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ORIGINAL REPORT

PROPRIOCEPTION MEDIATES THE ASSOCIATION BETWEEN SYSTEMIC INFLAMMATION AND MUSCLE WEAKNESS IN PATIENTS WITH KNEE OSTEOARTHRITIS: RESULTS FROM THE AMSTERDAM OSTEOARTHRITIS COHORT

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Objectives: **To determine whether systemic inflammation is associated with poor proprioception; to confirm that systemic inflammation is associated with muscle weakness; and to determine whether poor proprioception mediates the association between systemic inflammation and muscle weakness in knee osteoarthritis.**

Design: **Cross-sectional study.**

Subjects: **A total of 689 participants with knee osteoarthritis from the Amsterdam Osteoarthritis (AMS-OA) cohort.**

Methods: **Systemic inflammation was assessed by erythrocyte sedimentation rate, knee proprioception by determining the joint motion detection threshold, and muscle strength with an isokinetic dynamometer. Linear regression models were used to estimate direct associations between systemic inflammation, proprioception and muscle strength, and the indirect association (mediation) between systemic inflammation and muscle strength via proprioception adjusted for potential confounders.**

Results: **Higher erythrocyte sedimentation rates were associated with poor proprioception ($p = 0.022$). Poor proprioception ($p < 0.001$) and higher erythrocyte sedimentation rates ($p < 0.001$) were associated with muscle weakness. Poor proprioception mediated the association between systemic inflammation and muscle weakness ($p = 0.035$).**

Conclusion: **Results suggest that systemic inflammation is associated with poor proprioception in knee osteoarthritis. Poor proprioception may be a pathway through which systemic inflammation is associated with muscle weakness in patients with knee osteoarthritis.**

Key words: osteoarthritis; knee; muscle strength; inflammation; proprioception.

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Muscle weakness is a prominent feature of knee osteoarthritis (OA) (1). Traditional factors contributing to muscle weakness in patients with knee OA are avoidance of activities (2), and pain (3). Presumed underlying factors of muscle weakness are poor proprioception (4) and more recently, systemic low-grade inflammation (5).

It has been suggested that the effect of systemic low-grade inflammation on muscle strength in knee OA is due to the catabolic effect of systemic low-grade inflammation, which results in reduced regenerative potential of muscle tissue (6). The association between systemic inflammation and muscle weakness in knee OA (5) has not been confirmed in a large sample. Not only muscle strength itself, but also the peripheral nervous system, might be affected by systemic low-grade inflammation (7). It can be hypothesized that the catabolic effect of systemic inflammation, which affects muscle tissue (5), also affects joint mechanoreceptors (7) and therefore proprioception. However, no studies have been conducted into knee OA to test this hypothesis. Provided this association exists, and knowing that systemic inflammation and poor proprioception were previously reported to be associated with muscle weakness (4), it can be hypothesized that poor proprioception mediates the association between systemic inflammation and muscle weakness. Mediation assumes that a precursor variable (i.e. systemic inflammation) has an association with a mediating variable (poor proprioception), which in turn affects the outcome variable (muscle weakness) (Fig. 1). To our knowledge, no studies have investigated whether poor proprioception may be a pathway through which systemic inflammation is associated with muscle weakness in knee OA.

The aims of the current study were therefore: (*i*) to determine whether systemic inflammation is associated with poor proprioception; (*ii*) to confirm that systemic inflammation is associated with muscle weakness; and (*iii*) to determine whether poor proprioception medi-

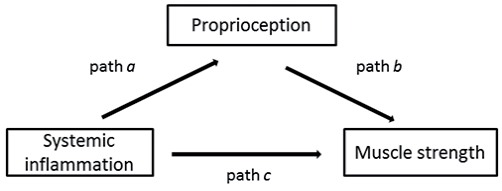

Fig. 1. Mediation model. Proprioception as a mediator of the association between systemic inflammation and muscle strength.

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ates the association between systemic inflammation and muscle weakness in patients with knee OA.

