Osteoarthritis and Cartilage 26 (2018) 495–500

Osteoarthritis and Cartilage

Knee extensor strength gains mediate symptom improvement in knee osteoarthritis: secondary analysis of a randomised controlled trial

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ARTICLE INFO

Article history:
Received 7 September 2017
Accepted 22 January 2018

Keywords:
Quadriceps
Exercise
Knee osteoarthritis
Pain
Function

SUMMARY

Objective: To determine if an increase in knee extensor strength mediates the effect of a 12-week knee extensor strength training program on pain and physical function improvement in people with knee osteoarthritis (OA).
Design: Secondary analysis from a randomised controlled trial comparing the effects of a 12-week knee extensor strengthening exercise program to a control group with no intervention.
Methods: Data from participants with complete data ($n = 97$) enrolled in a previous clinical trial were analysed. Baseline and 12-week follow-up assessments included peak isometric knee extensor strength, pain and physical function. Peak knee extensor strength (Nm/kg) was assessed on an isokinetic dynamometer and subscales of the Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index were used to assess pain and physical function. Twelve-week change in pain and physical function were regressed separately, on 12-week change in knee extensor strength and group allocation. Covariates included baseline pain or physical function as appropriate, and baseline knee extensor strength, age, sex and knee alignment (stratification variable).
Results: Improved knee extensor strength mediated the effect of the strengthening program on both pain relief (mediated effect size = 0.69, 95% confidence intervals (CI) 0.05–1.33, $P = 0.03$), and improved physical function (mediated effect size = 1.86, 95% CI 0.08–3.64, $P = 0.04$), at 12 weeks.
Conclusions: Increased knee extensor strength partially mediates the effect of a knee extensor strength training program on pain and physical function improvement in people with knee OA.

Introduction

Knee osteoarthritis (OA) is a chronic musculoskeletal condition with symptoms including joint pain and physical dysfunction[1]. Exercise can provide modest symptomatic improvement[2,3] and is among the core treatments recommended by clinical guidelines[4–6] for knee OA[2,3]. Despite strong evidence supporting the effectiveness of exercise as a treatment for knee OA since 2002[3], little is known about the mechanisms underpinning improvements in symptoms in people undergoing exercise therapy[7]. Mediation analyses using data from randomised controlled trials (RCTs) are required to explore mechanisms of effects[8], yet no study to date has performed such analyses to determine mechanisms of exercise effects on knee OA symptoms. Understanding mechanisms may help researchers and clinicians to tailor exercise programs towards specific mechanistic factors and thereby optimise treatment effects.

In a previous RCT[9], we compared the effects of a 12-week knee extensor strengthening program to a control group with no intervention on symptoms of knee OA. The strengthening group demonstrated a 26% increase in knee extensor strength and improved pain compared to the control group[9]. Although self-reported physical function also improved in the strengthening group, no between-group statistical difference was observed[9]. Several mechanisms could potentially explain the relief in symptoms such as improvements in knee muscle strength[10–12], proprioception[7,11], inflammation[10–12], depression and self-efficacy[11]. Despite the plethora of possible mechanisms[7,10–12], knee extensor strength is particularly relevant to investigate[7].

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https://doi.org/10.1016/j.joca.2018.01.018
1063-4584/

Knee extensor weakness is a typical feature of knee OA[13,14], and is associated with the development of symptomatic knee OA[15] as well as functional decline over time in people with knee OA[16]. Evidence from observational[17,18] and pre–post exercise studies[19–22] reports associations between change in knee extensor muscle strength and change in pain[20–22] and self-reported physical function[17–20] in people with knee OA[17–22] or at risk for knee OA[17]. However, to date no study has used analytical approaches that investigate whether gains in knee extensor strength mediate symptom improvement. Using our clinical trial data[9], we aimed to evaluate the hypotheses that the effect of a knee muscle strengthening exercise program on improved self-reported pain and physical function is mediated by an increase in knee extensor muscle strength.

Methods

This is a secondary analysis of data from a RCT comparing the effects of a knee extensor strengthening program to a control group with no intervention in people with knee OA, with and without varus malalignment[9]. This RCT received ethics approval from the University of Melbourne Human Research Ethics Committee and all participants provided written informed consent.

