The Knee 40 (2023) 122–134

Contents lists available at ScienceDirect

The Knee

journal homepage:

Targeted exercises can improve biomechanical markers in individuals with knee osteoarthritis: A secondary analysis from a cluster randomized controlled trial

Alix Cagnin [a,b], Manon Choinière [a,c], Nathalie J. Bureau [a,c], Madeleine Durand [a,c], Neila Mezghani [a,d], Nathaly Gaudreault [e], Nicola Hagemeister [a,b,*]

[a] *Research Centre of the Centre Hospitalier de l'Université de Montréal (CRCHUM), Montreal, Quebec, Canada*
[b] *Laboratoire de Recherche en Imagerie et Orthopédie de l'École de Technologie Supérieure (ÉTS), Montreal, Quebec, Canada*
[c] *Université de Montréal, Montreal, Quebec, Canada*
[d] *Université TÉLUQ, #1105, Montreal, Quebec, Canada*
[e] *Faculté de Médecine et des Sciences de la Santé, School of Rehabilitation, Sherbrooke Research and Development Centre, Université de Sherbrooke, Sherbrooke, Quebec, Canada*

A R T I C L E I N F O

Article history:
Received 31 August 2022
Revised 7 October 2022
Accepted 26 October 2022

Keywords:
Biomechanical markers
Knee OA
Targeted exercises
Clinical outcomes
Biomechanics
Gait

A B S T R A C T

Background: It is not clear whether exercise therapy significantly improves knee biomechanics during gait in osteoarthritis (OA) patients. This study aimed to determine whether targeted exercises based on a knee kinesiography exam improve biomechanical markers (BMs) compared with conventional primary care (CPC) management.
Methods: This was a secondary analysis of a cluster randomized controlled trial in which patients were assigned to one of three groups: (1) Control (CPC), (2) Exercise, and (3) Exercise&Education. Fourteen known BMs in knee OA patients were assessed. The primary outcome was the global evolution ratio (GER), which was calculated as the sum of improved BMs over the sum of deteriorated BMs 6 months after baseline assessment. GER scores were categorized with three different sets of cut-off values into clinical levels: (a) Deteriorated, (b) Stabilized, and (c) Improved. Ordinal logistic regressions were performed on the per-protocol population to determine whether there was a relationship between group assignment and GER levels.
Results: Of the 221 eligible participants, 163 were included. Two different regression models showed that patients from Group 3 (Exercise&Education) were 2.5-times more likely to be in an upper GER level (i.e., Stabilized or Improved) than patients from the control group (both odds ratio (OR) > 2.46, Wald $X^2(1) \geq 7.268$, $P \leq 0.01$). They also reported significantly more improvement in pain and function (Knee Injury and Osteoarthritis Outcome Score, both $P \leq 0.01$).
Conclusions: Results suggest that targeted exercises can improve biomechanical markers in knee OA patients compared with CPC treatment. Further studies are needed to confirm these findings and refine the biomechanical markers to address to maximize patients' clinical outcomes.

* Corresponding author at: Research Centre of the Centre Hospitalier de l'Université de Montréal (CRCHUM), 900 rue Saint-Denis, Montreal, Quebec H2X 0A9, Canada.
E-mail address: nicola.hagemeister@etsmtl.ca (N. Hagemeister).

https://doi.org/10.1016/j.knee.2022.10.008
0968-0160/

1. Introduction

Knee osteoarthritis (OA) is a chronic multifactorial disease associated with pain, functional disability, and altered knee biomechanics. Knee OA can still not be cured, but conservative treatments are recommended to reduce symptoms and pain to allow patients to maximize their health and function. Exercise therapy is widely recognized as an effective non-pharmacological treatment modality and is a recommended component in most clinical practice guidelines for patients with knee OA [1–3]. While studies have consistently shown that exercise in this population reduces pain, improves function, and enhances quality of life, it is still not clear whether exercises concurrently improve knee biomechanics during gait [4–10]. Altered knee biomechanics is a known risk factor for OA progression, but not all patients with knee OA present with the same alterations. Therefore, generalized exercise prescriptions that are not patient-specific or based on an individual's movement pattern may improve function, but may not change gait biomechanics [8–11].

Dynamic biomechanical markers (BMs) in knee OA patients have been widely reported in the literature and some, such as varus thrust or a dynamic flexion contracture, are predictive of OA progression [12–14]. In addition to pathology development, these BMs may influence treatment outcomes, and therefore they should be a focus point in conservative care strategies, particularly when providing patient-specific exercise prescriptions [15–18]. Assessment of BMs, which can be carried out by quantifying three-dimensional (3D) knee kinematics during walking, could guide healthcare professionals in the choice of tailored exercises. However, the lack of space and validated-regulated tools to quantify them in clinical settings leads to generic exercise programs, even in cases when supervision and individualized follow up is added as part of clinical care [2,19,20].

Results from a large cluster randomized controlled trial (RCT) recently demonstrated the value of adding a knee kinesiography exam in the management of knee OA in primary care [21]. This exam objectively assesses in the clinical setting 14 known BMs related to knee OA drawn from the literature to support healthcare professionals in tailoring their conservative care strategies based on patient's individual mechanical alterations. Exercise recommendations are then provided to specifically target the identified BMs. Results from this RCT revealed that patients who benefited from this type of functional examination had significantly better outcomes with respect to pain, function, and satisfaction 6 months after the exam compared with conventional care alone, and those who had complementary education and supervision showed further improved clinical outcomes.

This study is a secondary analysis focusing on the biomechanical markers' evolution of the knee OA patients from the above RCT. The aim was to determine whether the recommended targeted exercises based on a knee kinesiography exam improved biomechanical markers at 6 months follow up compared with conventional primary care management where no specific exercises were suggested to the patients.

2. Materials and methods

2.1. Study design

Data analysed in the present study were collected as part of a cluster RCT carried out in the Province of Quebec, Canada (http://www.isrctn.com/ISRCTN16152290) [21]. Participants were recruited through August 2015 to October 2017 in primary care clinics throughout the Province. Primary care physicians were asked to enroll patients with a clinical diagnosis of knee OA in the study. They were included if (1) knee OA was the main cause of their knee pain, (2) they rated their worst pain as $\geq$4 on a 0–10 pain intensity scale in the 7 days prior to the assessment by the research team, and (3) they had a Kellgren–Lawrence (KL) grade 2 or higher on standardized radiographs [22]. Patients were excluded if they (1) were on a waiting list for total knee replacement, (2) had met an orthopaedic surgeon OA specialist in the past, (3) were suffering from rheumatoid arthritis or active cancer, (4) were pregnant, or (5) were unable to walk on a treadmill for 15 min without support. For patients with bilateral knee OA, only data from the most painful knee was collected.

2.2. Ethics

As stated in the original RCT, all participants gave informed consent to this work. The clinical trial was approved by the Research Ethics Boards of the École de technologie supérieure (MP-02-2015-5891/H20150505) and the Centre Hospitalier de l'Université de Montréal (CE.14.339), and it is registered ('Osteoarthritis Project', ID ISRCTN16152290) and available at http://www.isrctn.com/ISRCTN16152290. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

2.3. Procedure

All procedure details (e.g., recruitment, allocation, therapist training, sample size) have been published elsewhere [21]. Briefly, participants of a same primary care clinic (defined as a cluster) were randomized 1:1:1 (with a permuted block; size of 3 and 6) to one of three intervention groups. The randomization sequence was managed using a computer-generated random listing with a pre-specified seed. Group 1 served as the control group with patients receiving conventional primary care management. Patients in Groups 2 and 3 received conventional primary care management plus personalized recommendations based on a knee kinesiography exam; however, patients in Group 3 also received an additional educational program. Recommendations in Groups 2 and 3 included treatment suggestions (e.g., bracing, specific cardiovascular activities) and a home-based tailored exercise program targeting BMs identified with the knee kinesiography exam. The educational program included an information session on OA, demonstration of the exercises by a trained therapist at baseline, and two optional follow ups 6 weeks and 4 months after the exam. For clarity purposes and because all three groups followed conventional medical management, the three groups were designated as Group 1 (Control), Group 2 (Exercise), and Group 3 (Exercise&Education) in this manuscript.

