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Knee internal contact force in a varus malaligned phenotype in knee osteoarthritis (KOA)

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SUMMARY

Purpose: Multiple phenotypes characterized by different disease mechanisms have been hypothesized to explain the large variability in the knee osteoarthritis (KOA) population. The purpose of this study was: to estimate and compare the medial and lateral knee compression forces (CF) during gait of three subgroups of KOA subjects characterized by different alignment and cartilage disruption patterns.
Methods: A secondary data analysis was conducted on a sample of 39 KOA subjects and 18 controls (C). The patients were classified in the different groups according to the following criteria:
Varus medial disease (VMD) (12): varus alignment and predominant medial cartilage degeneration Varus generalized disease (VGD) (17): varus alignment and cartilage degeneration that extends to the lateral compartment.
Neutral alignment (NA) (10): neutral alignment.
The total, medial and lateral CF corrected for body weight were estimated using an inverse dynamics model (AnyBody Modeling System, AnyBody Technology) during stance.
Results: The impulse of the medial compressive force (MCF) (overall effect of the CF over the stance) was significantly higher ($P < 0.01$) in the VMD compared to all the other groups. Peak MCF was higher in the VMD compared to all the other groups, but the difference reached significance only when compared to the VGD group ($P < 0.05$).
The results of the regression analysis showed a significant relationship in the VMD group between alignment and impulse of the MCF ($R^2 = 0.62$; $P < 0.01$). This relationship disappears in the other groups.
Conclusions: These findings suggest the existence of a phenotype characterized by increased MCF.

Introduction

Knee osteoarthritis (KOA) is one of the most common degenerative joint diseases and a major cause of disability in the world[1,2]. KOA is a multi-factorial disease initiated by biological, morphological and biomechanical factors[3]. It is thought that various phenotypes, characterized by different disease mechanisms, should be identified in the KOA population[4,5]. The identification of KOA phenotypes would allow for targeted treatment; whereby subgroups of patients characterized by distinct disease mechanisms may demonstrate treatment effects which may otherwise be lost when looking at KOA as a whole[6].

Previous research has shown that knee malalignment is a key factor in a hypothesized KOA phenotype characterized by disrupted biomechanics[7,8]. In particular, knee varus malalignment has been found to be associated with a greater risk of medial disease[9,10] and increased moments around the knee, commonly measured through the knee adduction moment (KAM)[11–14]. Despite this, previous research has failed in identifying significant differences in the knee compressive force (CF) between a group of subjects with varus alignment and medial KOA and a group of controls[15]. Moreover, biomechanical interventions (e.g., lateral

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wedged insoles; knee braces) aiming at unloading the medial compartment showed inconclusive results when tested on these subjects[16]. A possible explanation is that subjects with varus alignment, medial disease and signs of cartilage degeneration extending to the lateral compartment may be characterized by different patterns of mechanical stress if compared to subjects with exclusive medial disease[5,17]. Indeed, it is not yet clear if subjects with varus alignment and predominantly medial disease have a higher medial compressive force (MCF) than subjects with KOA and normal alignment or subjects with varus alignment and a disease that spreads to the lateral compartment. Identifying and comparing subgroups of subjects who may respond better to biomechanical interventions may help the development of treatments to improve the load distribution and KOA progression in malaligned knees.

Therefore, the aims of this study were: (1) to compare the knee joint CF and medical resonance imaging (MRI) biomarkers in a group of subjects with varus malalignment and predominant medial disease (VMD) with a group of KOA subjects with varus malalignment and more generalized disease (VGD); a group of KOA subjects with neutral alignment (NA); and a group of controls (C); (2) to explore the relationship between alignment and MCFs across subgroups of subjects.