Participants

Men and women were recruited from the community using advertisements between May 2005 and August 2006, Melbourne, Australia. Participants were included if they reported: medial knee pain, medial compartment osteophytes and medial joint space narrowing greater than lateral joint space narrowing, according to a standard atlas[23]. Exclusion criteria included: (1) any history of lower-limb joint replacement, (2) knee surgery within the previous 6 months, (3) intra-articular steroid or hylan G-F 20 injection within the previous 6 months, (4) systemic arthritis, (5) greater than 5° of valgus malalignment assessed on a radiograph [as the purpose of the original RCT was to compare people with and without varus malalignment], (6) currently participating or intending to start a lower-limb strengthening program within the next 3 months, (7) presence of any other medical condition that precluded safe participation in an exercise program, and (8) seeking or currently receiving physiotherapy for knee OA.

Intervention

The trial has been previously reported including randomisation (stratified by knee alignment), allocation, blinding procedures and the primary findings[9]. Following baseline assessment, eligible participants were randomly allocated to 12 weeks of strength training or a control group. The exercise intervention is reported in accordance with the TIDieR guidelines[24]. The intervention included knee extensor exercises to target knee extensor muscle weakness, which is often reported in people with knee OA[13,14]. Six physiotherapists in private practice with clinical experience in musculoskeletal disorders delivered the face-to-face intervention. One of the authors (BWL) visited each of the six physiotherapists at their practice to provide training and the study manual. The exercise group attended an individual physiotherapy session seven times over a 12-week period, and home exercises were performed five times weekly. Two days of rest per week could be determined by the participant. The intervention only targeted the study leg. In the case of bilateral knee OA, the most symptomatic leg was considered the study leg. The intervention included five non-weight bearing knee extensor strengthening exercises. Three of the exercises were a variation of a knee extension, two of which included isometric holds at 30° and 60° knee flexion with the weight; the other two exercises were a variation of a straight leg raise. Study physiotherapists provided participants in the intervention group with exercise instruction sheets, ankle cuff weights and black Theraband (Ohio, USA). Prior to randomisation, author (BWL) performed a 10 repetition maximum test (10-RM) on all participants to determine the appropriate starting weight for exercise (see Supplementary material for further details on this procedure). The 10-RM information for each participant randomised to the intervention group was delivered to the study physiotherapist. Based on unpublished pilot data and clinical expertise (BWL, RSH, KLB) at the time of the trial, participants began their exercises using 50% of their 10-RM weight for knee extension exercises and 25% of their 10-RM for straight leg raise exercises. Isometric exercises were held for 10 s and included to avoid participants having to flex and extend their painful knee for each exercise. Participants performed two sets of 10 repetitions in the first 2 weeks and 3 sets of 10 repetitions thereafter for each of the 5 exercises. The exercises were performed at a self-selected pace with emphasis on movement quality. Physiotherapists increased the ankle weight and duration of isometric holds if participants performed the exercise in a smooth manner with consistent speed and relative comfort. Adherence was assessed using a training diary kept by the participant. Adherence was reported as the percentage of home exercises completed, that is the number of days the participant performed the prescribed strengthening exercise divided by the maximum number of days the strengthening exercise were prescribed (i.e., 60 days). Participants allocated to the control group did not receive any intervention and were asked not to begin any new treatment or strengthening program for the duration of the study.

Pain and physical function

At baseline and 12-week follow-up, self-reported pain and physical function were assessed using the respective Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index subscales[25]. The WOMAC pain subscale incorporates five items, with overall scores ranging between 0 (no pain) and 20 (maximum pain). The physical function subscale includes 17 items with overall scores ranging between 0 (no difficultly with physical function) and 68 (extreme difficulty with physical function). Higher scores indicate more severe pain and physical dysfunction. The WOMAC has been demonstrated as valid, reliable and responsive in several OA studies[26].

Knee muscle strength

At baseline and 12-week follow-up, maximal isometric knee extensor strength was assessed using a KinCom 125-AP isokinetic dynamometer (Chattecx, Chattanooga, TN, USA) at 60° knee flexion. Participants were familiarised with testing procedures and performed submaximal efforts before performing three maximal trials while receiving strong verbal encouragement to 'push as hard as you can'. The distance (m) from the ankle cuff to the rotation axis of the dynamometer was measured as the lever arm length, and the highest peak force (Newtons) was multiplied by the lever arm (Nm), which was then divided by body mass (Nm/kg) for analysis. The test–retest reliability for isometric knee muscle strength assessment has been reported as very good (correlation coefficient $\geq$0.83) in women with knee OA[27].