2.4. Biomechanical markers

In this RCT, BMs were assessed at baseline with a knee kinesiography exam [23]. This active exam assessing the 3D motion of the knee was performed on a conventional treadmill in a clinical setting. Patients are asked to walk for approximately 5 min at their comfortable speed to warm up and the KneeKG® exoskeleton (Emovi inc., Canada) was then fixed on their leg. After a few calibration movements to identify the functional axis of the lower limb, two 45-s trials were recorded to capture the joint motion during weight-bearing activity, in flexion/extension, adduction/abduction (i.e., varus/valgus), and external/internal tibial rotation. Data from the most repeatable trial were compiled to generate three mean kinematic curves, one in each cardinal plane of movement. All trials were time-normalized to a complete gait cycle, where 0% represents initial contact and 100% represents the subsequent ipsilateral heel strike. For each participant, 14 known BMs in knee OA patients were then assessed by comparing their value with normative ones drawn from the OA literature. Each BM was ranked as ‘Absent’, ‘Moderate’, or ‘Severe’ and details on the cut-off values used for defining each status are presented in Table 1. For six BMs, there was no ‘Moderate’ status due to lack of relevant data in the literature.

2.5. Targeted exercises

Patients in all groups underwent the knee kinesiography assessment, but the ones allocated to the control group did not have access to the results. For patients in Group 2 (Exercise) and Group 3 (Exercise&Education), a trained therapist (n = 10 involved in the study) consulted these results and conducted a musculoskeletal assessment that evaluated ranges of motion, strength, etc. to provide them with tailored exercises. Each patient received about five home-exercises which included stretching, strengthening, and targeted neuromuscular exercises. The main objectives of these exercises were to (A) address the BMs with a ‘Moderate’ or ‘Severe’ status, (B) while ensuring other BMs did not worsen to minimize the mechanical risk of knee OA progression. All exercises needed to be land-based and performable at home without supervision to ensure that patients would be equally able to adhere to the program (e.g., Supplementary Figure S1). Therapists were invited to suggest complementary treatment recommendations (e.g., cardiovascular activity, nutrition, etc.) if they deemed it necessary to support both exercises’ objectives (i.e., A and B). Patients from Group 2 received their exercises from their primary care physician without further mandatory intervention. Patients from Group 3 had an additional educational program within 2 weeks after the exam, in which they met with the therapist who explained and demonstrated the appropriate exercises. They also had access to two optional follow ups at 6 weeks and 4 months where the intensity and/or the nature of the recommended exercises was modified as needed.

Table 1
Cut-off values drawn from osteoarthritis literature used to define the 14 known biomechanical markers’ status.

Biomechanical markers / Status	Absent	Moderate	Severe
Sagittal plane			
Knee flexion at heel strike [13,24]	Angle ≤ 10° at 1% GC	NA	>10°
Knee extension at heel strike [25]	Angle ≥ 2° at 1% GC	NA	<2°
Limited flexion excursion during loading [26,27]	Amplitude ≥ 14° at 1–20% GC	[8°; 14°]	<8°
Fixed flexion during stance [26,27]	Amplitude ≥ 17° at 1–70% GC	[0°; 17°]	<0°
Decrease of maximum flexion during swing [26,28]	Maximum ≥ 47° at 1–100% GC	NA	<47°
Decrease of sagittal plane range of motion [26]	Amplitude ≥ 58° at 1–100% GC	[50°; 58°]	<50°
Frontal plane			
Knee varus at heel strike [29]	Angle ≤ 2° at 1% GC	NA	>2°
Knee valgus at heel strike [29]	Angle ≥ −2° at 1% G	NA	<−2°
Varus thrust during loading [30,31]	Amplitude ≤ 2.5° at 1–20% GC	[2.5°; 7°]	>7°
Valgus thrust during loading [30,31]	Amplitude ≥ −2.5° at 1–20% GC	[−7°; −2.5°]	<−7°
Knee varus during stance [29,32]	Amplitude ≤ 2° at 20–54% GC	[2°; 5°]	>5°
Knee valgus during stance [29,32]	Amplitude ≥ −2° at 20–54% GC	[−5°; −2°]	<−5°
Transverse plane			
External tibia rotation at heel strike [33]	Angle ≤ 4.5° at 1% GC	[4.5°; 7.5°]	>7.5°
Internal rotation of the tibia with regard to the femur during loading [33]	Amplitude ≥ 1° at 1–20% GC	NA	<−1°

Sagittal plane: flexion (+)/extension (−); frontal plane: adduction (+)/abduction (−) or varus (+)/valgus (−); transverse plane: external (+)/internal (−) tibia rotation. GC, gait cycle; NA, not applicable.

2.6. Sample size

The sample size was based on the primary outcome of the original RCT [21]. For the present study, a second knee kinesiography exam was performed to assess BMs at 6 months follow up. Due to budget restrictions, of the 449 patients who completed the RCT, only the first 317 (70.6%) to reach the 6 months follow up were enrolled and eligible for the follow up exam.

2.7. Outcomes

2.7.1. Primary outcome

Because the combination of BMs identified with a 'Moderate' or 'Severe' status at baseline differed from one patient to another, the targeted exercises also differed. To account for this variation, the ratio of the sum of improved BMs over the sum of deteriorated BMs was used as the primary outcome of this study (Equation (1)). A BM was considered as improved if it changed from 'Severe' to 'Moderate' or from 'Moderate' or 'Severe' to 'Absent' at 6 months. A BM was considered as deteriorated if it changed from 'Absent' to 'Moderate' or 'Severe', or from 'Moderate' to 'Severe'. This global evolution ratio (GER) summarizes the evolution of all the BMs in a single outcome, allowing a combined assessment of both exercises' objectives (i.e., A and B). It also avoids analytical issues with performing multiple underpowered sub-analyses on small groups of patients with biomechanical similarities at baseline.

$$GER = \frac{\sum Improved\ BMs}{\sum Deteriorated\ BMs} \quad (1)$$

2.7.2. Secondary outcomes

All participants were asked to complete the Knee Injury and Osteoarthritis Outcome Score (KOOS) at baseline and 6 months follow up [34]. This questionnaire assesses the impact of knee OA on five domains (symptoms, pain, activities of daily living, sports and recreation, and quality of life). The score on each sub-scale ranges from 0 (extreme symptoms) to 100 (no symptoms).

2.8. Statistical analyses

Given the nature of this study's aims, the analyses were performed on the per-protocol population. Patients from Group 2 and Group 3 were asked at 3 months and 6 months follow ups whether they performed the recommended exercises during the past 3 months. Thus, the per-protocol population was defined as patients who had complete data from both knee kinesiography exams (from all three groups) and who declared performing the recommended exercises during the 6-month study period (in Group 2 and Group 3). One-way analysis of variance (ANOVA) and chi-squared tests were used to assess between-group differences in patient characteristics and BMs (including the total number of BMs with a 'Moderate' or 'Severe' status) at baseline.

The GER cannot be analyzed as a continuous variable because patients who did not deteriorate a single BM at 6 months would have an infinite GER value. For this reason, GER was categorized in three clinical levels: (a) Deteriorated, (b) Stabilized, and (c) Improved. As the choice of cut-off values to distinguish the three GER clinical levels can affect the primary outcome, a sensitivity analysis strategy was used [35]. In order to assess the robustness of the findings, all analyses were performed with three different sets of cut-off values. These were considered as Inclusive, Reasonable, and Restrictive cut-off value categorizations.

For the Inclusive categorization (GER_Cat1), the Deteriorated and Improved levels correspond to a GER smaller than 1 and greater than 1, respectively, with the Stabilized level corresponding to a GER being equal to 1 (see Table 2). Therefore, for this categorization, patients with fewer improved than deteriorated BMs are in level (a) Deteriorated level, patients with as many improved as deteriorated BMs are in level (b) Stabilized level, and patients with more improved than deteriorated BMs are in level (c) Improved level.

For the Reasonable categorization (GER_Cat2), the Deteriorated and Improved levels correspond to a GER ≤ 0.5 and ≥ 2, respectively. Therefore, for this categorization, patients with two-times fewer improved than deteriorated BMs are in level (a) Deteriorated level.