METHODS

Cohort characteristics

Data from 689 participants of the Amsterdam Osteoarthritis (AMS-OA) cohort with unilateral or bilateral diagnosis of knee OA according to the American Rheumatism Association (ACR) were included in this study (8). In analysis, patients with missing data for 1 variable were excluded from further analysis. However, included and excluded patients, did not differ on demographic characteristics. The AMS-OA cohort consists of patients with established knee and/or hip OA according to the ACR criteria (8), who have been referred to an outpatient rehabilitation centre (Reade, Centre for Rehabilitation and Rheumatology, Amsterdam, the Netherlands). Participants were assessed by rheumatologists, radiologists and rehabilitation physicians. Exclusion criteria were: total knee replacement, rheumatoid arthritis (RA) or any other form of inflammatory arthritis (i.e. crystal arthropathy, septic arthritis (SpA)). All the participants provided written inform consent according to principles of the Declaration of Helsinki. The AMS-OA cohort was approved by the Slotervaart Hospital/Reade Institutional Review Board (number U/2782/0851).

Systemic inflammation

Systemic inflammation was assessed by erythrocyte sedimentation rate (ESR). ESR values were measured in serum from patients' blood samples and were determined by the standard Westergren method (9). In this method, ethylendiaminetetraacetic acid (EDTA) anticoagulated blood samples were pre-diluted with saline solution and aspirated into the Westergren pipette graduated from 0 to 200 mm. The rate at which red blood cells sedimented in 1 h was measured (mm/h). Blood samples were collected from each participant following a standardized protocol and according to clinical practice at Reade.

Proprioception

Proprioception was assessed using a knee joint motion detection task, expressed as the joint motion detection threshold. The device to assess proprioception consisted of a chair with a computer-controlled motor and transmission system and 2 attached free-moving arms. Each arm supported the participant's lower leg and moved in the sagittal plane. Subjects were seated with their knees flexed at 90°. An arm attached to the device moved the knee towards extension at a speed of 0.3°/s. Subjects were asked to press a button the moment they perceived a change in the position of the knee joint. The difference in knee angle between the starting position and the position at the moment the subject pressed the button was used as an indicator for proprioception. This measurement of proprioception has showed adequate reproducibility and validity (4). The mean joint proprioception in degrees obtained from the left and right knee was used for the analysis.

Muscle strength

Muscle strength was assessed for flexion and extension of the knee using an isokinetic dynamometer (EnKnee; Enraf – Nonius, Rotterdam, the Netherlands). The measurements were performed in a sitting position at an angular velocity of 60°. Subjects performed one test measurement. After a 30 s rest participants performed 3 maximal quadriceps strength measurements during knee extension and 3 maximal hamstring strength measurements during knee flexion. This assessment has shown adequate reproducibility and validity (4). The mean strength for the quadriceps and hamstring muscles (in Nm per kg body weight; Nm/kg) of the left and right knee was used for the analysis.

Other measures

Demographic data, including age, sex and body mass index (BMI) were recorded. BMI was calculated as body mass in kg divided by height in m^2. Kellgren & Lawrence score (KL-score) from the more severe knee was used to assess the radiographic severity of the disease (10). Pain from the left and right knee was assessed with a numerical rating scale (NRS). Information related to comorbidities was collected with the Cumulative Illness Rating Scale (CIRS) (11) and the number of diseases on which the patient scored a severity of 2 or higher was calculated.

Statistical analysis

Descriptive statistics were used to characterize the study population. Numbers (percentage) were used for categorical variables, means (standard deviation; SD) for continuous variables. Continuous variables that were not normally distributed were characterized by medians (interquartile range; IQR). The Kolmogorov–Smirnov and Shapiro–Wilk tests were used to evaluate normality of distribution of systemic inflammation, proprioception and muscle strength. Because the results of these tests indicated that data for systemic inflammation and proprioception variables were not normally distributed ($p < 0.05$), a logarithmic transformation was applied prior to conducting the statistical analyses.