Other measures

At baseline, radiographic disease severity was assessed using the Kellgren & Lawrence (KL) grading scale[28]. Participants were

graded as either grade 2 (definitive osteophytes with possible narrowing of joint space), grade 3 (moderate multiple osteophytes, definite narrowing of joint space and some sclerosis and possible deformity of bone ends) or grade 4 (large osteophytes, marked narrowing of joint space, severe sclerosis and definite deformity of bone ends). Anatomic knee alignment was assessed from radiographs according to previously described methods[29].

Statistical analysis

Stata software, version 13.1 (Statcorp, College Station, TX, USA) was used for statistical analyses and significance was set at $P < 0.05$. Independent *t*-tests were used to compare baseline characteristics of participants who had complete data and those who had incomplete data. Incomplete data were defined as missing either pain, physical function or strength data. Statistical analyses were performed on complete cases, such that participants with incomplete data were not included in the mediation analyses.

A two-stage analytical approach to mediator analysis as recommended by Wearden and Emsley[30] was used. In the first stage, linear regression was used to determine the effect of the intervention on knee extensor strength (putative mediator). The model was adjusted for baseline knee extensor strength. This analysis assesses whether pathway *a* in Fig. 1 is present. Given that knee extensor strength significantly increased in the intervention group compared to the control group, a full mediation analysis was conducted using the 'medeff' function in Stata[31].

The second stage involved fitting two regression models for each outcome (pain and physical function). Age, sex, knee alignment (stratification variable in original trial), baseline knee extensor strength and baseline outcome values were considered as potential confounders of the mediator (change in knee extensor strength)–outcome (symptom) relationship (Fig. 1 pathway *c*). These variables could reasonably be considered to influence not only strength but also symptoms and were entered into each of the subsequent regression models. The first model estimated the direct effect of the intervention and the effect of change in knee extensor strength on the outcome (Fig. 1 pathways *b* and *c*). The second model estimated the effect of the intervention on change in knee extensor strength (Fig. 1 pathway *a*). These two models permitted the total effect of the intervention on the outcome to be decomposed into the direct effect (Fig. 1 pathway b) and the indirect effect (Fig. 1 pathways *a* and *c*). The direct effect refers to the effect of the intervention on outcome that does not occur through the change in knee extensor strength. Residuals of each linear model conformed to appropriate assumptions, such that scatter plots of residuals verified the assumptions of normality and constant variance. The 'paramed' function in Stata[32] determined the proportion of effect mediated: estimated as the ratio of the indirect effect to the total effect. Finally, a linear regression model was used to estimate the association between the between-group increase in knee extensor strength (Nm/kg) from baseline and change in symptoms. In this model, change in symptom was entered as the outcome, change in strength was the independent variable and age, sex, alignment baseline symptom and knee extensor strength were entered as confounding variables.

Results

Of the 107 participants enrolled into the original study, 97 (91%) returned and were included in the current analysis. There were no between-group differences in the baseline characteristics of participants randomised to the exercise group and control group (Table I). In general, the sample was middle-aged and overweight and had slightly more females than males. Participants who had incomplete data were more symptomatic compared to participants who had complete data (mean difference in pain 2.5, 95% confidence intervals (CI) [0.6–4.4] and mean difference in physical function 7.8, 95% CI [0.8–14.7]). No other statistical differences were observed for any other variables used in this study. Participants in the intervention group reported to complete on average ± consisted with 91 ± 14% days of the prescribed home exercises.