Table 2
The cut-off values for each of the three categorizations.

Cut-off categorizations / GER levels	(a) Deteriorated	(b) Stabilized	(c) Improved
GER_Cat1 (*Inclusive*): Less or more improved than deteriorated BMs	GER < 1	GER = 1	GER > 1
GER_Cat2 (*Reasonable*): 2-times less or more improved than deteriorated BMs	GER ≤ 0.5	0.5 < GER < 2	GER ≥ 2
GER_Cat3 (*Restrictive*): 3-times less or more improved than deteriorated BMs	GER ≤ 0.33	0.33 < GER < 3	GER ≥ 3

BM, biomechanical marker; GER, global evolution ratio.

For the Restrictive categorisation (GER_Cat3), the Deteriorated and Improved levels correspond to a GER smaller than or equal to 0.33 and greater than or equal to 3, respectively, meaning that patients with three-times fewer improved than deteriorated BMs are in level (a) Deteriorated level.

For each categorization, an ordinal logistic regression was performed to determine whether the group assignation was a predictor of the GER level at 6 months. Possible baseline confounders including age, body mass index (BMI), sex, KL OA severity grade, and KOOS pain score were entered as covariates in the model if they were associated with the GER level at a minimal P-value < 0.25 in a univariable analysis [36]. The pain sub-scale was the only one from the KOOS considered in the regression model as pain scores were shown to be associated with BMs in several prior studies and to avoid multicollinearity between independent variables [16,37,38].

Mixed ANOVAs with repeated measures on one factor (i.e., time) were used to assess between-group differences on the KOOS sub-scales' evolution between baseline and 6 months follow up (time). Post-hoc analyses were performed for any time*group interaction with a significant $P \leq 0.05$ and a Bonferroni correction was applied for multiple comparisons. All test results that were based on chi-squared or F-ratio values were divided by the design effect and adjusted P-values were used to determine the significance of between-group differences accounting for the cluster design of the RCT [39,40]. All analyses were performed using IBM SPSS Statistics v.25.0 (IBM Corp., released 2017; Armonk, NY, USA).

3. Results

3.1. Participants' characteristics

The flow diagram of study participants is displayed in Figure 1. Of the 317 patients who were contacted to have a second knee kinesiography exam at 6 months, 221 (69.7%) accepted and were included in this analysis (Group 1 (Control): 71; Group 2 (Exercise): 72; Group 3 (Exercise&Education): 78). In Group 2 and Group 3, respectively, 33 (45.8%) and 59 (75.6%) patients declared they had performed the recommended exercises for 6 months. Among the per-protocol population considered, the average cluster size was 4 (n = 163 patients from 47 clinics) thus the design effect was equal to 1.09 considering the conservative estimation of intracluster correlation coefficient (ρ = 0.03) used for the initial RCT sample size calculation [21,41].

Table 3 displays the between-group differences in patients' characteristics and values for each biomechanical marker at baseline. Notably, all intervention groups were comparable in terms of characteristics, including the KL severity grade distribution at baseline ($P = 0.71$). Post-hoc analysis showed there were no statistically significant differences in patients' BMs. Patients in the control group had fewer BMs with a 'Moderate' or 'Severe' status at baseline compared with patients from Group 2 (Exercise) and Group 3 (Exercise&Education) but this difference was not quite significant after Bonferroni correction (both 5.3 vs. 6.0; $P = 0.069$ and $P = 0.053$, respectively). Differences on the varus thrust during loading between patients in the control group (1.52°) and patients from Group 2 (2.23°) and Group 3 (1.91°) were not significant after Bonferroni correction either ($P = 0.12$ and $P = 0.26$, respectively).

3.2. Primary outcome

3.2.1. Descriptive statistics

The proportions of patients from each intervention group classified in each GER clinical level (i.e., Deteriorated/Stabilized/Improved) are shown in Figure 2, based on the three cut-off categorizations (GER_Cat1 (Inclusive), GER_Cat2 (Reasonable) GER_Cat3 (Restrictive)). For GER_Cat1 and GER_Cat2, more than half of the control group patients globally deteriorated their BMs after 6 months (52.1% and 50.7%, respectively), while half of patients were stable (50.7%) for GER_Cat3. Independently of the cut-off categorization used, the Deteriorated level was always the one with the smallest proportion of patients in Group 2 and Group 3 (all $\leq$ 27.3% and $\leq$ 27.1%, respectively). Additionally, when looking at Group 2 (Exercise) specifically, and for all three categorizations, the majority of patients in this intervention group were systematically in the Stabilized level (for all categorizations $\geq$ 39.4%) while the majority of patients from Group 3 (Exercise&Education) improved for GER_Cat1 and GER_Cat2 (both $\geq$ 42.4%) and stabilized for GER_Cat3 (49.2%).

For all cut-off categorizations, the highest proportion of deteriorated patients was in Group 1 (Control), the highest proportion of stabilized patients was in Group 2 (Exercise), and the highest proportion of improved patients was in Group 3 (Exercise&Education). Looking at GER_Cat2, one can notice that it is equivalent to a categorization based on the tertiles of the global GER values distribution (i.e., Deteriorated: 0–33%; Stabilized: 33–67%; Improved: 67–100%).

3.2.2. Ordinal logistic regressions

Tables 4 and 5, respectively, display the results of the univariable and multivariable ordinal logistic regression analyses for each of the three categorizations. For GER_Cat1, only the age and the KOOS pain score at baseline were included in the multivariable ordinal logistic regression model along with the group assignation. Accounting for the design effect, the model showed an adequate fit with the data (likelihood ratio χ^2 (4) = 10.687; $P = 0.03$) and indicated that the group assignation was the only significant predictor of the GER level. The odds of patients from Group 3 (Exercise&Education) being in an upper GER level (Stabilized or Improved with regard to Deteriorated, Improved with regard to Stabilized) were 2.46 (95% confidence