First, univariate linear regression analyses were performed to estimate associations between systemic inflammation, proprioception and muscle strength. Secondly, confounding effects of potentially relevant variables (i.e. age and sex) were determined. When one of these variables changed the regression coefficient by more than 10%, this variable was considered to be a confounder (12) and was included in the multivariable regression analysis. Finally, mediation analysis was performed to assess the indirect association of systemic inflammation with muscle strength via proprioception, without and with adjustment for confounders. The mediation model is presented in Fig. 1. Path a represents the association between the independent variable and the mediator variable, and path *b* represents the association between the mediator variable and the dependent variable. Path c represents the direct association between the independent variable and the dependent variable. Proprioception is shown to be a mediator of the association between systemic inflammation and muscle strength if the indirect association between systemic inflammation and muscle strength (path $a \times$ path b) differs significantly from zero (13). To examine a statistically significant mediation effect, we incorporated the bootstrapping method with 95% confidence interval (95% CI), as this method is recommended (14). All analyses were performed using SPSS software, version 22.0 (SPSS, Chicago, IL, USA). Statistical significance was accepted at $p < 0.05$. The mediation analysis was implemented using the PROCESS macro for SPSS developed by Preacher & Hayes (14).

Table I. Descriptive statistics for demographic and biomechanical variables

Characteristics	Value	*n*
Demographics		
Age, years, mean (SD)	62.2 (8.8)	689
Female, *n* (%)	480 (69.7)	689
Body-mass index, kg/m^2, mean (SD)	30.5 (6.2)	689
Pain last week (NRS), (range 0–10), mean (SD)	5.5 (2.2)	689
KL grade ≥2, *n* (%)	397 (57.6)	689
CIRS ≥2, *n* (%)	246 (40.2)	613
ESR, mm/h, median (IQR)	9.0 (5–16)	689
Biomechanical factors		
Proprioception, degrees, median (IQR)	2.5 (1.5–4.2)	689
Muscle strength, Nm/kg, mean (SD)	0.81 (0.4)	689

NRS: numeric rating scale; KL: Kellgren – Lawrence score; CIRS: cumulative illness rating score; ESR: erythrocyte sedimentation rate; IQR: interquartile range.

RESULTS

Descriptives

The characteristics of the study population are shown in Table I. The mean±SD age was 62.2±8.8 years. Women (n=480) composed 69.7% of the study group. The median scores for the systemic inflammation level and proprioception were 9 mm/h (IQR 5–16) and 2.5° (IQR 1.5–4.2), respectively. Mean±SD muscle strength of the study population was 0.81±0.4 Nm/kg.

Regression analyses

Association between systemic inflammation and proprioception (Fig. 2; path a). In univariate linear regression analysis, higher values of ESR were significantly associated with poor proprioception (B=0.09; p<0.001). ESR explained 1.5% of variance in proprioception (p<0.001). In multivariable regression analysis, the influence of each potential confounder (i.e. age, sex) was determined. Both age and sex were found to be confounders. In the multivariable regression analysis, including both age and sex at the same time (Table II), it was shown that higher levels of ESR were still associated with poor proprioception after adjusting for age and sex (B=0.06; p=0.022).

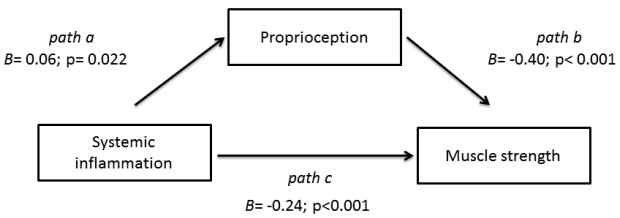

Fig. 2 Mediation model. Path a: direct association between systemic inflammation and proprioception; path b: direct association between proprioception and muscle strenght; path c: direct association between systemic inflammation and muscle strength

Table II. Univariable and multivariable regression analysis of systemic inflammation (ESR in mm/h) on proprioception (°), adjusted for age and sex, in patients with knee OA (n=689)

	Proprioception (°)		
Independent factors	B	*p*	95% CI
ESR	0.09	0.001	0.03–0.14
ESR + age[a]	0.09	0.003	0.02–0.13
ESR + sex[b]	0.08	0.005	0.02–0.13
ESR[a,b]	0.06	0.022	0.01–0.11

Linear regression analysis with proprioception as dependent variable, adjusted for age[a] and sex[b].
ESR: erythrocyte sedimentation rate; OA: osteoarthritis; CI: confidence interval.