Methods

Sample selection

A secondary data analysis was performed on data from a sample of subjects collected at Glasgow Caledonian University from a previous study (www.clinicaltrials.gov NCT02314715). KOA subjects were included if they: have KOA diagnosis confirmed by a physician using American College of Rheumatology (ACR) criteria, are aged 40 years and over. Controls participants were included if they: have no history of unilateral/bilateral KOA, in the past 3 months had no current chronic/stable knee pain, are aged 40 years or over. Potential participants were excluded if they: had neuromuscular illness (e.g., Multiple Sclerosis, Parkinson's disease), have had knee surgery for KOA in the past 12 months (e.g., knee arthroplasty, arthroscopic debridement), have had injection to or around the knee, have insulin dependent diabetes, are unable to walk up and down the stairs. The original sample included 18 healthy controls (C) and 61 subjects with clinical diagnosed tibiofemoral KOA. For the purpose of the current study, subjects with a body mass index (BMI) higher than 40 were excluded due to the soft tissues artefacts error that may emerge from the 3D gait analysis ($n = 5$)[18,19]. Ten subjects were excluded because they had valgus alignment $\leq -2°$. Six subjects were excluded because they presented conditions that could significantly alter the load distribution during the gait (cane use [$n = 1$], contralateral total knee replacement [$n = 5$])[20]. One subject was excluded because it was not possible to obtain three sets of gait analysis data in which all the markers were visible. A total of 18 controls and 39 subjects were therefore used for the current study.

MRI

The most symptomatic knee of each subject was imaged using a 1.5T Siemens Avanto with i-pat 8 channel knee coil (pixel size varying from 0.41667 mm to 0.5625 mm, depending on the sequence). MRIs were assessed according to the Boston Leeds Osteoarthritis Knee Score (BLOKS) (cartilage lesions: $K = 0.73$; 95% CI 0.60–0.85; bone marrow lesion (BML): $K = 0.72$; 95% CI 0.58–0.87; meniscal damage: $K = 0.79$, 95% CI 0.40–1.00) by an experienced radiologist blinded to subjects' clinical characteristics and groups. Scans were taken the same day or within 2 weeks of the gait analysis assessment. Biomarkers, describing the size of cartilage loss and the size of full thickness lesions, were used to classify the patients in the three KOA groups (NA, VGD, VMD) The two scores were combined in a single number where the portion before the decimal point represents the score for the size of the lesion and the portion after the decimal point represents the score for the amount of full thickness cartilage loss (Table I). A BLOKS score equal or higher than 2.0 in the medial compartment and equal or lower than 1.0 in the lateral compartment was used as a cut-off to identify subjects with predominant medial disease. A BLOKS score equal or lower than 1.0 in the lateral compartment signifies that the cartilage degeneration involves less than 10% of the articular surface and that there are no full thickness lesions.

The presence of BML and meniscal damage assessed with the BLOKS score was also used to characterize the different groups. Size of BML by bone volume in percentage was used for the purpose of this study (BLOKS 0–3). BML scored 2 or higher were considered in the analysis as large BML. For the meniscal damage, we used dichotomous scores indicating the presence of meniscal tears, and meniscal maceration.

Gait analysis

Each subject's kinematic data during self-selected normal walking speed was recorded using an eight-infrared-camera system (Qualisys AB, Gothenburg, Sweden). Ground reaction forces were collected using a floor embedded force plate (9286BA, Kistler Group, Winterthur, Switzerland). Both systems were synchronized and data sampled at 120 Hz. An estimation of the Hip Knee Ankle (HKA) angle was carried out using the infrared camera following

Table I
Adapted BLOKS score

Size of cartilage loss as % of articular surface area	% of the cartilage loss that is full thickness	Combined score (size of cartilage loss and % of full thickness used in the current study)*	Description of the combined score
0	0	0.0	No lesions
1	0	1.0	<10% of region, no full thickness
1	1	1.1	<10% of region, <10% full thickness
2	0	2.0	10–75% of region, no full thickness
2	1	2.1	10–75% of region, <10% full thickness
2	2	2.2	10–75% of region, 10–75% full thickness
3	0	3.0	>75% of region, no full thickness
3	1	3.1	>75% of region, <10% full thickness
3	2	3.2	>75% of region, 10–75% full thickness
3	3	3.3	>75% of region, >75% full thickness

* The score describing the size of cartilage loss and the size of full thickness lesions were used to classify the patients in the three KOA groups (NA, VGD, VMD). The two scores were combined in a single number where the portion before the decimal point represents the score for the size of the lesion and the portion after the decimal point represents the score for the amount of full thickness cartilage loss (Table I).

the process described by Gibson *et al.* (2010) (Pearson's correlation coefficient between optical and radiographic frontal alignment measurements $r = 0.75$; intraclass correlation coefficient = 0.85)[21]. A standing reference pose was captured before the walking trials with 31 markers placed on palpable bony landmarks throughout the lower limb to define an anatomical reference frame for each segment. A set of 26 markers was used for tracking the dynamic trials (Additional File 1).