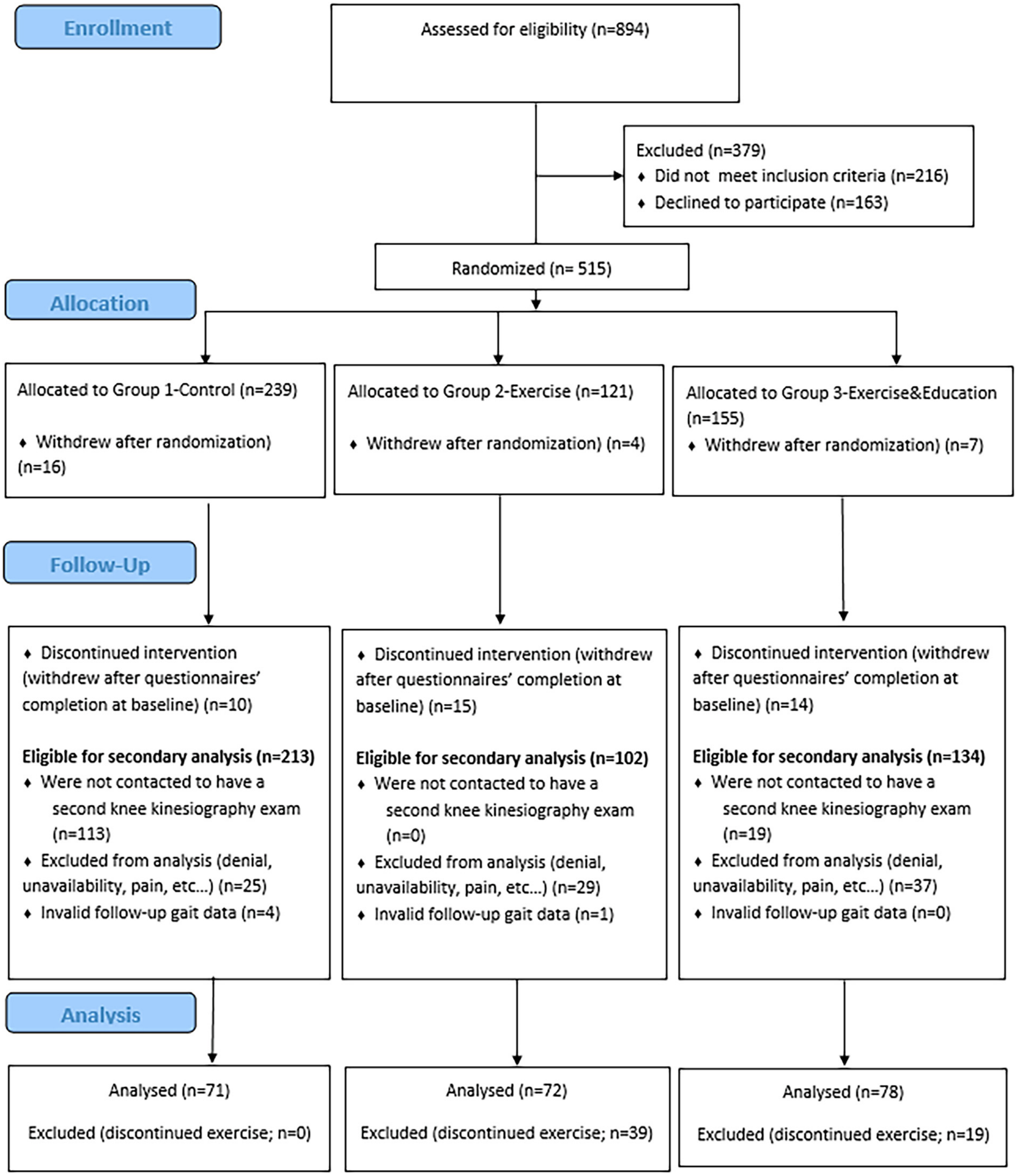

Figure 1. Flow diagram of study participants. This diagram describes patients' participation from enrollment in the original randomized control trial to the inclusion in this secondary analysis.

interval: 1.28–4.74) times those of patients from Group 1 (Control), a significant effect (Wald χ^2 (1) = 7.268; P = 0.01) given that the other variables were held constant.

For GER_Cat2, a similar model was run as the age and the KOOS pain score at baseline were once again the only variables associated with the GER level in the univariable analysis (both P < 0.25; Table 4). Accounting for the design effect, the multivariate model also showed a significant fit with the data (likelihood ratio χ^2 (4) = 11.331; P = 0.02). The odds of patients

Table 3
Between-group differences in patients' characteristics and biomechanical markers at baseline.

	Group 1 (Control) n = 71	Group 2 (Exercise) n = 33	Group 3 (Exercise&Education) n = 59	ANOVA or Chi-squared test
Patients' characteristics	*Mean (95% CI) or n (%)*	*Mean (95% CI) or n (%)*	*Mean (95% CI) or n (%)*	*P*
Age	62.3 (60.1;64.5)	63.3 (61.1;65.5)	63.3 (61.1;65.6)	0.75
BMI	29.5 (28.3;30.8)	30.4 (28.5;32.2)	29.6 (28.4;30.7)	0.71
Sex (women)	48 (67.6%)	22 (66.7%)	35 (59.3%)	0.62
Severity KL grade				0.71
Grade 2	25 (35.2%)	9 (27.3%)	15 (25.4%)	
Grade 3	27 (38.0%)	13 (39.4%)	22 (37.3%)	
Grade 4	19 (26.8%)	11 (33.3%)	22 (37.3%)	
Biomechanical markers				
Total number of BMs with 'Moderate'or 'Severe' status	5.3 (4.9;5.6)	6.0 (5.6;6.4)	6.0 (5.6; 6.4)	0.02*
Sagittal plane	*Mean, ° (95% CI)*	*Mean, ° (95% CI)*	*Mean, ° (95% CI)*	
Flexion/extension angle at heel strike	12.28 (10.78;13.77)	11.24 (9.29;13.20)	12.90 (11.26;14.54)	0.50
Flexion excursion amplitude during loading	5.95 (5.06;6.83)	5.68 (4.36;7.01)	6.71 (5.63;7.79)	0.42
Flexion/extension amplitude during stance	13.66 (12.21;15.10)	11.57 (9.71;13.43)	12.39 (10.73;14.06)	0.25
Maximum flexion angle during swing	59.80 (58.47;61.14)	57.91 (55.46;60.36)	60.29 (58.95;61.64)	0.18
Sagittal plane range of motion	55.40 (53.77;57.03)	53.18 (50.33;56.04)	53.38 (51.28;55.47)	0.25
Frontal plane				
Varus/valgus angle at heel strike	4.65 (3.48;5.81)	4.39 (2.70;6.07)	4.33 (2.91;5.74)	0.94
Varus thrust during loading	1.52 (1.27;1.78)	2.23 (1.66;2.80)	1.91 (1.58;2.24)	0.03*
Valgus thrust during loading	0.53 (0.34;0.72)	0.34 (0.16;0.53)	0.36 (0.22;0.50)	0.27
Varus/valgus amplitude during stance	3.74 (2.49;5.00)	4.44 (2.51;6.37)	4.03 (2.51;5.55)	0.85
Transverse plane				
External/internal tibia rotation angle at heel strike	2.94 (2.14;3.74)	2.42 (1.14;3.71)	2.97 (2.06;3.88)	0.75
External/internal rotation of the tibia in regards of the femur during loading	−0.17 (−0.78;0.45)	−0.01 (−1.15;1.14)	−0.15 (−0.92;0.62)	0.97

All *P*-values are adjusted for a design effect of 1.09. ANOVA, analysis of variance; BM, biomechanical marker; BMI, body mass index; CI, confidence interval; KL, Kellgren–Lawrence.
* $P \leq 0.05$.
** $P < 0.005$.

from Group 3 (Exercise&Education) being in an upper GER level were similar to the first model (2.51; 1.30–4.83) relative to patients from Group 1 (Control) (Wald χ^2 (1) = 7.578; *P* = 0.008). There were no other significant predictors.

For GER_Cat3, only the KL grade (*P* = 0.08; Table 4) was included in the multivariate model along with the group assignation. The model showed a non-significant fit with the data (likelihood ratio χ^2 (4) = 5.139; *P* = 0.16) and no significant predictor of the GER level (all *P* > 0.05). For each multivariate model, the assumption of proportional odds across the GER levels was met according to Brant's test of parallel lines (all *P* > 0.42).

3.3. Secondary outcomes

Table 6 displays the results of the mixed ANOVAs on the KOOS subscales and the subsequent post-hoc analyses. The time*group interaction was significant for pain and function during activities of daily living (ADL) scores, meaning that the effect of the intervention was not the same over time in each group on these two sub-scales (both *P* = 0.03). Post-hoc analyses revealed there was a simple main effect of time on these two scores in Group 2 (Exercise) and Group 3 (Exercise&Education) (all $P \leq 0.01$) but not in the control group (both *P* = 1.0). There was no simple main effect of group on either sub-scale (all *P* > 0.05). Figure 3 shows the group mean scores on the pain and ADL sub-scales at baseline and 6 months. Patients from Group 2 and Group 3 who performed the recommended exercises for 6 months significantly improved their scores on pain and ADL sub-scales compared with the control group.

4. Discussion

This study examined the impact of targeted exercises on knee biomechanical markers in knee OA individuals. Results suggest that such exercises based on a knee kinesiography exam have a significant impact on both biomechanical markers and KOOS after 6 months compared with conventional primary care management. Adding an educational session where exercises are demonstrated by a therapist and two follow up sessions significantly improve biomechanical markers. To our knowledge, this is the first study to report such an impact of a home-based exercise program on biomechanical markers.