Association between proprioception and muscle strength (Fig. 2; path b). In univariate linear regression analysis, poor proprioception was significantly associated with muscle weakness (B=–0.48; p<0.001). Proprioception explained 6.9% of variance in muscle strength (p<0.001). In multivariable regression analysis, the influence of each potential confounder (i.e. age, sex) was determined. Sex was found to be a confounder (Table III), but poor proprioception was still significantly associated with muscle weakness after adjusting for sex (B=–0.40; p<0.001).

Association between systemic inflammation and muscle strength (Fig. 2; path c). In univariate linear regression analysis, higher values of ESR were significantly associated with muscle weakness (B=–0.42; p<0.001). ESR explained 10.6% of variance in muscle weakness (p<0.001). In multivariable regression analysis, the influence of each potential confounder (i.e. age, sex) was determined. Sex was found to be a confounder (Table IV), but higher levels of ESR were still associated with muscle weakness after adjusting for sex (B=–0.24; p<0.001). Each path and its associated regression coefficients are presented in Fig. 2.

Table III. Univariable and multivariable regression analysis of proprioception (°) on muscle strength (Nm/kg), adjusted for sex, in patients with knee OA (n=689)

	Muscle strength (Nm/kg)		
Independent factors	B	*p*	95% CI
Proprioception	–0.48	<0.001	–0.61 to –0.34
Proprioception + sex[a]	–0.40	<0.001	–0.51 to –0.29

Linear regression analysis with muscle strength as dependent variable, adjusted for sex[a]. OA: osteoarthritis; CI: confidence interval.

Table IV. Univariable and multivariable regression analysis of systemic inflammation (mm/h) on muscle strength (Nm/kg), adjusted for sex, in patients with knee OA (n=689)

	Muscle strength (Nm/kg)		
Independent factors	B	*p*	95% CI
ESR (mm/h)	–0.42	<0.001	–0.51 to –0.32
ESR + sex[a]	–0.24	<0.001	–0.32 to –0.16

Linear regression analysis with muscle strength as dependent variable, adjusted for sex[a]. ESR: erythrocyte sedimentation rate; OA: osteoarthritis; CI: confidence interval.

Mediation analysis. The hypothesis that systemic inflammation is associated with muscle weakness via poor proprioception was confirmed. In univariate linear regression analysis, the indirect association between systemic inflammation and muscle weakness via poor proprioception was statistically significant (B=–0.04, 95% CI=–0.06, –0.02; p=0.004). Of the total variance between systemic inflammation and muscle weakness (10.6%), 1.8% was explained by the mediation of poor proprioception. In multivariable mediation analysis, the influence of each potential confounder (i.e. age and sex) was determined. Both age and sex were found to be confounders. In the multivariable mediation analysis including age and sex at the same time it was shown that the indirect association between systemic inflammation and muscle weakness via poor proprioception was still statistically significant (B=–0.02, 95% CI=–0.04, –0.01; p=0.035).

The analyses were also re-run with data from quadriceps strength and proprioception measures of only the painful (arthritic) knee. The results were similar (data not shown).

DISCUSSION

The current study determined the associations between low-grade systemic inflammation, proprioception and muscle strength among participants of the AMS-OA cohort with established knee OA. The main findings showed that: (*i*) systemic inflammation was associated with poor proprioception; (*ii*) systemic inflammation was associated with muscle weakness; and (*iii*) poor proprioception mediated the association between systemic inflammation and muscle weakness.

To our knowledge, this is the first study showing that systemic inflammation, assessed by ESR, is associated with poor proprioception in patients with established knee OA. Even after adjustment for relevant confounders (i.e. age and sex) our results showed statistically significant associations. Based on previous observations (7), we hypothesized that the catabolic effect of systemic inflammation may lead to alterations in electrophysiological properties of joint mechanoreceptors. This could evoke abnormal afferent discharge affecting joint proprioceptive acuity. Local inflammatory features could also lead to poor proprioception; however, neither joint effusion nor synovitis was assessed in our study. Further studies are needed, particularly in patients with knee OA and systemic inflammation with objectified local knee joint inflammation.