Data processing

The medial, lateral and total knee CF were estimated using an adaptation of the anatomically scaled model from Lund *et al.* and Marra *et al.* which showed a strong ability to predict instrumentally measured internal knee CFs ($R^2 = 0.73$ and $R^2 = 0.85$ respectively)[22,23]. Briefly, a stick-figure model was created based on markers on anatomical landmarks from the standing reference trial, which subsequently estimated joint kinematics through an inverse kinematics approach during the dynamic trials[24]. The joint morphology of the stick-figure, the estimated joint angles and measured ground reaction forces and moments were used as input to a lower extremity model based on the Twente Lower Extremity (TLEM) data set[25]. The generic musculoskeletal model was morphed to the joint morphology of the stick-figure based on a Radial Basis Function (RBF) interpolation scheme as explained in Lund *et al.*[22]. To estimate muscle and joint reaction forces, an inverse dynamic analysis approach was applied using muscle activities (muscle force divided by instantaneous muscle strength) cubed as muscle recruitment criterion subject to the dynamic equilibrium equations and inequality constraints ensuring that the muscles can only pull and not push. To account for the muscle discretization in the TLEM data set, a normalization factor based on the muscle physiological cross sectional area (PCSA) was applied. The model estimated the knee joint reaction forces and moments in a tibial coordinate system defined as described by Grood and Suntay[26]. Finally, the medial and lateral knee CFs were estimated based on the total knee CF and the abduction/adduction moment assuming moment arms as described by Seedhom *et al.*[27].

The medial, lateral and total peak CF and the CF impulse (overall effect of the CF) were calculated as the average of the medial, lateral and total peak CF and CF impulse during the three trial repetitions and during the stance phase, respectively. All the estimated forces were corrected for body weight (BM*9.81). All the simulations were run using the AnyBody Modeling System v. 6.0.5 (AnyBody Technology, Aalborg, Denmark).

Classification process

The KOA subjects were classified using MRI cartilage biomarkers assessed with the BLOKS (see Table I) and the HKA. The patients were classified in the different groups based on the following criteria: VMD group (12): varus alignment ($\geq 2^\circ$) and cartilage degeneration predominantly in the medial compartment (BLOKS $\geq$ 2.0 in the tibial or femoral medial compartment and BLOKS $\leq$ 1.0 in both femur and tibial lateral compartments). VGD group (17): varus alignment ($\geq 2^\circ$) and cartilage degeneration that extends to the lateral compartment (BLOKS > 1.0 in the lateral compartment or BLOKS lateral compartment $\geq$ BLOKS in the medial compartment). NA (10): neutral alignment ($-2^\circ < x < 2^\circ$).

Statistical analysis

Kruskal–Wallis test with post hoc Bonferroni correction was used to evaluate differences in demographic and disease characteristics. To examine between-group differences in the estimated knee CF, one-way analysis of covariance (ANCOVA) was used with walking speed included as a covariate. Assumptions for the use of the ANCOVA models were evaluated before running the analysis. Sidak post hoc correction and bias-corrected and accelerated bootstrap (1000 samples) were performed. Differences in the presence of BML and meniscal damage were assessed using a Fisher's exact test with Bonferroni correction for multiple comparisons. Due to the possibility that subjects classified in the VGD group may have a milder disease (e.g., medial and lateral compartment BLOKS score = 1.0) a sensitivity analysis was performed excluding subjects with maximal BLOKS score = 1.0. The relationship between alignment and medial compartment load was further analysed with a regression model, introducing group membership as a moderator (i.e., a variable that changes the size and/or direction of the relationship between two other variables). Bonferroni post hoc correction and bias-corrected and accelerated bootstrap (1000 samples) were performed. Assumptions for the use of the moderation model were evaluated before running the analysis. Statistical significance was set at $P < 0.05$, all the P values reported are adjusted for multiple comparisons. Statistics were performed with SPSS version 22 (IBM Corp., Armonk, NY).