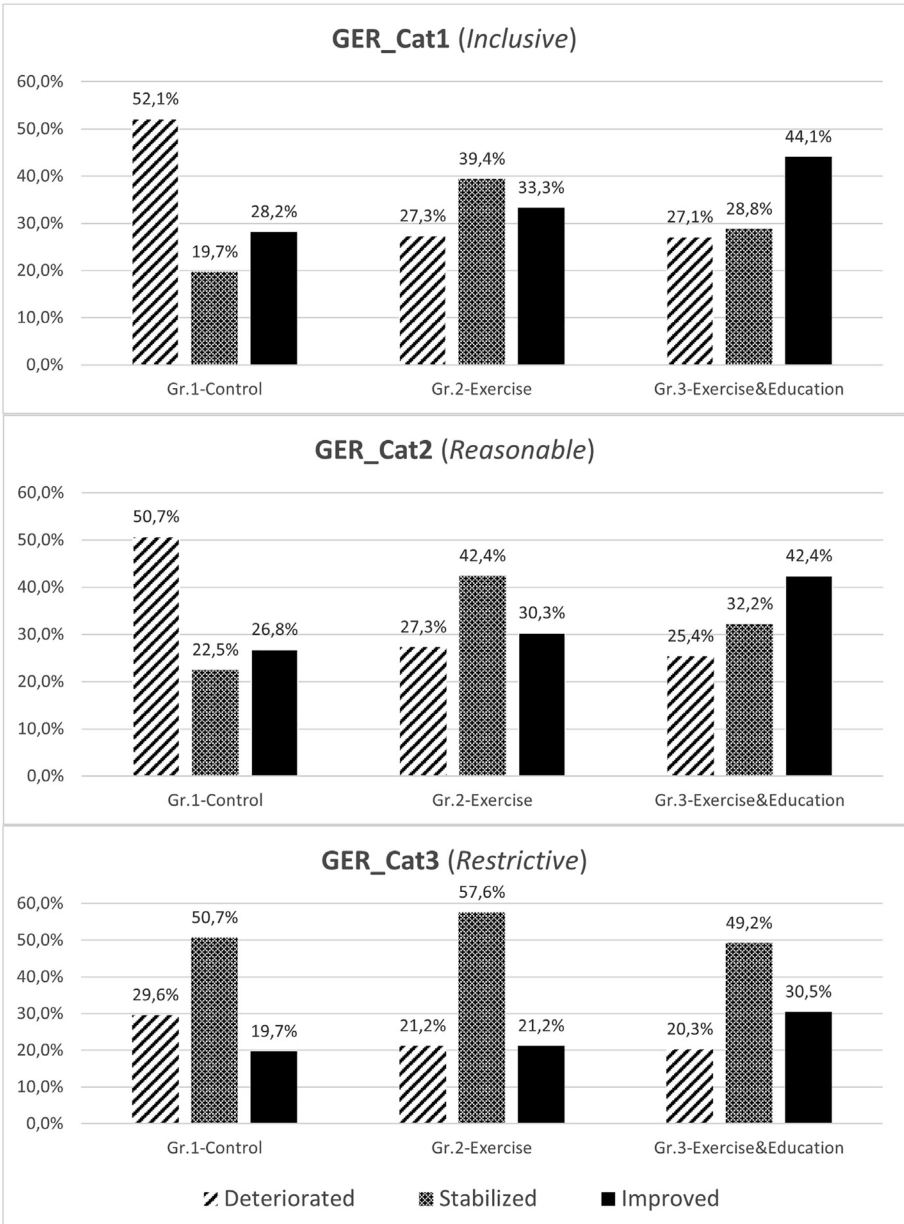

Figure 2. Proportion of patients from each intervention group classified in each global evolution ratio (GER) level. The first histogram presents the proportion of patients from each group classified in each GER level based on the Inclusive categorization (GER_Cat1), the second one presents this proportion based on the Reasonable categorization (GER_Cat2), and the third one presents this proportion based on the Restrictive categorization (GER_Cat3). The legend to identify each clinical level (i.e., Deteriorated, Stabilized, Improved) is the same for all histograms and is provided at the bottom of the figure.

4.1. Significance of the results

Ordinal logistic regression models (i.e., with GER_Cat1 and GER_Cat2 categorizations) showed that the patients' intervention group assignation was significantly associated with the GER level. In these two models, the odds were 2.5-times higher for patients in an upper level to come from the Group 3 (Exercise&Education) rather than from the control group. Being in an upper GER level clinically translated into a global stabilization and/or an improvement of BMs known to be associated with knee OA progression. The results were similar for the two distinct GER categorizations, one in which patients were considered globally stabilized only if their number of improved and deteriorated BMs was the same (GER_Cat1), as well as the one in which patients were considered stabilized only if their number of improved BMs was within two-times more or less than their number of deteriorated BMs (GER_Cat2).

Table 4
Univariable ordinal logistic regression analysis of associations between global evolution ratio (GER) levels and covariates for each categorization.

	Odds ratio	95% CI	*P*
GER_Cat1 (Inclusive)			
Age *	1.02	0.99 ; 1.06	0.20 *
BMI	1.00	0.94 ; 1.06	0.96
KOOS pain *	(−) 0.99	0.97 ; 1.01	0.20 *
Sex	1.40	0.77 ; 2.53	0.29
KL grade	1.21	0.85 ; 1.74	0.31
GER_Cat2 (Reasonable)			
Age *	1.03	0.99 ; 1.06	0.14 *
BMI	(−) 1.00	0.96 ; 1.06	0.99
KOOS pain *	(−) 0.99	0.97 ; 1.01	0.22 *
Sex	1.28	0.71 ; 2.30	0.44
KL grade	1.20	0.83 ; 1.71	0.35
GER_Cat3 (Restrictive)			
Age	1.02	0.98 ; 1.05	0.31
BMI	(−) 0.98	0.92 ; 1.04	0.49
KOOS pain	(−) 0.99	0.98 ; 1.01	0.55
Sex	1.10	0.60 ; 2.03	0.76
KL grade *	1.43	0.98 ; 2.08	0.08 *

All *P*-values in the last column on the right are adjusted for a design effect of 1.09. Odds ratio (OR) with (−) corresponds to a negative regression coefficient Beta. BMI, body mass index; CI, confidence interval; KL, Kellgren–Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score.
* $P \leq 0.25$.

Table 5
Multivariable ordinal logistic regression analysis of associations between global evolution ratio (GER) levels and identified predictors for each categorization.

	Odds ratio	95% CI	*P*
GER_Cat1 (Inclusive)			
Age	1.02	0.99 ; 1.06	0.21
KOOS pain	(−) 0.99	0.97 ; 1.01	0.19
Group 1 (Control) (reference)	NA	NA	NA
Group 2 (Exercise)	1.86	0.85 ; 4.03	0.14
Group 3 (Exercise&Education) **	2.46	1.28 ; 4.74	0.01 **
GER_Cat2 (Reasonable)			
Age	1.03	0.99 ; 1.06	0.14
KOOS pain	(−) 0.99	0.97 ; 1.01	0.19
Group 1 (Control) (reference)	NA	NA	NA
Group 2 (Exercise)	1.79	0.82 ; 3.88	0.16
Group 3 (Exercise&Education) **	2.51	1.30 ; 4.83	0.008 **
GER_Cat3 (Restrictive)			
KL Grade	1.38	0.95 ; 2.02	0.11
Group 1 (Control) (reference)	NA	NA	NA
Group 2 (Exercise)	1.26	0.57 ; 2.77	0.59
Group 3 (Exercise&Education)	1.64	0.84 ; 3.19	0.16

All *P*-values in the last column on the right are adjusted for a design effect of 1.09. Odds ratio with (−) corresponds to a negative regression coefficient Beta. CI, confidence interval; KL, Kellgren–Lawrence; KOOS, Knee Injury and Osteoarthritis Outcome Score; NA, not-applicable.
* $P \leq 0.05$; ** $P \leq 0.01$.

No conclusion can be drawn up based on the third categorization (i.e., three-times more or less improved than deteriorated BMs) which did not lead to a model with an adequate fit with the data. This categorization may have been too restrictive to detect a change in the GER with the data used in this study. Indeed, GER_Cat3 condensed a majority of patients in the Stabilized level, at the expense of the levels in the two extremes (i.e., Deteriorated and Improved). This may have led to a sub-powered model, especially due to the limited sample in the Group 2 (Exercise) in which two levels had fewer than than 10 patients (n = 33; GER_Cat3: 7 patients deteriorated, 19 stabilized, 7 improved). Studies with a larger number of patients allocated in each intervention group would be needed to conclude on the quality of this restrictive categorization for the GER.