Previously, the association between systemic inflammation and muscle weakness has been reported in a smaller number of patients (n=285) from the AMS-OA cohort (5). Our results confirm this association in a larger sample from the same cohort and increase the validity of the previous findings. It has been suggested that this association might be explained as a result of the catabolic effect of circulating inflammatory markers that can considerably accelerate the process leading to muscle wasting and sarcopaenia (6). Our findings are also in agreement with other studies that reported the association between inflammatory markers and lower muscle strength in patients with OA (15) and in patients with RA (16).

Our results showed that poor proprioception was associated with muscle weakness. We have replicated the findings from the study by van der Esch et al. (4), who showed that poor proprioception is associated with muscle weakness in patients with knee OA. The values of proprioception are comparable with those reported in previous studies where a similar method of assessment was used (17). Comparison with other studies is hampered by differences in measurement methods. Some studies used joint position sense (18–20), whereas we used joint motion sense. The manner in which poor proprioception leads to muscle weakness is not clear. It is generally accepted that sensory feedback through knee joint mechanoreceptors regulates muscle activity around the knee joint. Knee OA is detrimental to the joint receptors, leading to reduced or affected afferent output from those mechanoreceptors. Impaired sensory feedback could influence spinal and supraspinal pathways, which may lead to arthrogenic reflex inhibition and limit activation of knee muscles (21).

The results from the multivariable mediation analysis showed that the association between systemic inflammation and muscle weakness was significantly mediated by poor proprioception, even after adjusting for age and sex as potential confounders. The mediation by poor proprioception can be explained by abnormal neural afferent discharges of mechanoreceptors. As a result of systemic inflammation, γ-motor neuron excitability could be decreased and lead to arthrogenic reflex inhibition (21). The change in physiological properties of mechanoreceptors by inflammation could be a pathway through which systemic inflammation affects muscle strength. More fundamental studies are needed to explore the suggested mechanism and to confirm the mediation of poor proprioception.

Distribution of the data of systemic inflammation was skewed and was log transformed. In order to be able to interpret the results of the regression analysis clinically, the coefficients were scaled by the IQR of the distribution of ESR and proprioception (22). Patients with an ESR of 16 mm/h (75th percentile) had lower proprioceptive accuracy of 0.22° compared with patients with an ESR of 5 mm/h (25th percentile). Furthermore, patients with a proprioception score of 4.2° (75th

percentile) had lower muscle strength of 0.09 Nm/kg compared with patients with a proprioception scores of 1.5° (25th percentile). Finally, patients with an ESR of 16 mm/h had lower muscle strength of 0.11 Nm/kg compared with patients with an ESR of 5 mm/h. This indicates that proprioception and muscle strength are more affected by higher levels of ESR. The explained variance in proprioception from systemic inflammation was 1.5%. The indirect effect of proprioception on the association between systemic inflammation and muscle weakness was 1.8%. It is difficult to determine the clinical significance of the observed effects. Theoretically, controlling inflammation by medication and improving proprioception might contribute to better outcome in rehabilitation, adding to the improvements in muscle strength and thus decrease in activity limitations. However, intervention studies are required to test this hypothesis.

The covariates included in the models were chosen based on the literature and statistical advice (12). There is evidence that age and sex are associated with systemic inflammation (23, 24), proprioception (25) and muscle strength (26). Radiographic Osteoarthritis has been shown to be associated with ESR and muscle strength (27, 28); however, statistical analysis revealed it did not change the regression coefficients by more than 10% for any of the paths, therefore, it has not been included in the multivariable regression analysis. Evidence showing that pain is associated with ESR, proprioception or muscle strength is conflicting (18, 29, 30) or lacking (31, 32). Because of a potentially causal link between pain, obesity and inflammatory markers (5, 33), we refrained from adjusting the analyses for pain and BMI, as this might result in overcorrection of the model. Nevertheless, chosen predictors explained a relatively small portion of the variance in the outcomes; thus, there are other factors contributing to the associations that require further investigation.