Results

There was no difference in age and disease duration between groups (Table II). Subjects in the C group had the lowest BMI ($P = 0.019$ compared to the VGD group) all other combinations were not significant. The VMD had the worst alignment but no statistical difference was identified between the VMD and VGD group. The VMD subjects walked at the lowest speed ($P = 0.02$ compared to C and $P = 0.034$ compared to NA), all other combinations were not significant. All the subjects classified in the VGD group had a BLOKS score in the lateral compartment (either tibia or femur) $\geq$1.0. Seven subjects classified in the VGD group had mild cartilage degenerations (highest BLOKS score in either compartment = 1.0) and were therefore excluded in the sensitivity analysis.

The impulse of the MCF was significantly higher in the VMD compared to all the other groups ($P = 0.005$ C; 0.004 NA; 0.006 VGD group respectively) (Table III). The MCF peak was higher in the VMD compared to the VGD group ($P = 0.008$) (Fig. 1), all other combinations were not significant. No statistical differences were found in the lateral compartment CF impulse. The lateral compressive force (LCF) peak was significantly higher in the C ($P = 0.005$) when compared to the VGD and VMD ($P = 0.027$ and 0.003 respectively), while the NA group showed a higher LCF peak only when compared to the VMD ($P = 0.005$), all other combinations were not significant. The peak of the total CF was lower in the VGD group compared with controls ($P = 0.03$) which showed the highest peak. The VMD showed the highest impulse of the total CF, this difference was significant only compared to the VGD group ($P = 0.04$). Sensitivity analysis showed no differences with the main analysis.

Subjects in the VMD group showed a higher prevalence of meniscal maceration in the medial compartment compared to all the other groups (VMD: 92%, VGD: 28%, NA 10%, C: 6%; $P < 0.05$); and a higher prevalence of large BML in the tibia medial compartment (VMD: 83%, VGD: 29%, NA 0%, C: 6%) and in the femur medial compartment (VMD: 58%, VGD: 18%, NA 10%, C: 6%) compared to all the other groups ($P < 0.05$). No differences were identified for these features in the lateral compartment. No differences were identified in the prevalence of meniscal tears both in the medial (C: 15%, NA: 20%, VGD: 45%, VMD: 20%) and lateral (C: 22.2%, NA 30%, VGD 23.5%, 8.3%) menisci.

To test the hypothesis that the group membership moderates the relationship between medial CF impulse and knee frontal alignment, a hierarchical multiple regression analysis was

Table II
Demographic and disease characteristic

	C (1)		NA (2)		VGD (3)		VMD (4)	
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Height (cm)	168.2	10	161.5	22	161.5	18.0	170.2	13
Weight (kg)	67.5	15	72.8	23	78.8	35	79	35
BMI ($kg*m^{-2}$)	23.6[3]	4.9	24.7	7.1	29.6[1]	6.8	28.5	7.7
Age (years)	63	18.6	62.9	7.5	62.5	8.2	65.1	11.6
Alignment (degrees)	2.6[4]	4.48	0.4[3,4]	1.7	3.0[2]	3.0	6.3[1,2]	4.6
Symptoms duration (years)*	0.0	0.0	9.0	10.5	5.0	9.0	6.5	14.5
Walking speed (m/s)	1.32[3,4]	0.22[3]	1.24	0.25	1.13[1]	0.14	1.07[1,2]	0.19

IQR: interquartile range.
All: significantly different from all the other phenotypes ($P < 0.05$).
1: Significantly different from group 1 (C) ($P < 0.05$)
2: Significantly different from group 2 (NA) ($P < 0.05$).
3: Significantly different from group 3 (VGD) ($P < 0.05$).
4: Significantly different from group 4 (VMD) ($P < 0.05$).
* The analysis for symptoms duration has been run excluding the control group which has disease duration equal to 0 by definition.