Despite the relatively limited sample size, two models (i.e., GER_Cat1, GER_Cat2) showed significant and similar results, suggesting that the targeted exercises have a positive impact on BMs. Among the three groups, Group 1 (Control) was least likely to improve and more commonly deteriorated, while patients in Group 3 (Exercise&Education) who were compliant with their exercises demonstrated the least likelihood of deterioration and the greatest likelihood of improvement. In these models, the contrast with the control group was striking, as more than half of the patients in the control group deteriorated. This highlights that individuals who seek medical care for knee OA, but do not have access to a targeted exercise plan, are

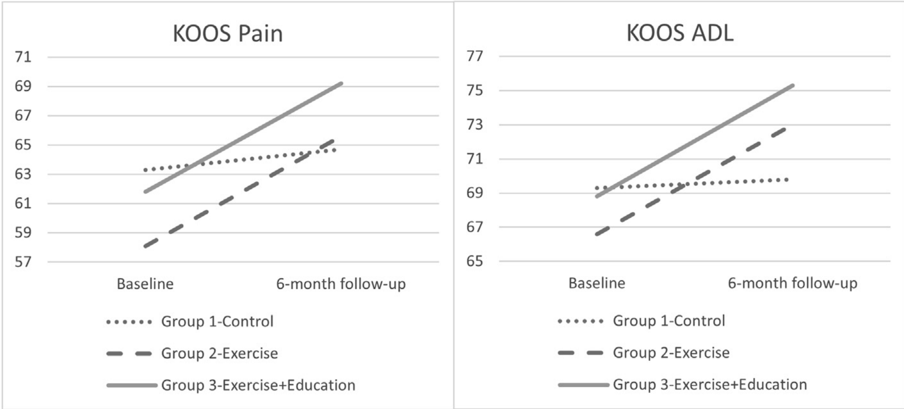

Figure 3. Knee Injury and Osteoarthritis Outcome Score (KOOS) pain and activities of daily living (ADL) mean scores at baseline and 6-month follow up in each intervention group. Evolutions of KOOS mean scores are displayed in dotted lines for Group 1 (Control), in dashed lines for Group 2 (Exercise), and in solid lines for Group 3 (Exercise&Education). Graph legends are provided at the bottom of the figure.

likely to demonstrate deterioration in their BMs in a relatively short period of time (6 months), even when self-reported outcomes remain stable (i.e., KOOS). Individuals who carried on with the conventional medical management were 2.5-times more likely to deteriorate than patients who had a knee kinesiography exam, an education session, and followed the recommended exercises. Between-group differences were also found on two KOOS subscales: patients from Group 2 (Exercise) and Group 3 (Exercise&Education) showed significant improvements in terms of pain and function during ADL, while patients from the control group did not. Furthermore, these results were noteworthy as patients from Group 3 tended to have more BMs to address at baseline (i.e., $P = 0.053$ after Bonferroni correction), suggesting more affected knee biomechanics.

Differences between Group 2 (Exercise) and the control group did not reach statistical significance for any of the categorizations. Although this can be partially explained by a lack of statistical power (i.e., Group 2 was the smallest group with the highest variability), this may be related to the components of the intervention. Group 3 received the additional educational program and had a much higher adherence rate for exercise (Group 2: 45.8% vs. Group 3: 75.6%). Results of the primary RCT analyses also suggested Group 3 had better functional performance and higher impression of change when compared with Group 2 [21]. Secondly, the additional educational program may have impacted the way in which the exercises were performed. A visual demonstration of the exercises, along with follow ups with a therapist for a maximum of two sessions, may have contributed to significant improvements in exercise technique, treatment adherence and, subsequently, BMs. Other studies reported that the demonstration of exercises is a more efficient way of prescribing home-based exercises [42–44]. Benefits of education for knee OA patients are well documented and results of the present study reinforce that supervised education should be part of any conservative treatment plan [1,2].

Despite the benefit of the additional education session, results in patients from Group 2 (Exercise) who did not have access to additional education are promising. This group only received a list of five targeted exercises with written explanations compared with the control group, but the outcomes were not grossly different from Group 3. This was the case for both the primary (i.e., odds ratio $\geq$ 1.79 and P-values $\leq$ 0.16 for GER_Cat1 and GER_Cat2) and secondary outcomes (i.e., significant improvement on pain and ADL KOOS sub-scales, both $P < 0.05$) compared with the control group. In real-life applications of care, education and supervision can be burdensome with respect to time and resources, contributing to the variability of conservative treatment cost-effectiveness [45–47]. However, results from this analysis suggest that providing targeted exercises, even without additional supervision and training (i.e., Group 2), may make a positive and substantial difference in outcomes for individuals with knee OA. Results further suggest that, independently of patients' characteristics, OA patients could benefit from such exercises. This is supported by the fact that GER outcomes did not vary between pain levels at baseline, KL grades, ages, BMIs, and sexes, while all these variables were considered in the models. This is notable knowing that some of these patient characteristics have been previously reported to influence the efficacy of other exercise programs on clinical outcomes [48–49]. Knowing that biomechanical markers have been used to predict response to such exercises [50], results from this study reinforce the value of integrating them in knee OA patient management.

The results obtained in this study are not surprising when one considers that the fundamental aim of a generic exercise program is to improve mobility and function. Even if the generic program succeeds in improving strength, range of motion, and function, it may have no effect on biomechanical markers and may not change the patient's mechanical risk profile for OA progression. BMs in patients with knee pain and OA vary, thus the exercises need to target the patient's individual movement alterations. This has been emphasized by Henriksen et al. (2017) who did not observe any difference in knee biomechanics during gait after a 12-week individualized therapeutic exercise program focusing on strength and coordination [8]. In the present study, BMs were objectively quantified directly in a clinical setting using a knee kinesiography exam and the exercise program was designed to address them specifically. Results from this study highlight the need to incorporate

Table 6
Between-group differences on Knee Injury and Osteoarthritis Outcome Score (KOOS) subscales between baseline and 6 months follow up.

	Group 1 (Control) n = 71	Group 2 (Exercise) n = 33	Group 3 (Exercise&Education) N = 59	Time*group interaction	Main effects time/group
KOOS (6-month minus baseline)	*Mean difference (95% CI)*	*Mean difference (95% CI)*	*Mean difference (95% CI)*	*P*	*P*
Symptoms	1.9 (−1.5;5.2)	7.6 (1.9;13.2)	6.3 (3.6;9.0)	0.08	<0.001**/0.90
Pain	1.4 (−2.2;5.0)	7.5 (3.7;11.2)	7.4 (4.2;10.7)	0.03*	*Post-hoc*
Activities of daily living	0.5 (−3.0;3.9)	6.5 (2.8;10.2)	6.4 (2.7;10.1)	0.03*	*Post-hoc*
Sports and recreation	6.1 (1.1;11.1)	2.9 (−4.2;9.9)	6.5 (1.5;11.6)	0.70	<0.001**/0.91
Quality of life	4.2 (0.2;8.3)	9.7 (2.5;16.8)	10.8 (6.2;15.4)	0.11	0.001**/0.39
***Post-hoc:* Time – simple main effect**	*Mean difference (P)*	*Mean difference (P)*	*Mean difference (P)*		
Pain	1.4 (P = 1.0)	7.5 (P < 0.005)**	7.4 (P < 0.001)**		
Activities of daily living	0.5 (P = 1.0)	6.5 (P = 0.01)*	6.4 (P = 0.01)*		

CI, confidence interval. KOOS: 0 = extreme symptoms and 100 = no symptoms; positive values indicate score improvement on the corresponding sub-scale. All *P*-values are adjusted for a design effect of 1.09. *P*-values in the post-hoc section are also adjusted with a Bonferroni correction.
* $P \leq 0.05$.
** $P < 0.005$.

objective and validated assessment tools to assist with developing patient-centered treatment plans aiming at the improvement of patient's movement profile and the risk reduction of OA progression.