Both the unadjusted and adjusted analysis confirmed that strength training significantly improved peak knee extensor strength compared to the control group (Table II). Therefore, increased knee extensor strength was considered a potential mediator of pain relief and improved physical function. Table III presents the results of the mediation analyses. Increased knee

Table I
Participant characteristics

	Exercise ($n = 49$)	Control ($n = 48$)
Age, yrs	65.7 (8.2)	63.8 (9.1)
Women, *n* (%)	27 (55%)	21 (44%)
Mass, kg	79.4 (13.5)	78.6 (15.1)
Body mass index, kg/m^2	28.6 (4.4)	29.1 (5.2)
WOMAC pain, (0–20)	6.6 (2.8)	7.2 (3.0)
WOMAC physical function, (0–68)	21.1 (10.9)	24.8 (10.3)
Knee alignment*, degrees	4.1 (3.3)	4.5 (3.2)
Bilateral knee OA, (yes/no)	19:30	18:30
Radiographic disease severity, *n* (%)		
KL grade 2	14 (29%)	14 (29%)
KL grade 3	14 (29%)	13 (27%)
KL grade 4	21 (43%)	21 (44%)

WOMAC: Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index; higher scores indicate more severe symptoms.
* Positive values indicate varus alignment.

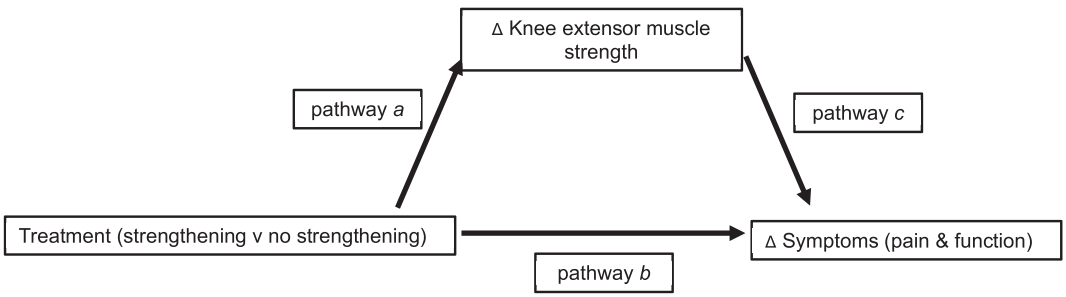

Fig. 1. Twelve-week change in knee extensor strength as a mediator of the effect of a 12-week knee extensor strengthening program (treatment) and symptoms (12-week change in pain and physical function). Pathway *a* is the effect of strengthening on knee extensor strength, pathway *b* is the direct effect of treatment on symptoms and pathway *c* is the effect of change in knee extensor strength on symptoms. Total effect is the sum of direct effect (pathway *b*) and indirect effect (pathway *a* multiplied by pathway *c*).

Table II
Mean (SD) of groups and mean difference in change between groups (mean, 95% confidence interval)

		Baseline		Follow-up		Unadjusted difference in change between groups (week 13–week 0)		*Adjusted difference in change between groups (week 13–week 0)	
		Exercise	Control	Exercise	Control	Exercise minus control	*P*	Exercise minus control	*P*
Putative mediator	Knee extensor strength (Nm/kg)	1.35 (0.52)	1.32 (0.55)	1.70 (0.60)	1.35 (0.57)	0.32 (0.21, 0.43)	<0.001	0.33 (0.22, 0.44)	<0.001

* Adjusted for baseline measures of knee extensor strength.

Table III
Effect size estimates of the total, direct and indirect effect of a knee strengthening program on symptoms measured at 12 weeks

Putative mediator	Outcome	Total effect			Direct effect			Indirect effect			Proportion mediated
		Effect estimate	SE	*P*	Effect estimate	SE	*P*	Effect estimate	SE	*P*	
Δ Knee extensor strength (Nm/kg)	Δ WOMAC pain	1.8 (0.8, 2.8)	0.5	0.001	1.1 (0.0, 2.2)	0.6	0.064	0.7 (0.1, 1.3)	0.3	**0.03**	38% (24%, 98%)
	Δ WOMAC function	2.9 (−0.2, 5.8)	1.5	0.052	1.0 (−2.3, 4.3)	1.7	0.536	1.9 (0.1, 3.6)	0.9	**0.04**	60% (−192%, 356%)

Covariates: baseline outcome score, baseline mediator score, age, sex, alignment.
WOMAC: Western Ontario and McMaster Universities (WOMAC) Osteoarthritis Index.
Bold indicates statistical significance.

