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Avoidance of activity and limitations in activities in patients with osteoarthritis of the hip or knee: a 5 year follow-up study on the mediating role of reduced muscle strength

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SUMMARY

Objective: To evaluate the mediating role of reduced muscle strength in the relationship between avoidance of activity and limitations in activities in patients with knee or hip osteoarthritis (OA).

Methods: A longitudinal cohort study with 5 years follow-up was conducted. Patients with knee or hip OA (n = 288) were recruited at rehabilitation centers and hospitals. Self-reported and performance based limitations in activities, avoidance of activity and muscle strength were assessed at baseline, 1, 2, 3 and 5 years follow-up. Generalized Estimating Equations (GEE) analyses were used to evaluate mediation.

Results: In patients with knee OA, reduced knee extensor muscle strength mediated the relationship between avoidance of activity and limitations in activities. In patients with hip OA reduced hip abductor muscle strength mediates the relationship between avoidance of activity and limitations in activities.

Conclusion: The results of this longitudinal study support the theory that avoidance of activity leads to deterioration of muscle strength and consequently to more limitations in activities in patients with knee and hip OA.

INTRODUCTION

Osteoarthritis (OA) is associated with impairments in body functions and structures, such as pain and reduced muscle strength, and limitations in activities, such as walking, stair climbing, rising from a chair, and getting in and out a car[1, 2 and 3]. Limitations in activities seem to deteriorate slowly over time[4].

The way in which patients cope with their condition, especially the passive coping style of avoiding physical activity, is a risk factor for future limitations in activities in

patients with knee or hip OA[5]. According to the avoidance model[6], the relationship between avoidance of activity and limitations in activities is mediated by reduced muscle strength (see Fig. 1). Patients tend to avoid physical activity in order to prevent pain. In the short-term, this seems an adaptive coping strategy, as pain in OA is frequently activity related[7 and 8]. However, in the long-term, avoidance of physical activity is hypothesized to lead to deterioration of muscle strength, resulting in greater limitations in activities.

[FIGURE 1]

Earlier cross-sectional research has confirmed that reduced knee extensor muscle strength is indeed a mediator in the relationship between avoidance of activity and limitations in activities in patients with knee OA[6, 7 and 8]. Up till now high quality longitudinal research on the mediating role of reduced muscle strength is lacking. Furthermore, the existing studies focused exclusively on patients with knee OA. The aim of the current study was to evaluate the mediating role of reduced muscle strength in the relationship between avoidance of activity and limitations in activities in patients with knee or hip OA, in a longitudinal study. It was hypothesized that in patients with knee OA avoidance of activity leads to deterioration of knee extensor muscle strength and consequently, to greater limitations in activities. In patients with hip OA, it was hypothesized that avoidance of activity leads to deterioration of hip abductor muscle strength and consequently, to greater limitations in activities.

METHODS

A 5 years prospective cohort study was conducted among 288 patients with knee or hip OA[5 and 9]. Patients were recruited from three rehabilitation centers and two hospitals (Departments of Orthopedics, Rheumatology or Rehabilitation Medicine). Inclusion criteria were: (1) diagnosis of hip or knee OA by a medical specialist according to radiological criteria or clinical criteria of the American College of Rheumatology[10 and 11]; (2) age between 50 and 84 years; (3) referral to hospital or rehabilitation center less than 1 year before inclusion; (4) at least moderate functional problems (Lequesne Algofunctional Index score ≥ 5)[12 and 13]; and (5) informed consent. Exclusion criteria were: (1) insufficient understanding of the Dutch language, and (2) expected death within 1 year after inclusion, due to terminal illness. Measurements were conducted at baseline, 1, 2, 3 and 5 years follow-up. The study was approved by the Medical Ethics Committee of the VU University Medical Centre, Amsterdam, the Netherlands.