4.2. Study limitations

This study has several limitations. First, as it consisted of a secondary analysis on a per-protocol population, the findings need to be replicated in other randomized studies. However, we are confident in the robustness of our results based on the quality of the study design (i.e., cluster RCT) and the statistical and clinical significance of the two regression models with distinct thresholds for the clinical levels of the GER. Second, the use of an orthosis during the 6-month follow up period has not been included as a covariate in the models. Although it could have had an impact on the improvement of some BMs in the two intervention groups, this would also have been the case for patients in the control group as well. Furthermore, less than 10% of the participants in the study reported buying an orthosis during the follow up period, and all knee kinesiography examinations were performed without knee brace or plantar orthotics. Third, it would have been interesting to compare outcomes in Group 2 and Group 3 with a control group in which generic exercises were suggested. However, this was not possible in the context of this secondary analysis, as the original RCT aimed at comparing the tailored care approach with the conventional primary care management as a whole. Finally, the use of the GER as the primary outcome has never been performed in other studies and this can be considered as a limitation. However, we believe that it represents a promising, innovative, and clinically meaningful outcome, which is important in the personalization of the conservative approach. This analytical approach avoids multiple mean comparisons and limits the loss of statistical power in sub-group analyses. The usefulness and relevance of this outcome needs to be further explored in future studies with larger sample sizes, additional populations, and different locations. It is also possible that the BMs should be differentially weighted in the GER's equation, in terms of their relationship to pain or rate of OA progression.

5. Conclusions

Targeted exercises can improve dynamic biomechanical markers in individuals with knee OA when compared with conventional primary care management. A knee kinesiography exam allowing objective assessment of biomechanical markers may provide healthcare professionals with useful information on the knee dynamic profile and subsequent targeted exercises to restore movement patterns, improve pain and function, and reduce the risk of OA progression. Further studies are needed to confirm the effect of a tailored exercise program on individual biomechanical markers in order to refine the modifiable targets to address to maximize patients' outcomes.

Funding

This work was funded by the Fonds de partenariat pour un Québec innovant et en santé (FPQIS) (government of Quebec, Canada), Emovi inc. and Sanofi–Aventis. Emovi inc. deployed the knee kinesiography exam in the clinics and Sanofi contributed to the knowledge transfer and burden of disease part of the project. Neither of them had access to patient data or had any involvement in the analysis/interpretation of the data, writing of the manuscript, or in the decision to submit this paper for publication.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Nicola Hagemeister reports financial support was provided by Emovi inc. Manon Choiniere reports financial support was provided by Emovi inc. Nathalie J Bureau reports financial support was provided by Emovi inc. Nicola Hagemeister reports financial support was provided by Sanofi-Aventis Canada Inc. Manon Choiniere reports financial support was provided by Sanofi-Aventis Canada Inc. Nathalie J Bureau reports financial support was provided by Sanofi-Aventis Canada Inc. Nathalie J Bureau reports financial support was provided by Quebec Health Research Fund. Nathalie J Bureau reports financial support was provided by Quebec Association of Radiologists. Nicola Hagemeister has patent #"A System for the Analysis of 3D Kinematic of the Knee". US 10/111 922 pending to Emovi inc. Nicola Hagemeister has patent #EP 00 972519.3 pending to Emovi inc.

Acknowledgments

The authors would like to thank Marc Dorais, biostatistician, who helped with designing and conducting the statistical analyses performed for this study.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.knee.2022.10.008.

References

[1] Bannuru RR, Osani MC, Vaysbrot EE, Arden NK, Bennell K, Bierma-Zeinstra SMA, et al. OARSI guidelines for the non-surgical management of knee, hip, and polyarticular osteoarthritis. Osteoarthr Cartil 2019;27(11):1578–89.
[2] Royal Australian College of General Practitioners. Guidelines for the Management of Knee and Hip Osteoarthritis. 2nd ed. East Melbourne, Vic: RACGP; 2018. p.1–82.
[3] Kolasinski SL, Neogi T, Hochberg MC, Oatis C, Guyatt G, Block J, et al. 2019 American College of Rheumatology/Arthritis Foundation Guideline for the Management of Osteoarthritis of the Hand, Hip, and Knee. Arthritis Rheumatol 2020;72(2):220–33.
[4] Fransen M, McConnell S, Harmer AR, Van der Esch M, Simic M, Bennell KL. Exercise for osteoarthritis of the knee: A Cochrane systematic review. Br J Sports Med 2015 Dec;49(24):1554–7. doi: https://doi.org/10.1136/bjsports-2015-095424.
[5] Lee AC, Harvey WF, Han X, Price LL, Driban JB, Bannuru RR, et al. Pain and functional trajectories in symptomatic knee osteoarthritis over up to 12 weeks of exercise exposure. Osteoarthr Cartil 2018;26(4):501–12.
[6] Wang TJ, Lee SC, Liang SY, Tung HH, Wu SF, Lin YP. Comparing the efficacy of aquatic exercises and land-based exercises for patients with knee osteoarthritis. J Clin Nurs 2011;20:2609–22. doi: https://doi.org/10.1111/j.1365-2702.2010.03675.x.
[7] Kuntz AB, Chopp-Hurley JN, Brenneman EC, Karampatos S, Wiebenga EG, Adachi JD, et al. Efficacy of a biomechanically-based yoga exercise program in knee osteoarthritis: A randomized controlled trial. PLoS ONE 2018 Apr 17;13(4):e0195653. doi: https://doi.org/10.1371/journal.pone.0195653.
[8] Henriksen M, Klokker L, Bartholdy C, Schjoedt-Jorgensen T, Bandak E, Bliddal H. No effects of functional exercise therapy on walking biomechanics in patients with knee osteoarthritis: exploratory outcome analyses from a randomised trial. BMJ Open Sport Exerc Med 2017 Mar 27;2(1):e000230. doi: https://doi.org/10.1136/bmjsem-2017-000230.
[9] Chang S-Y, Lin Y-J, Hsu W-C, Hsieh L-F, Lin Y-H, Chang C-C, et al. Exercise alters gait pattern but not knee load in patients with knee osteoarthritis. Biomed Res Int 2016;2016:1–12.
[10] Khalaj N, Abu Osman NA, Mokhtar AH, Mehdikhani M, Wan Abas WA. Effect of exercise and gait retraining on knee adduction moment in people with knee osteoarthritis. Proc Inst Mech Eng H 2014 Feb;228(2):190–9. doi: https://doi.org/10.1177/0954411914521155.
[11] Bennell KL, Kyriakides M, Metcalf B, Egerton T, Wrigley TV, Hodges PW, et al. Neuromuscular versus quadriceps strengthening exercise in patients with medial knee osteoarthritis and varus malalignment: A randomized controlled trial. Arthritis Rheumatol 2014;66(4):950–9.
[12] Sharma L, Chang AH, Jackson RD, Nevitt M, Moisio KC, Hochberg M, et al. Varus thrust and incident and progressive knee osteoarthritis. Arthritis Rheumatol 2017;69(11):2136–43.
[13] Grelsamer RP, Weinstein CH. Applied biomechanics of the patella. Clin Orthop Relat Res 2001 Aug;389:9–14. doi: https://doi.org/10.1097/00003086-200108000-00003.
[14] Omori G, Narumi K, Nishino K, Nawata A, Watanabe H, Tanaka M, et al. Association of mechanical factors with medial knee osteoarthritis: A cross-sectional study from Matsudai Knee Osteoarthritis Survey. J Orthop Sci 2016 Jul;21(4):463–8. doi: https://doi.org/10.1016/j.jos.2016.03.006.
[15] Lane NE, Brandt K, Hawker G, Peeva E, Schreyer E, Tsuji W, et al. OARSI-FDA initiative: defining the disease state of osteoarthritis. Osteoarthr Cartil 2011;19(5):478–82.
[16] Bennell KL, Dobson F, Roos EM, Skou ST, Hodges P, Wrigley TV, et al. Influence of biomechanical characteristics on pain and function outcomes from exercise in medial knee osteoarthritis and varus malalignment: Exploratory analyses from a randomized controlled trial. Arthritis Care Res (Hoboken) 2015;67(9):1281–8.
[17] Favre J, Jolles BM. Gait analysis of patients with knee osteoarthritis highlights a pathological mechanical pathway and provides a basis for therapeutic interventions. EFORT Open Rev 2017 Mar 13;1(10):368–74. doi: https://doi.org/10.1302/2058-5241.1.000051.
[18] Farrokhi S, Voycheck CA, Tashman S, Fitzgerald GK. A biomechanical perspective on physical therapy management of knee osteoarthritis. J Orthop Sports Phys Ther 2013 Sep;43(9):600–19. doi: https://doi.org/10.2519/jospt.2013.4121.
[19] Skou ST, Roos EM. Good Life with osteoArthritis in Denmark (GLA:D™): Evidence-based education and supervised neuromuscular exercise delivered by certified physiotherapists nationwide. BMC Musculoskelet Disord 2017 Feb 7;18(1):72. doi: https://doi.org/10.1186/s12891-017-1439-y.
[20] Anwer S, Alghadir A, Brismée J-M. Effect of home exercise program in patients with knee osteoarthritis: A systematic review and meta-analysis. J Geriatr Phys Ther 2016;39(1):38–48.
[21] Cagnin A, Choinière M, Bureau NJ, Durand M, Mezghani N, Gaudreault N, et al. A multi-arm cluster randomized clinical trial of the use of knee kinesiography in the management of osteoarthritis patients in a primary care setting. Postgrad Med 2020;132(1):91–101.
[22] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16(4):494–502.
[23] Lustig S, Magnussen RA, Cheze L, Neyret P. The KneeKG system: A review of the literature. Knee Surg Sports Traumatol Arthrosc 2012 Apr;20(4):633–8. doi: https://doi.org/10.1007/s00167-011-1867-4.
[24] Hunter DJ. Focusing osteoarthritis management on modifiable risk factors and future therapeutic prospects. Ther Adv Musculoskelet Dis 2009;1(1):35–47. doi: https://doi.org/10.1177/1759720x09342132.