Table III
Comparison of the compartmental compressive force

	C (1)		NA (2)		VGD (3)		VMD (4)	
	$Mean_{adj}$	SE	$Mean_{adj}$	SE	$Mean_{adj}$	SE	$Mean_{adj}$	SE
MCF impulse (Bw*s)	0.85	0.03	0.84	0.04	0.82	0.03	1.01[all]	0.04
MCF peak (Bw)	2.13	0.06	2.07	0.08	1.97[4]	0.06	2.30[3]	0.08
LCF impulse (Bw*s)	0.48	0.03	0.49	0.04	0.42	0.03	0.39	0.04
LCF peak (Bw)	1.44[3,4]	0.08	1.34[4]	0.1	1.13[1]	0.08	1.00[1,2]	0.1
Total CF impulse	1.33	0.04	1.33	0.06	1.24[4]	0.04	1.40[3]	0.05
Total peak	3.50[3]	0.10	3.40	0.12	3.10[1]	0.1	3.25	0.12

Adj: adjusted for walking speed.
SE: standard error.
MCF impulse and peak $P < 0.01$. Total compressive force impulse and peak $P < 0.05$.
Means presented in the table are adjusted for walking speed.
Bw*s: Body weight seconds.

conducted. In the first step, two variables were included: alignment and group membership. These variables accounted for a significant amount of variance in medial contact force impulse, $R^2 = 0.293$, $F = 11.19$, $P < 0.001$ (no heteroskedasticity present). To avoid potentially problematic high multicollinearity with the interaction term, the variables were centred and an interaction term between alignment and group membership was created[28]. Next, the interaction term between alignment and group membership was added to the regression model, which accounted for a significant proportion of the variance in medial CF impulse ($\Delta R^2 = 0.124$, $\Delta F = 11.26$, $P = 0.001$). Examination of the results showed an enhancing effect that group membership has on the relationship between alignment and medial impulse of the CF, with higher deformity being significantly related to higher medial load only in the VMD group, $b = 0.04$, 95% CI [0.018, 0.07], $t = 3.41$, $P = 0.0016$ (Table IV). This relationship disappears in the other malaligned group (Fig. 2).

Discussion

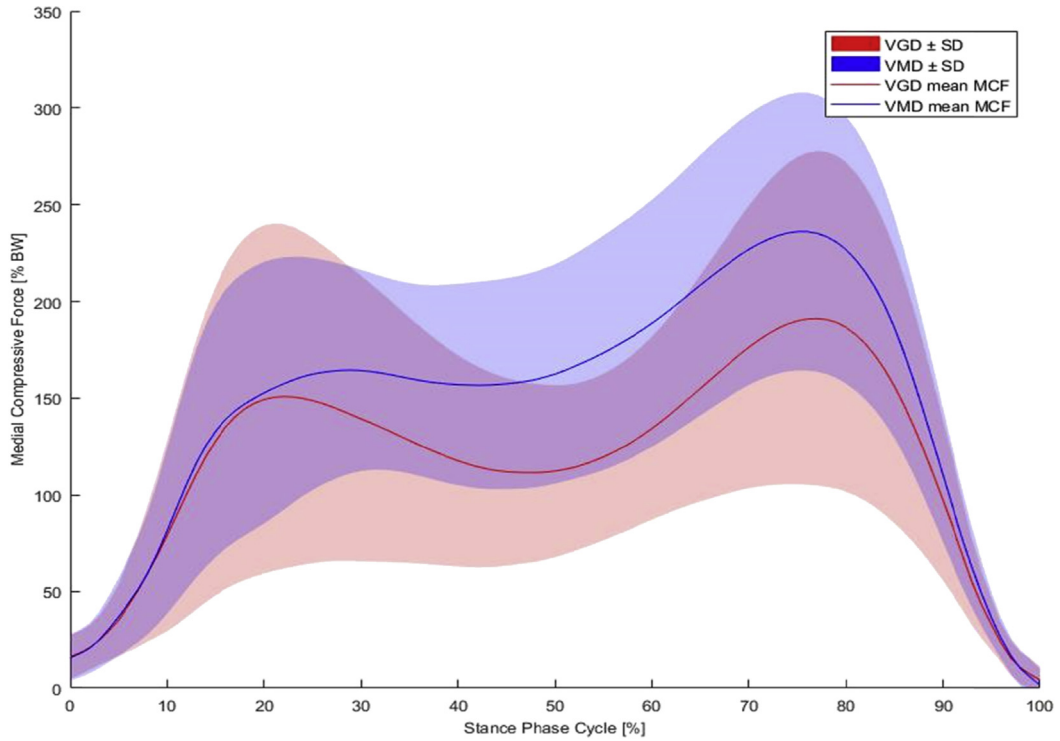
In this study, we explored the existence of a biomechanical KOA phenotype characterized by varus malalignment and predominant joint damage in the medial tibiofemoral compartment (VMD) and compared it to two groups of KOA subjects (NA, VGD) and a group of controls (C) to identify differences in load distribution and disease characteristics. The VMD showed the highest impulse of the MCF and the lowest impulse and peak of the LCF combined with a higher prevalence of meniscal maceration and large BML's in the medial compartment.