extensor strength mediated pain relief and accounted for 38% of the improvement in pain. Notably the direct effect did not reach statistical significance; while the indirect effect of the strengthening program acting through increased knee extensor strength did − indicating that improved knee extensor strength is a mediator of pain relief. Specifically, a 1-unit (1 Nm/kg) increase in knee extensor strength from baseline was associated with a 2.2-unit reduction (95% CI −4.2 to −0.3) in pain from baseline. Increased knee extensor strength also partially mediated improvement in physical function and accounted for 60% of the improvement. However, the confidence interval for this estimate was very wide 95% CI (−192%, 356%), reflecting the imprecision of this estimate and that it could be 0. Nevertheless, the corresponding direct effect did not reach statistical significance suggesting that improvement in physical function due to the strengthening program was largely determined by gains in knee extensor strength. Specifically, a 1-unit increase in knee extensor strength from baseline was associated with a 6.3-unit reduction (95% CI −12.0 to −0.6) in physical function from baseline.

Discussion

Increased knee extensor strength mediated the effect of a 12-week knee extensor strengthening program on symptoms in people with knee OA. Although concurrent associations between change in knee extensor strength and change in knee OA symptoms have been demonstrated previously[19–22], within the context of a RCT, this is the first study to apply a formal statistical test of mediation. Evidence that increased knee extensor strength partially explains symptom improvement in people with knee OA can potentially facilitate exercise prescription to further improve outcomes.

The primary goal of knee OA treatment is to reduce pain and improve physical function[3]. Hence, our finding that gains in knee extensor strength mediate 38% and 60% of the improvement in pain and physical function, respectively, in individuals with knee OA is particularly relevant. Although exercise irrespective of type has been described as beneficial for knee OA symptoms[3], our observations provide new evidence of *how* a knee extensor strengthening program yields symptomatic benefits. This may assist clinicians engaging with and educating patients with knee OA as to how they might expect symptomatic benefits from strengthening exercises.

Based on our regression equations, the 0.33 Nm/kg (26%) average increase in knee extensor strength from baseline was associated with a 0.73-unit improvement (95% CI −1.37 to −0.10) in WOMAC pain and a 2.08-unit improvement (95% CI −3.95 to −0.21) in WOMAC physical function. In the current study, the intervention group improved in pain (−1.90 WOMAC units [95% CI −2.90, −0.89]) and physical function (−3.11 WOMAC units [95% CI −6.10, −0.12]) compared to controls[9]. Hence, the increase in knee extensor strength only partially mediated symptom improvement. This is also evidenced by the unaccounted proportion of improvement in pain (68%) and physical function (40%). The proportion of symptom improvement unaccounted for could be attributed to several other hypothesised mediators including exercise-related improvements in proprioception[7,11], inflammation[10–12], depression and self-efficacy[11], none of which were assessed in our study.

The intervention group increased knee extensor strength by a mean of 26% compared to the control group. In the context of strength gains in people with knee OA, the strength gains in the current study are higher than mean increases of 17% in response to resistance training in people with knee OA reported in a systematic review[33]. Evidence-based guidelines to improve muscle strength do not exist specifically for people with knee OA. Nevertheless, the American College of Sports Medicine[34] recommends exercising 2–3 days per week, at 60–70% of a 1-RM and performing 8–12 repetitions for 2–4 sets to improve muscle strength. While the repetitions and sets prescribed in the current study are in line with ACSM recommendations[34] the intensity (50% of 10-RM upon commencing the exercise program) and frequency (5 days per week) prescribed were not. Hence, training parameters used in the current study were arguably suboptimal for improving muscle strength. Knee extensor strength could potentially be further increased in the current study by prescribing a more intensive exercise program[35,36] (i.e., greater intensity, less frequency), which may yield greater symptomatic benefits as demonstrated in hip OA.[37]

Although we determined that knee extensor strength gains in part mediate symptom improvement it remains unclear *how* strength gains mediate symptom improvement. Indeed, symptom improvement, and in particular pain relief, could mediate increases in knee extensor strength. The aetiology of pain in knee OA is poorly

understood and can be influenced by several factors including, but not limited to genetics, psychological factors, previous experience and current mood[38]. With respect to physical function, the knee extensors are among primary muscles used to perform the majority of tasks assessed in the physical function component of the WOMAC questionnaire, such as walking, stair ambulation, and rising from a chair[24]. Therefore, given that knee muscle weakness is often a feature of knee OA[13,14], it is reasonable to observe that an increase in extensor strength mediates in less difficulty with physical function.