[25] Mündermann A, Dyrby CO, Andriacchi TP. Secondary gait changes in patients with medial compartment knee osteoarthritis: increased load at the ankle, knee, and hip during walking. Arthritis Rheum 2005;52(9):2835–44.
[26] Astephen JL, Deluzio KJ, Caldwell GE, Dunbar MJ. Biomechanical changes at the hip, knee, and ankle joints during gait are associated with knee osteoarthritis severity. J Orthop Res 2008;26(3):332–41.
[27] Schmitt LC, Rudolph KS. Influences on knee movement strategies during walking in persons with medial knee osteoarthritis. Arthritis Rheum 2007;57 (6):1018–26. doi: https://doi.org/10.1002/art.22889.
[28] Gok H, Ergin S, Yavuzer G. Kinetic and kinematic characteristics of gait in patients with medial knee arthrosis. Acta Orthop Scand 2002;73(6):647–52. doi: https://doi.org/10.1080/000164702321039606.
[29] Moisio K, Chang A, Eckstein F, Chmiel JS, Wirth W, Almagor O, et al. Varus–valgus alignment: Reduced risk of subsequent cartilage loss in the less loaded compartment. Arthritis Rheum 2011;63(4):1002–9.
[30] Boivin K. Développement d'une approche d'évaluation clinique de la cinématique tridimensionnelle du genou durant la marche pour des patients gonarthrosiques. Ph.D. Thesis. École Polytechnique de Montréal, Montréal, Canada; 2010.
[31] Kuroyanagi Y, Nagura T, Kiriyama Y, Matsumoto H, Otani T, Toyama Y, et al. A quantitative assessment of varus thrust in patients with medial knee osteoarthritis. Knee 2012;19(2):130–4.
[32] Sharma L, Song J, Felson DT, Cahue S, Shamiyeh E, Dunlop DD. The role of knee alignment in disease progression and functional decline in knee osteoarthritis. JAMA 2001;286(2):188–95.
[33] Andriacchi TP, Briant PL, Bevill SL, Koo S. Rotational changes at the knee after ACL injury cause cartilage thinning. Clin Orthop Relat Res 2006;442:39–44.
[34] Roos EM, Lohmander LS. The Knee injury and Osteoarthritis Outcome Score (KOOS): From joint injury to osteoarthritis. Health Qual Life Outcomes 2003 Nov;3(1):64. doi: https://doi.org/10.1186/1477-7525-1-64.
[35] Thabane L, Mbuagbaw L, Zhang S, et al. A tutorial on sensitivity analyses in clinical trials: The what, why, when and how. BMC Med Res Method 2013;13:92.
[36] Katz MH. Multivariable Analysis – A Practical Guide for Clinicians and Public Health Researchers. Third Edition. Cambridge University Press; 2011. doi: 10.1017/CBO9780511974175.
[37] Nakagawa TH, Moriya ÉT, Maciel CD, Serrão AF. Frontal plane biomechanics in males and females with and without patellofemoral pain. Med Sci Sports Exerc 2012 Sep;44(9):1747–55. doi: https://doi.org/10.1249/MSS.0b013e318256903a.
[38] Nebel MB, Sims EL, Keefe FJ, Kraus VB, Guilak F, Caldwell DS, et al. The relationship of self-reported pain and functional impairment to gait mechanics in overweight and obese persons with knee osteoarthritis. Arch Phys Med Rehabil 2009;90(11):1874–9.
[39] Donner A. Some aspects of the design and analysis of cluster randomization trials. J R Stat Soc: Ser C: Appl Stat 1998;47(1):95–113.
[40] Campbell MK, Mollison J, Steen N, Grimshaw JM, Eccles M. Analysis of cluster randomized trials in primary care: a practical approach. Fam Pract 2000;17(2):192–6. doi: https://doi.org/10.1093/fampra/17.2.192.
[41] Campbell MJ. Cluster randomized trials in general (family) practice research. Stat Methods Med Res 2000;9(2):81–94.
[42] Ay S, Dogan SK, Evcik D. Is there an effective way to prescribe a home-based exercise program in patients with knee osteoarthritis? A randomized controlled study. Turkiye Fiziksel Tip ve Rehabilitasyon Dergisi 2013;59(1):1–6. doi: https://doi.org/10.4274/tftr.70894.
[43] Coleman S, Briffa NK, Carroll G, Inderjeeth C, Cook N, McQuade J. A randomised controlled trial of a self-management education program for osteoarthritis of the knee delivered by health care professionals. Arthritis Res Ther 2012 Jan 27;14(1):R21. doi: https://doi.org/10.1186/ar3703.
[44] Lee FI, Lee TD, So WK. Effects of a tailor-made exercise program on exercise adherence and health outcomes in patients with knee osteoarthritis: A mixed-methods pilot study. Clin Interv Aging 2016 Oct;5(11):1391–402. doi: https://doi.org/10.2147/CIA.S111002.
[45] Kigozi J, Jowett S, Nicholls E, Tooth S, Hay EM, Foster NE, et al. Cost-utility analysis of interventions to improve effectiveness of exercise therapy for adults with knee osteoarthritis: The BEEP trial. Rheumatol Adv Pract 2018;2(2):rky018. doi: https://doi.org/10.1093/rap/rky018.
[46] Pinto D, Robertson MC, Hansen P, Abbott JH. Cost-effectiveness of nonpharmacologic, nonsurgical interventions for hip and/or knee osteoarthritis: systematic review. Value Health 2012 Jan;15(1):1–12. doi: https://doi.org/10.1016/j.jval.2011.09.003.
[47] Skou ST, Roos EM, Laursen M, Arendt-Nielsen L, Rasmussen S, Simonsen O, et al. Cost-effectiveness of 12 weeks of supervised treatment compared to written advice in patients with knee osteoarthritis: A secondary analysis of the 2-year outcome from a randomized trial. Osteoarthr Cartil 2020 Jul;28 (7):907–16. doi: https://doi.org/10.1016/j.joca.2020.03.009.
[48] Legha A, Burke DL, Foster NE, van der Windt DA, Quicke JG, Healey EL, et al. Do comorbidities predict pain and function in knee osteoarthritis following an exercise intervention, and do they moderate the effect of exercise? Analyses of data from three randomized controlled trials. Musculoskeletal Care 2020 Mar;18(1):3–11. doi: https://doi.org/10.1002/msc.1425.
[49] Chapple CM. Physiotherapy for Osteoarthritis of the Knee: Predictors of Outcome at One Year (Thesis, Doctor of Philosophy). University of Otago; 2012. Retrieved from http://hdl.handle.net/10523/2194.
[50] Mezghani M, Hagemeister N, Ouakrim Y, Cagnin A, Fuentes A, Mezghani N. 3D kinematics and decision trees to predict the impact of a physical exercise program on knee osteoarthritis patients. Appl Sci 2021;11:834.