Knee alignment is thought to be one of the main factors that influence knee load distribution[29,30]. Despite this, our results suggest that varus malalignment, in the presence of lateral compartment degeneration, is not associated with CF of the medial compartment. Indeed, the moderation model clearly shows that knee static malalignment is associated with the medial CF only in the VMD.

Previous results identified no statistical difference in the peak of the MCF between KOA subjects and controls[15]. This may be due to the fact that only subjects with varus malalignment and predominant medial disease have a higher MCF, presenting a mechanically driven disease. To verify this hypothesis, we ran a sensitivity analysis where we compared the controls and NA group with a varus malaligned group formed by the combination of the VMD and VGD. This analysis showed no difference between the groups in the peak and impulse of the MCF. The same analysis showed no difference when we increased the cut-off to identify subjects with varus malalignment to 3°. This confirms the hypothesis that varus malalignment alone is not an effective indicator of increased medial load.

The impulse of the CF was more sensitive than the peak in identifying differences between the analysed groups. This finding suggests that the impulse may be a better variable to analyse the difference in load pattern between groups[31]. These results are in line with previous studies that identified an association between the impulse of the KAM, but not the peak, and disease progression[32,33]. The continuous load applied on the cartilage due to the inability to unload the medial compartment, as suggested by the higher impulse, may be more important for the disease progression than isolated force peaks[33–35].

BML and meniscal damage are common findings in the medial compartment of subjects with KOA and varus malalignment[36,37]. For this reason, it has been hypothesized that these features are a consequence of loading. The higher prevalence of large BML's and



The graph reports the mean medial compressive force of VGD and VMD groups during stance (initial contact to toe-off). The shaded areas represent the SD of the mean medial contact force at each point.

Fig. 1. Comparison of the MCF between VMD and VGD group during stance.

meniscal maceration in the medial compartment of the VMD seems, therefore, to support the notion that biomechanical alterations leading to an increase in MCF have a key role in the disease pathomechanics of this specific phenotype.

The difference in disease characteristics (MRI biomarkers) could be explained by a multi-stage disease model where longer disease duration is associated with worse damage (e.g., more meniscal degeneration, more BML, larger cartilage damage). No statistical difference in disease duration was identified between groups, suggesting that the VMD (no or mild lateral compartment disease) should not be considered as an earlier disease stage of the VGD group. Seven subjects classified in the VGD group showed a mild lateral disease with a BLOKS score = 1.0. Despite this, the sensitivity analysis showed that the differences in CF between VGD group and VMD were still significant when these subjects were excluded from the analysis.

The VMD showed a more severe malalignment compared to all the other groups, however, the difference was not statistically significant. Moreover, the alignment was positively associated with the impulse of the medial CF only in the VMD phenotype suggesting that higher varus deformity is associated with higher MCF in this phenotype only. Therefore, it may be hypothesized that alignment and increased medial load represent disease key factors in the VMD group while different factors may be responsible for the progression of the disease to the lateral compartment in the VGD group. However, whether differences in internal CF are clinically significant needs more exploration. Further studies looking at KOA incidence and progression are needed to understand the role of increased CF in the disease mechanics. In addition, biomechanical treatments aiming to reduce the load on the medial compartment should be tested in subjects with exclusive medial tibiofemoral

Table IV
Conditional effect of malalignment on the impulse of the MCF in the different groups

Groups	Effect	SE	*t*	*P*
NA	−0.007	0.019	−0.38	0.7
VGD	0.018	0.014	1.32	0.2
VMD	0.043	0.013	3.41	0.002

Effect: *b* value of the slope representing the relationship between alignment and medial contact force impulse in the different groups.

