	0.008*
<i>Mean pressure [MPa]</i>	6.088 (0.516)	6.377 (1.317)	0.851	-	6.103 (0.856)	-
<i>Max pressure [MPa]</i>	12.904 (1.214)	13.358 (2.748)	0.957	-	13.288 (2.137)	-
<b>Lateral Condyle</b>						
<i>Contact force [BW]</i>	1.35 (0.29)	1.15 (0.33)	0.229	-	1.16 (0.29)	-
<i>Mean pressure [MPa]</i>	6.001 (0.848)	5.501 (1.285)	0.661	-	6.096 (1.557)	-
<i>Max pressure [MPa]</i>	12.998 (1.81)	11.709 2.931)	0.695	-	13.565 (4.04)	-
<b>Midstance</b>						
<b>Total knee</b>						
<i>Contact force [BW]</i>	1.2 (0.38)	1.45 (0.67)	0.454	-	1.25 (0.33)	-
<i>Mean pressure [MPa]</i>	3.329 (0.422)	3.864 (0.723)	0.05	-	3.616 (0.507)	-
<i>Max pressure [MPa]</i>	7.348 (0.97)	8.758 (1.792)	0.123	-	7.714 (1.309)	-
<b>Medial Condyle</b>						
<i>Contact force [BW]</i>	0.82 (0.22)	1.09 (0.46)	0.061	-	0.85 (0.19)	-
<i>Mean pressure [MPa]</i>	3.592 (0.516)	4.383 (0.883)	0.021*	0.01*	3.895 (0.545)	0.133
<i>Max pressure [MPa]</i>	7.063 (1.088)	8.722 (1.844)	0.058	-	7.375 (1.05)	-
<b>Lateral Condyle</b>						
<i>Contact force [BW]</i>	0.42 (0.21)	0.4 (0.28)	0.416	-	0.45 (0.2)	-
<i>Mean pressure [MPa]</i>	2.793 (0.539)	2.762 (0.733)	0.299	-	3.134 (0.638)	-
<i>Max pressure [MPa]</i>	5.94 (1.169)	5.639 (1.401)	0.084	-	6.945 (1.529)	-
<b>Second peak</b>						
<b>Total knee</b>						
<i>Contact force [BW]</i>	2.77 (0.65)	2.52 (0.81)	0.317	-	2.48 (0.41)	-
<i>Mean pressure [MPa]</i>	5.073 (0.583)	5.381 (0.511)	0.202	-	5.316 (0.504)	-

<i>Max pressure [MPa]</i>	11.608 (1.834)	12.194 (1.378)	0.542	-	11.806 (1.272)	-
<b>Medial Condyle</b>						
<i>Contact force [BW]</i>	1.87 (0.39)	1.77 (0.44)	0.16	-	1.61 (0.22)	-
<i>Mean pressure [MPa]</i>	5.686 (0.781)	6.135 (0.617)	0.277	-	5.87 (0.535)	-
<i>Max pressure [MPa]</i>	11.534 (1.849)	12.134 (1.359)	0.489	-	11.806 (1.272)	-
<b>Lateral Condyle</b>						
<i>Contact force [BW]</i>	1.02 (0.34)	0.84 (0.48)	0.562	-	0.98 (0.25)	-
<i>Mean pressure [MPa]</i>	4.152 (0.626)	4.047 (0.838)	0.271	-	4.574 (0.608)	-
<i>Max pressure [MPa]</i>	8.368 (1.144)	8.515 (1.657)	0.259	-	9.371 (1.294)	-

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**Highlights**

- Cartilage defects did not affect gait kinematics and kinetics of the lower limbs
- Compartmental loading is not altered in presence of an isolated cartilage defect
- Changes in the surrounding cartilage may contribute to osteoarthritis progression

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