This study has some strengths and limitations. An important strength was the large sample of patients ($n = 689$) with established knee OA, recruited in a clinical setting. Several limitations should also be mentioned. First, proprioceptive accuracy was derived from articular and peri-articular mechanoreceptors, but proprioception can also be derived from muscle spindles. To reflect proprioception derived from muscle spindles, future studies should also include measurements of sense of active joint position. Secondly, ESR is an indirect measure of inflammation and is affected by a multitude of factors (34). Thirdly, lack of information on local inflammatory characteristics is a limitation, as neither knee joint effusion nor synovitis was assessed. Finally, a cross-sectional design was used; however, to better understand the mechanisms underpinning muscle weakness, longitudinal studies are needed with a focus on the assessment of systemic and local inflammation and active and passive measurements of proprioception.

In conclusion, this study is the first to provide evidence to suggest that systemic inflammation is associated with poor proprioception in patients with knee OA. Moreover, systemic low-grade inflammation is also associated with muscle weakness. Finally, the results indicate that poor proprioception may be a pathway by which systemic inflammation is associated with muscle weakness in knee OA. Longitudinal studies are needed to explore in more depth the mechanisms underpinning muscle weakness in patients with knee OA.

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The authors declare no conflicts of interest.

REFERENCES

1. Bennell KL, Hunt MA, Wrigley TV, Lim BW, Hinman RS. Role of muscle in the genesis and management of knee osteoarthritis. Rheum Dis Clin North Am 2008; 34: 731–754.
2. Holla JF, van der Leeden M, Knol DL, Peter WF, Roorda LD, Lems WF, et al. Avoidance of activities in early symptomatic knee osteoarthritis: results from the CHECK cohort. Ann Behav Med 2012; 44: 33–42.
3. Muraki S, Akune T, Teraguchi M, Kagotani R, Asai Y, Yoshida M, et al. Quadriceps muscle strength, radiographic knee osteoarthritis and knee pain: the ROAD study. BMC Musculoskelet Disord 2015; 16: 305.
4. van der Esch M, Steultjens M, Harlaar J, Knol D, Lems W, Dekker J. Joint proprioception, muscle strength, and functional ability in patients with osteoarthritis of the knee. Arthritis Rheum 2007; 57: 787–793.
5. Sanchez-Ramirez DC, van der Leeden M, van der Esch M, Gerritsen M, Roorda LD, Verschueren S, et al. Association of serum C-reactive protein and erythrocyte sedimentation rate with muscle strength in patients with knee osteoarthritis. Rheumatology (Oxford) 2013; 52: 727–732.
6. Ferrucci L, Penninx BW, Volpato S, Harris TB, Bandeen-Roche K, Balfour J, et al. Change in muscle strength explains accelerated decline of physical function in older women with high interleukin-6 serum levels. J Am Geriatr Soc 2002; 50: 1947–1954.
7. Xu GY, Huang LY, Zhao ZQ. Activation of silent mechanoreceptive cat C and Adelta sensory neurons and their substance P expression following peripheral inflammation. J Physiol 2000; 528: 339–348.
8. Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986; 29: 1039–1049.
9. Patton WN, Meyer PJ, Stuart J. Evaluation of sealed vacuum extraction method (Seditainer) for measurement of erythrocyte sedimentation rate. J Clin Pathol 1989; 42: 313–317.

10. Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957; 16: 494–502.
11. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc 1968; 16: 622–626.
12. Kleinbaum DG, Kupper LL, Nizam A., Muller KE. Applied regression analysis and other multivariable methods. 4th edn. Belmont: Thomson Brooks/Cole; 2008.
13. Shrout PE, Bolger N. Mediation in experimental and non-experimental studies: new procedures and recommendations. Psychol Methods 2002; 7: 422–445.
14. Preacher KJ, Hayes AF. Asymptotic and resampling strategies for assessing and comparing indirect effects in multiple mediator models. Behav Res Methods 2008; 40: 879–891.
15. Levinger I, Levinger P, Trenerry MK, Feller JA, Bartlett JR, Bergman N, et al. Increased inflammatory cytokine expression in the vastus lateralis of patients with knee osteoarthritis. Arthritis Rheum 2011; 63: 1343–1348.
16. Schiottz-Christensen B, Lyngberg K, Keiding N, Ebling AH, Danneskiold-Samsoe B, Bartels EM. Use of isokinetic muscle strength as a measure of severity of rheumatoid arthritis: a comparison of this assessment method for RA with other assessment methods for the disease. Clin Rheumatol 2001; 20: 423–427.
17. Holla JF, van der Leeden M, Peter WF, Roorda LD, van der Esch M, Lems WF, et al. Proprioception, laxity, muscle strength and activity limitations in early symptomatic knee osteoarthritis: results from the CHECK cohort. J Rehabil Med 2012; 44: 862–868.
18. Bennell KL, Hinman RS, Metcalf BR, Crossley KM, Buchbinder R, Smith M, et al. Relationship of knee joint proprioception to pain and disability in individuals with knee osteoarthritis. J Orthop Res 2003; 21: 792–797.
19. Hurley MV, Scott DL, Rees J, Newham DJ. Sensorimotor changes and functional performance in patients with knee osteoarthritis. Ann Rheum Dis 1997; 56: 641–648.
20. Marks R. An investigation of the influence of age, clinical status, pain and position sense on stair walking in women with osteoarthrosis. Int J Rehabil Res 1994; 17: 151–158.
21. Hurley MV, Newham DJ. The influence of arthrogenous muscle inhibition on quadriceps rehabilitation of patients with early, unilateral osteoarthritic knees. Br J Rheumatol 1993; 32: 127–131.
22. Harrell FE. Regression modeling strategies. Springer: New York; 2001.
23. Nestel AR. ESR adaptation for age – a forgotten pearl. BMJ 2012; 344: e1403.
24. Hayes GS, Stinson IN. Erythrocyte sedimentation rate and age. Arch Ophthalmol 1976; 94: 939–940.
25. Pai YC, Rymer WZ, Chang RW, Sharma L. Effect of age and osteoarthritis on knee proprioception. Arthritis Rheum 1997; 40: 2260–2265.
26. Doherty TJ. The influence of aging and sex on skeletal muscle mass and strength. Curr Opin Clin Nutr Metab Care 2001; 4: 503–508.
27. Oiestad BE, Juhl CB, Eitzen I, Thorlund JB. Knee extensor muscle weakness is a risk factor for development of knee osteoarthritis. A systematic review and meta-analysis. Osteoarthritis Cartilage 2015; 23: 171–177.
28. Hanada M, Takahashi M, Furuhashi H, Koyama H, Matsuyama Y. Elevated erythrocyte sedimentation rate and high-sensitivity C-reactive protein in osteoarthritis of the knee: relationship with clinical findings and radiographic severity. Ann Clin Biochem 2015; 53: 548–553.
29. Hall MC, Mockett SP, Doherty M. Relative impact of radiographic osteoarthritis and pain on quadriceps strength, proprioception, static postural sway and lower limb function. Ann Rheum Dis 2006; 65: 865–870.
30. Shakoor N, Furmanov S, Nelson DE, Li Y, Block JA. Pain and its relationship with muscle strength and proprioception in knee OA: results of an 8-week home exercise pilot study. J Musculoskelet Neuronal Interact 2008; 8: 35–42.
31. Brandt KD, Heilman DK, Slemenda C, Katz BP, Mazzuca SA, Braunstein EM, et al. Quadriceps strength in women with radiographically progressive osteoarthritis of the knee and those with stable radiographic changes. J Rheumatol 1999; 26: 2431–2437.
32. Amin S, Baker K, Niu J, Clancy M, Goggins J, Guermazi A, et al. Quadriceps strength and the risk of cartilage loss and symptom progression in knee osteoarthritis. Arthritis Rheum 2009; 60: 189–198.
33. Hunter DJ, McDougall JJ, Keefe FJ. The symptoms of osteoarthritis and the genesis of pain. Med Clin North Am 2009; 93: 83–100.
34. Crowson CS, Rahman MU, Matteson EL. Which measure of inflammation to use? A comparison of erythrocyte sedimentation rate and C-reactive protein measurements from randomized clinical trials of golimumab in rheumatoid arthritis. J Rheumatol 2009; 36: 1606–1610.