Measurements

Avoidance of activity

To assess the level to which patients avoid physical activity when in pain, the subscale resting of the Pain Coping Inventory (PCI) was used[14 and 15]. This subscale consists of five items, which assess the level to which patients avoid activity when experiencing pain. Items are answered on a 4-point scale (1 rarely/never; 2 occasionally; 3 often; 4 very often), with a higher score indicating a more frequent

use of resting as a strategy for coping with pain. The items are as follows: (1) When I am in pain, I cease my activities; (2) When I am in pain, I limit myself to simple activities; (3) When I am in pain, I take care to avoid physical activity; (4) When I am in pain, I rest by sitting down or reclining; and (5) When I am in pain, I adopt a comfortable posture. The sum of scores on all five items is used as the score for avoidance of activity. A higher score means more frequent avoidance of activity. The PCI has been shown to be a reliable and valid measure for pain coping in patients with various chronic pain, including OA[14 and 15].

Limitations in activities

Self-reported limitations in activities were measured using the physical functioning subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC)[16 and 17]. A higher score on the WOMAC (0–68) reflects more limitations in activities.

Performance based limitations in activities were measured using a 10 m timed walking test[18]. Each patient was asked to walk to the end of a pre-set distance of 10 m, at his or her natural walking speed. A stopwatch was used to measure in seconds the time patients walked the 10 m distance. If necessary, patients could use an assistive device during the timed walking test. Use of devices was recorded and consequently, devices were also used at 1, 2, 3 and 5 years follow-up. A higher score on the timed walking test reflects more limitations in activities.

Muscle strength

Isometric muscle strength of knee extension and hip abduction was measured in both legs with a hand held dynamometer, the MicroFet, using a break-test[19]. Patients were asked to deliver maximum strength against the researcher resistance. A standardized protocol, describing postures, instructions and procedure was used. The measurements of muscle strength were repeated twice. The average muscle strength was used in the analyses.

Demographic and clinical data

Demographic and clinical data were collected on age, gender, height, weight, location of OA, duration of complaints, and level of education. Body mass index (BMI) was calculated. At each assessment, all measurements were conducted at one visit and were performed by a research assistant.

Statistical analysis

Knee extension muscle strength and hip abduction muscle strength were calculated, by calculating the sum score for the left and right leg, according to Steultjens *et al.* Ref. [20]. Prior to this calculation, scores for muscle strength on the MicroFet were divided by body weight.

Multiple imputation (MI) was used to impute missing data, using the Multivariate Imputation by Chained Equations (MICE) procedure[21 and 22]. Ignoring missing data, by restricting the analyses to subjects with complete data, can lead to biased results if missing values are not missing completely at random (MCAR). In our dataset, missing data were Missing at Random (MAR), i.e., missing data depended on other observed data. For example, subjects with complete data at 5 years follow-up were

younger and had a shorter duration of complaints, a higher level of education, fewer limitations in activities, greater muscle strength, less pain and less comorbidity compared with subject without complete data. MI was done by fitting models to predict missing values for a given variable based on all other observed variables, including the outcome variable. This makes the MAR assumption plausible. Five imputed data sets were created, each of which was analyzed separately. The results of the five analyses were combined using Rubin's rules to produce pooled estimates of mean effects and standard deviations[23 and 24].

All analyses were performed separately for patients with knee OA and patients with hip OA. Because patients with both knee and hip OA were included as well, all analyses were adjusted for having OA in the other joint. Knee extension muscle strength was used in the analyses on knee OA, while abduction muscle strength was used in the analyses on hip OA.

All analyses were performed using Generalized Estimating Equations (GEE) analyses[25, 26 and 27]. GEE corrects for the dependency of individual observations: the relationships are investigated for each individual separately; the final result is obtained by getting the study population average of all individual relationships. The correction for dependency of the observations is performed by assuming a so-called working correlation structure. An unstructured correlation structure was used. All analyses were performed using STATA 10.0.

To investigate whether muscle strength mediates the relationship between avoidance of activity and limitations in activities, the causal step method was used as described by Baron and Kenny[28 and 29]. This method indicates a series of requirements which must be true for the mediation model to hold (see Fig. 2). The steps require: (1) The total effect of the independent variable on the dependent variable must be significant (analysis 1). (2) The path from the independent variable to the mediator must be significant (analysis 2). (3) The path from the mediator to the dependent variable must be significant and the effect of the independent variable on the dependent variable should be smaller than in analysis 1, since this effect should now be accounted for by the effect of the mediator on the dependent variable (analysis 3).