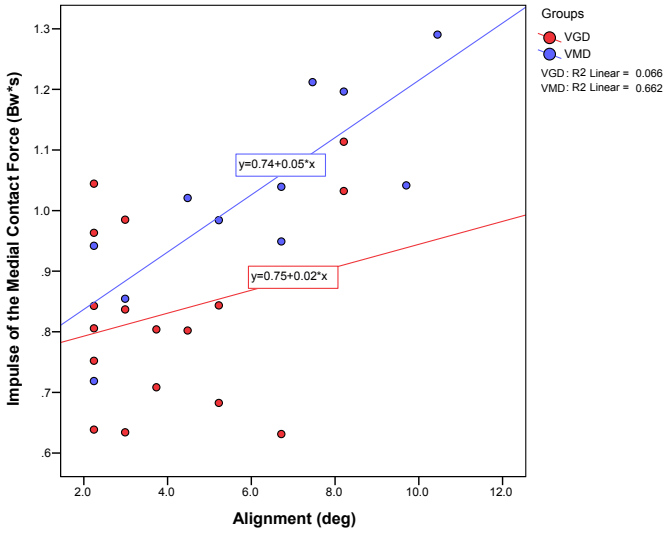


Fig. 2. Relationship between alignment and MCF in the VMD and VGD group. The blue and red boxes show the equations describing the respective lines. R2 statistics, describing the goodness of the models are reported on the side of the graph.

degeneration in order to understand their real effectiveness. This paper suggests that the use of MRI semi quantitative score and malalignment may be useful in the identification of these subjects. Despite the considerable cost of MRI, improved treatment allocation may maximise treatment effects and ultimately result in a more efficient use of resources.

Due to the cross-sectional study design, inferences of causality cannot be made. Malalignment alone may be responsible for the development of KOA in the VMD due to excessive mechanical load, but the between-group differences identified in this paper may also be a consequence of the existing knee pathology. Previous studies showed that varus malalignment is related to disease progression in the medial compartment. Whether malalignment alone is sufficient for determining the development of KOA remains inconclusive[7]. Moreover, the generalizability of these results can only be made with caution, and the external validity of these estimates will also be affected by the inclusion and exclusion criteria. In fact, the exclusion of 22 subjects from the original sample may have influenced the results increasing the likelihood of identifying subjects with higher medial load.

One of the limitations of this study is the absence of full limb radiographs to measure the HKA angle. However, the non-radiographic method used in this study was previously validated in obese individuals, reducing the error due to soft tissues artefacts[21]. Another limitation of this study is the use of a musculoskeletal model to estimate the knee CF due to the inability of directly measuring this in patients. In the current sample, only the impulse and the maximal peak of the knee CF were analysed. In healthy subjects, force curves during the stance phase of gait commonly show two peaks. However, the first peak could not be included in the analysis due to its absence in some subjects who showed a CF curve characterized by a single peak at a time point in the stance phase more commonly associated with the second force peak. Finally, the limited sample size may have hidden differences between the groups (e.g., difference in MCF between VGD and NA groups). To mitigate the possible bias emerging from a small sample size, we performed a bootstrapping analysis to increase the statistical power of the tests and limit the influence that extreme values may have on the mean of small samples.

Conclusions

In this study, we analysed the difference in knee CF between several KOA groups characterized by different knee alignment and cartilage degeneration patterns. Our finding showed that frontal alignment alone is not an effective indicator of increased medial CF. In fact, among the subjects showing varus malalignment, only the ones without lateral compartment degeneration were linked to increased medial CF suggesting the existence of a phenotype in which biomechanics may represent a key factor in the disease process. Moreover, our analysis showed that the impulse of the CF performs better than the maximal peak of the force in identifying subjects characterized by an increased medial load.

Targeting the right patient with the right treatment constitutes a priority in KOA care. The identification of a subgroup characterized by an increased medial load may be critical for developing a better treatment allocation which may ultimately result in an increased treatment response when biomechanical interventions are tested in this specific phenotype.

Authors' contribution

All persons designated as authors qualify for authorship. Each author participated in the work and made substantial contributions to all of following sections below:

(1) The conception and design of the study, or analysis and interpretation of data.
(2) Drafting the article or revising it critically for important intellectual content.
(3) Final approval of the version to be submitted.

Andrea Dell'Isola (andrea.dellisola@gcu.ac.uk) takes responsibility for the integrity of this work.

Conflict of interest statement

The authors are not in any conflict of interest with regards to the work presented in this paper.

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Supplementary data

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