It can be speculated that the gains in knee extensor strength observed in our study resulted from muscle hypertrophy and/or neural adaptation, as reported in healthy individuals undergoing strength training[39]. However, several factors such as knee pain severity, anxiety, joint effusion and other sources of arthrogenous inhibition can influence an assessment of knee muscle strength[14]. It is therefore possible that alterations in these factors also contributed to an increase in knee muscle strength. Indeed, clinical attention to such factors may also increase knee muscle strength. Another consideration is body mass. However, body mass did not change over the 12-week study period and our observations remained similar when examining changes in non-normalised knee strength (Nm) (data not shown).

Our study extends existing knowledge by demonstrating that gains in knee extensor strength mediate symptom improvement using data from a clinical trial, which exclusively examined the effect of five simple knee extensor exercises. However, our finding should be interpreted with caution. Pain and physical function were considered as independent outcomes in the current study as pain and physical function WOMAC subscales reportedly fulfil criteria for face, content and construct validity[25]. However, change in pain and change in physical function are correlated ($r = 0.84$; $P < 0.001$ for the exercise group), and change in pain is likely be associated with change in physical function and potentially *vice versa*. Another consideration is the use of peak knee extensor strength. Individuals rarely maximally contract their lower-limb muscles during activities of daily living but instead use an unknown individual-specific proportion of their maximal strength. It is therefore possible that other submaximal muscle measures such as muscle endurance may be more closely related to physical function. Nevertheless, we assessed maximal muscle strength given its potential use in clinical practice and previous work demonstrating the reliability of the strength measures in people with knee OA[27].

There are also several limitations of this study. First, mediation analysis assumes there is no unmeasured confounding between the change in knee muscle strength and change in symptoms (Fig. 1 pathway *c*). Although we addressed this assumption by including baseline variables that may confound this relationship, we cannot rule out the existence of unmeasured variables. Second, our analysis is based on participants with complete data. Third, given that our mediator and outcomes were measured at the same time-points, the direction of effect cannot be conclusively determined. Future research should aim to assess putative mediators (i.e., knee muscle strength) at time-points preceding treatment outcomes. Fourth, our findings can only be generalised to self-reported measures of pain and physical function using the WOMAC and only to peak isometric knee extensor strength assessed at 60° knee flexion using a dynamometer. Further to this, other aspects of muscle function (e.g., submaximal strength and/endurance) may be more relevant to understand improvement in physical function than peak isometric strength. Similarly, caution should be used in extrapolating our findings beyond the 12-week knee extensor exercise program used in the current study. Fifth, although we aimed to determine if increased knee muscle strength mediated the effect of a knee muscle strengthening regime, other potential mediators such as proprioception[7,11], inflammation[10–12], depression, self-efficacy[11] and pain medication, were not assessed in the current study. Finally, our small sample size and large variation in symptom improvement may have attributed to the notable variation in the proportion of symptoms, mediated by increased knee extensor strength, particularly physical function.

In conclusion, we found evidence to suggest that an increase in knee extensor strength mediates the effect of a knee extensor strengthening program on knee OA symptom improvement. Understanding that increased knee extensor strength in part underpins symptom improvement in people with knee OA, may facilitate researchers and clinicians to improve exercise programs to increase knee extensor strength. Further research is required to confirm these observations and investigate the dose–response relationship between an increase in knee extensor strength and improvement in knee OA symptoms.

Authors' contribution

MH, RSH, TVW, JK, KLB conceived and design the study. BWL acquired the data. MH and JK performed data analyses. MH, RSH, TVW, JK, BWL, KLB interpreted the data. MH wrote the first draft of the manuscript. All authors revised the manuscript for intellectual content and approved final version for submission.

Conflict of interest

The authors have no competing interests to declare.

Role of the funding source

MH is supported by a Sir Randal Heymanson Research Fellowship from the University of Melbourne. RSH is supported by a Future Fellowship from the Australian Research Council (FT130100175). KLB is supported by a NHMRC Principal Research Fellowship (APP1058440). The study sponsors did not play any role in the study design, collection, analysis or interpretation of data, writing of the manuscript, decision to submit the manuscript for publication.

Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.joca.2018.01.018.

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