The statistical significance of the mediation effect was established with the Sobel–Goodman test[30]. Multivariate GEE analyses were performed with the independent and dependent variables at baseline, 1, 2, 3 and 5 years follow-up assessment. The interpretation of the regression coefficient (*B*) derived from the GEE analyses is as follows: one unit difference in the independent variable on average over time is associated with B units change in the dependent variable on average over time.

[FIGURE 2]

There are several assumptions in investigating mediation effects. First of all, there may be no misspecification of causal order (reverse-causal effects). The conclusions from a mediation analysis are valid only if the causal assumptions are valid (Judd & Kenny). In case of reversed causality between variables in the model, mediation analysis may lead to invalid conclusions. Although the direction of causation cannot be determined by statistical analysis, a statistical approach to rule out reverse causality has been suggested[31]. Accordingly, mediation analysis was applied to alternative models in which the determinant, mediator and outcome variables have

been interchanged. In alternative model I it was investigated if limitations in activities cause reduced muscle strength and consequently more avoidance of activity. In alternative model II it was investigated if avoidance of activity leads to limitations in activities and consequently to reduced muscle strength. If the results look similar to the results of the hypothesized model, one would be less confident in the hypothesized model. Secondly, the mediator may not be an interaction term in the relationship under investigation. Therefore, potential effect modification of muscle strength in the relationship between avoidance of activity and limitations in activities was tested. At last, potential confounders should be taken into account. The analysis was adjusted for the following potential confounders; age, gender, duration of complaints, BMI, educational level, and comorbidity.

RESULTS

Patients

Patients with OA of the hip or knee that visited the department in the year prior to inclusion (n = 775) were contacted by mail and were asked to participate in the study. Of those patients who volunteered (n = 364), 288 were included. Seventy-six patients were excluded. Reasons of exclusion are shown in Fig. 3. Patients who were included in the study (N = 288) did not differ with regard to age and gender from patients who were initially contacted (N = 775). Included patients suffered more frequently from both hip and knee OA (26.5% vs 6.2%) and less frequently from only knee OA (48.4% vs 59.5%) and only hip OA (25.1% vs 34.3%) compared to patients who were initially contacted.

[FIGURE 3]

Of the 288 patients who were included in the study, 211 patients (73%) also participated after 5 years (see Fig. 3). Baseline characteristics of completers were compared with non-completers. Patients who completed the study were younger and had a shorter duration of complaints, a higher level of education, fewer limitations in activities, more muscle strength, less pain and less comorbidity. The baseline characteristics of the study population after MI of missing data are presented in Table I. The majority of the patients (79%) originated from Departments of Orthopedics. The other 21% came from Departments of Rheumatology and Departments of Rehabilitation Medicine.

[TABLE 1]

The mediating effect of reduced muscle strength in patients with knee OA

The results of the analyses aimed at establishing the mediating effect of reduced muscle strength on the relationship between avoidance of activity and limitations in activities are presented in Table II (self-reported limitations in activity) and Table III (performance based limitations in activity). The criteria for the mediating effect of reduced knee extensor muscle strength were met in patients with knee OA. Namely, avoidance of activity was significantly associated with more self-reported and performance based limitations in activities (analysis 1). Furthermore, avoidance of activity was also significantly associated with reduced knee extensor muscle strength (analysis 2). In analysis 3, reduced knee extensor muscle strength was associated with more self-reported and performance based limitations in activities, and the

impact of avoidance of activity on self-reported and performance based limitations in activities was reduced compared with analysis 1. The Sobel–Goodman mediation tests showed that the mediation effect of knee extensor muscle strength was statistically significant, with approximately 17% of the total effect of avoidance of activity on self-reported limitations in activities being mediated and approximately 13% of the total effect of avoidance of activity on performance based limitations in activities being mediated.

[TABLE 2] [TABLE 3]

The mediating effect of muscle strength in patients with hip OA

After adjustment for potential confounders, the criteria for the mediating effect of reduced hip abduction muscle strength were met in patients with hip OA (see Table II and Table III). Namely, avoidance of activity was significantly associated with more self-reported and performance based limitations in activities (analysis 1). Furthermore, avoidance of activity was also significantly associated with reduced hip abduction muscle strength (analysis 2). In analysis 3, reduced hip abduction muscle strength was associated with more self-reported and performance based limitations in activities, and the impact of avoidance of activity on self-reported and performance based limitations in activities was reduced compared with analysis 1. The Sobel–Goodman mediation tests showed that the mediation effect of hip abduction muscle strength was statistically significant, with approximately 10% of the total effect of avoidance of activity on self-reported limitations in activities being mediated and approximately 8% of the total effect of avoidance of activity on performance based limitations in activities being mediated.

Assumptions

The results of the reverse-causal effect analysis (testing alternative model I and II) did not indicate reversed causality. Namely, alternative model I could not be confirmed, neither in patients with knee OA nor in patients with hip OA (data not shown). Furthermore, alternative model II could not be confirmed for patients with hip OA. Although significant mediation was found for patients with knee OA using alternative model II, the effects were very small (data not shown). Finally, muscle strength was not found to be an effect modifier of the relationship between avoidance of activity and limitations in activities (initial model).

DISCUSSION

This is the first longitudinal study evaluating the mediating role of muscle strength in the relationship between avoidance of activity and limitations in activities in patients with knee OA and patients with hip OA. The results show that in patients with knee OA reduced knee extensor muscle strength mediates the relationship between avoidance of activity and limitations in activities. In patients with hip OA reduced hip abductor muscle strength mediates the relationship between avoidance of activity and limitations in activities.

The findings of the current study confirm the validity of the avoidance model[6] as explanation for deterioration of limitations in activities in patients with knee and hip OA. The findings of the current study confirm the findings of previous research by Steultjens *et al.* [7] and Holla *et al.* [8] and Dekker *et al.* Ref. [6]. Although the results of

these cross-sectional studies are consistent with the hypothesis that muscle strength mediates the relationship between avoidance of activity and limitations in activities, no conclusion regarding causality could be drawn. The current longitudinal study is the first study providing evidence that more avoidance of activity over time results in a reduction of knee extensor muscle strength in patients with knee OA and reduction of hip abductor muscle strength in patients with hip OA over time, leading to deterioration of limitations in activities. In case of reversed causality between variables in the hypothesized model, mediation analysis may lead to invalid conclusions. Reversed causal effect analysis of two alternative models indicated no reversed causality, except for patients with knee OA using alternative model II: the reverse-causal effect analyses indicated that more avoidance in activity may lead to limitations in activities and consequently to reduced muscle strength. However, the regression coefficients were very small, which practically rules out reversed causality. Therefore, it was concluded that the initial hypothesized model seems to be the most plausible model. However, it should be noticed that the direction of causation cannot be determined by statistical analysis [31]. Further experimental research is required to evaluate the direction of causality.

Although evidence in favor of mediation of muscle strength was found in patients with knee and hip OA, the indirect effect of muscle strength (respectively 13–17% in patients with knee OA and 8–10% in patients with hip OA) on the relationship between avoidance of activity and self-reported and performance based limitations in activities was rather small. This indicates that there are other pathways through which avoidance of activity affects limitations in activities. For instance, inactive patients could develop low-self-efficacy beliefs about their capability to perform activities, which can result in the inability to perform certain activities[7]. Several studies have indeed shown that inactivity is associated with low-self-efficacy[32], and that low-self-efficacy leads to more limitations in activities[33 and 34].

The mediation effect of muscle strength in the relationship between avoidance of activity was smaller in patients with hip OA, compared to patients with knee OA. In hip OA, we assessed abduction muscle strength: one explanation for finding a small mediating effect could be that reduced muscle strength in other directions of movement also mediates between avoidance and limitations in activity. Namely, we have previously demonstrated that muscle strength in various directions of movement is strongly correlated with limitations in activities[20]. On the other hand, whereas the knee joint is particularly stabilized by muscle strength, the stability of the hip joint is to a large extent provided by its shape (i.e., ball and socket joint). Therefore it could be hypothesized that muscle weakness plays a less important role in the development of limitations in activity in hip OA patients than in knee OA patients.

Based on the results of the current study it seems important that clinicians assess and monitor the tendency to avoid physical activity, so that patients can be identified in which therapeutic exercise therapy is indicated. Therapeutic exercise therapy in these patients could not only focus on improving muscle strength, but could also include strategies directed changing patients' physical activity, such as behavioral graded activity treatment[35 and 36].

This study has a few limitations. First, because elderly patients were recruited at hospitals and rehabilitations centers, the conclusions of our study cannot be

generalized to the population of patients with OA of the hip and or knee in general. However, there is no specific reason why our conclusions would not apply to other patients than those attending hospitals and rehabilitation centers. Indeed, Holla *et al.* [8] obtained evidence to support the validity of the avoidance model in patients with early symptomatic OA. Secondly, we used the resting subscale of the PCI which asks patients whether they avoid activity when they experience pain (self-reported avoidance). It remains unclear whether patients who report that they avoid activity when they experience pain are actually less physically active. On the other hand, the impact of self-reported avoidance on limitations in activities has been consistently observed across a range of studies: self-reported avoidance is a crucial factor in both self-reported and performance based limitations in activities. Finally, some subjects dropped out of this longitudinal study (73% of the subjects completed the 5 year follow-up). On the other hand, the sophisticated technique of MI was used which is likely to give unbiased results [24, 37 and 38].

In conclusion, the results of this longitudinal study support the theory that avoidance of activity leads to deterioration of knee extensor muscle strength in patients with knee OA and deterioration of hip abductor muscle strength in patients with hip OA and consequently to more limitations in activities.

Author contributions

The authors declare the following contributions to the preparation of the manuscript: Study conception and design (all authors); collection and assembly of data (Pisters and van Dijk); analysis (Pisters, Veenhof, Dekker) and interpretation of data (all authors); drafting of the manuscript (Pisters); critical revision of the manuscript for important intellectual content (all authors); final approval of the manuscript (all authors); obtaining of funding (Veenhof). All authors take responsibility for the integrity of the work.

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Conflict of interest statement

All authors declare that there are no conflicts of interest.

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TABLES AND FIGURES

Fig. 1. Hypothesized model of the associations between pain, avoidance of activities, reduced muscle strength and limitation in activity.

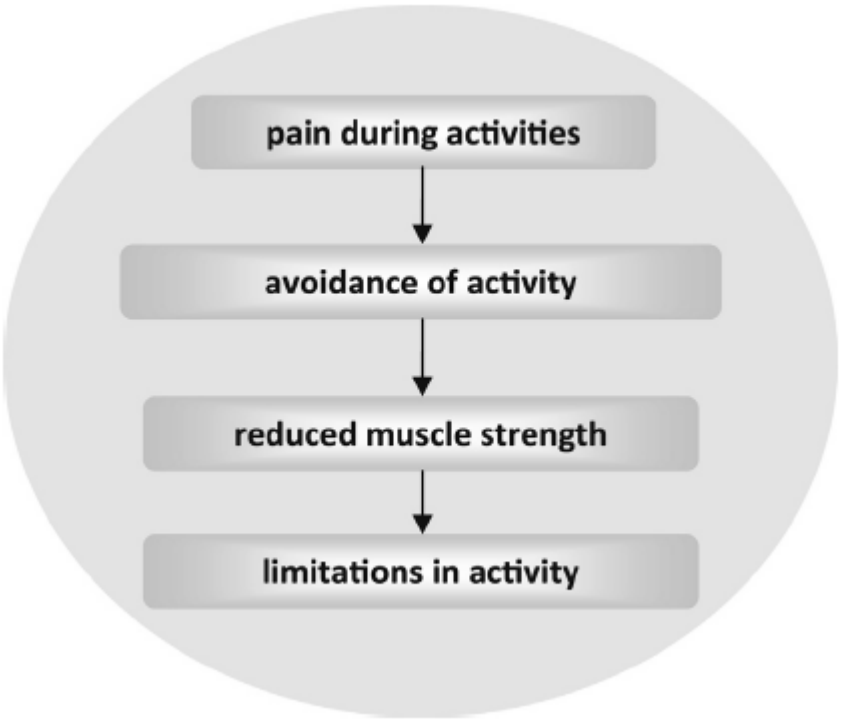

Fig. 2. Analytic model for establishing mediation.

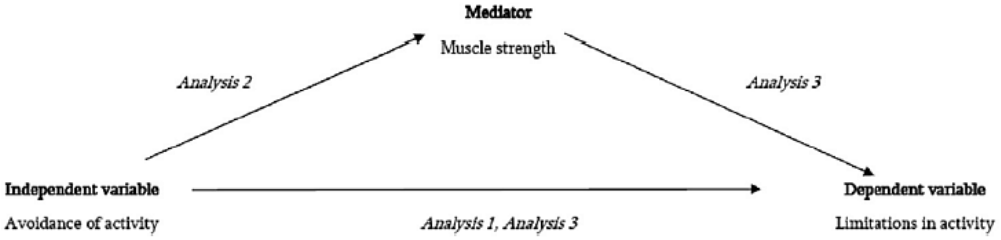

Fig. 3. Flowchart of exclusion and lost to follow-up.

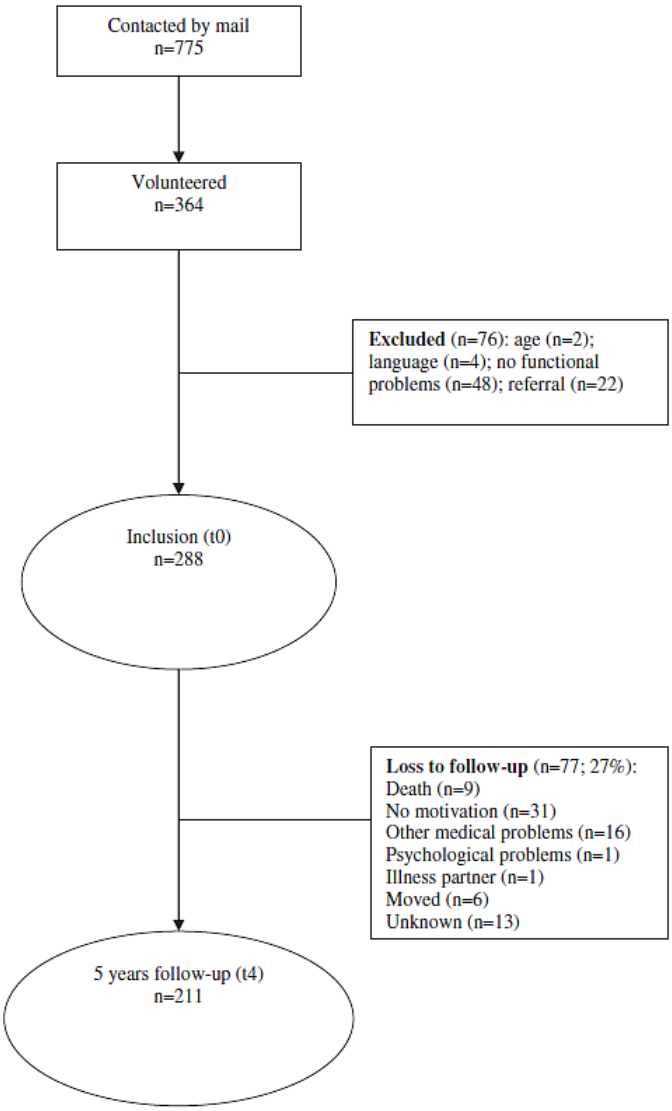

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Table I
Baseline characteristics of the study population

	Study population	
	Knee OA ($n = 216$)	Hip OA ($n = 149$)
Age, years: mean (sd)	66.1 (8.5)	66.7 (9.0)
Gender, male: % (n)	57 (26.4)	43 (28.9)
Duration of complaints, years: mean (sd)	11.4 (11.4)	8.7 (10.2)
BMI, kg/cm^2: mean (sd)	28.5 (4.5)	26.9 (3.9)
Education: n (%)		
No or lower education (≤6 years)	18.6 (40)	18.8 (28)
Medium education (>6 and ≤12 years)	67.4 (145)	66.4 (99)
Higher education (>12 years)	14.0 (30)	14.8 (22)
WOMAC (physical functioning; range 0–68): mean (sd)	30.3 (13.6)	30.2 (12.9)
Muscle strength, in Newton/kg		
Hip abduction: mean (sd)	2.1 (0.6)	2.2 (0.6)
Knee extension: mean (sd)	1.9 (0.6)	1.9 (0.6)
Avoidance of activity (pain coping, resting)	2.3 (0.6)	2.3 (0.6)

Table II
The mediating effect of muscle strength on the relationship between avoidance of activity and self-reported limitations in activities

	Analyses	Dependent variable	Independent variable	Regression coefficient [95% CI]	Level of significance	Adjusted for potential confounders* [95% CI]	Level of significance
Knee OA	1	Limitations in activities	Avoidance of activity	6.994 [4.596; 9.392]	<0.001	6.521 [4.162; 8.879]	<0.001
($n = 216$)	2	Knee extensor muscle strength	Avoidance of activity	−0.282 [−0.439; −0.125]	0.001	−0.235 [−0.354; −0.116]	<0.001
	3	Limitations in activities	1. Knee extensor muscle strength	−2.268 [−4.026; −0.510]	0.016	−2.244 [−4.220; −0.269]	0.029
			2. Avoidance of activity	6.358 [3.955; 8.761]	<0.001	5.961 [3.659; 8.264]	<0.001
Hip OA	1	Limitations in activities	Avoidance of activity	5.938 [2.658; 9.217]	<0.001	6.211 [3.269; 9.154]	<0.001
($n = 149$)	2	Hip abductor muscle strength	Avoidance of activity	−0.144 [−0.337; 0.049]	0.138	−0.199 [−0.362; −0.036]	0.018
	3	Limitations in activities	1. Hip abductor muscle strength	−1.983 [−4.928; 0.962]	0.157	−2.091 [−4.186; 0.003]	0.050
			2. Avoidance of activity	5.770 [2.513; 9.027]	0.001	5.819 [2.861; 8.777]	<0.001

* Potential confounders were age, gender, duration of complaints, BMI, educational level, and comorbidity.

Table III
The mediating effect of muscle strength on the relationship between avoidance of activity and performance based limitations in activities

	Analyses	Dependent variable	Independent variable	Regression coefficient [95% CI]	Level of significance	Adjusted for potential confounders* [95% CI]	Level of significance
Knee OA	1	Limitations in activities	Avoidance of activity	1.615 [1.074; 2.156]	<0.001	1.684 [0.983; 2.385]	<0.001
($n = 216$)	2	Knee extensor muscle strength	Avoidance of activity	−0.282 [−0.439;-0.125]	0.001	−0.235 [−0.354; −0.116]	<0.001
	3	Limitations in activities	1. Knee extensor muscle strength	−0.662 [−1.151; −0.172]	0.011	−0.518 [−1.018; −0.017]	0.043
			2. Avoidance of activity	1.427 [0.855; 1.998]	<0.001	1.553 [0.842; 2.263]	<0.001
Hip OA	1	Limitations in activities	Avoidance of activity	1.381 [0.738; 2.024]	<0.001	1.398 [0.586; 2.211]	0.001
($n = 149$)	2	Hip abductor muscle strength	Avoidance of activity	−0.144 [−0.337; 0.049]	0.138	−0.199 [−0.362; −0.036]	0.018
	3	Limitations in activities	1. Hip abductor muscle strength	−0.706 [−1.081; −0.330]	<0.001	−0.630 [−0.973; −0.286]	0.001
			2. Avoidance of activity	1.314 [0.665; 1.963]	<0.001	1.283 [0.480; 2.086]	0.002

* Potential confounders were age, gender, duration of complaints, BMI, educational level, and comorbidity.