Course and predictors of upper leg muscle strength over 48 months in subjects with knee osteoarthritis: Data from the osteoarthritis initiative

A.H. de Zwart a,b,*, M. van der Leeden a,b,c, L.D. Roorda a, M. van der Esch a,b,d, J.W.R. Twisk b,e, W.F. Lems a,b,d,e,f,g, J. Dekker b,c,h

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SUMMARY

Objectives: Weakness of upper leg muscles has a negative impact on future disease and functional status in subjects with knee osteoarthritis (OA). The aims of the present study were to (i) describe the course of muscle strength over 48 months and (ii) identify baseline predictors for a decline in upper leg muscle strength over time in subjects with knee OA.

Methods: Data were obtained from the Osteoarthritis Initiative (OAI) database, a multicenter, observational study of knee OA. Upper leg muscle strength (in N/kg) was measured at baseline, 24 and 48 months. Potential baseline predictors included demographics, OA-specific and health and lifestyle related factors. Linear mixed model analyses were performed.

Results: A total of 1390 subjects with knee osteoarthritis were included. A statistically significant decline of muscle strength was found between baseline and 24 months ($B_{0} = -0.186$, 95%CI [-0.358,-0.014], $p = 0.03$), but not between other time points (24 – 48 months $p = 0.89$, and baseline and 48 months $p = 0.058$). Predictors of a decline in muscle strength over time included demographic predictors (older age, being female, higher body mass index (BMI)), one lifestyle predictor (lower dietary protein intake) and one OA-specific predictor (radiographic severity).

Conclusions: Muscle strength declined over time in subjects with knee OA. The identified predictors may help clinicians to select and treat subjects with knee OA at risk of a decline in muscle strength.

1. Introduction

Weakness of the upper leg muscles is common in subjects with knee osteoarthritis (OA) [1]. Low muscle strength is related to pain and activity limitations, and has been linked to symptomatic progression of the disease [2–7]. Recently, muscle weakness has also been reported to be a risk factor for the development and radiographic progression of knee OA [8,9]. Further, the positive effect of physical exercise on muscle strength and OA symptoms is well documented [10].

Despite the important role of muscle strength in patients with knee OA, knowledge on the course of muscle strength is scarce. Only six observational studies are available that describe the course of muscle strength over time in subjects with knee OA [11–16]. Three studies reported an increase in muscle strength over a course of two or three years [14–16]. However, as a substantial portion of patients received treatment during the study course, indicating that the observed increase could be the result of the received treatment. In contrast, three studies of the same cohort [17] (the Osteoarthritis Initiative) reported a decrease in muscle strength over a course of 24–48 months [11–13]. These studies, however, did not report on the total group of subjects with knee OA, but on specific
subgroups, which were categorized based on changes in knee function or pain over time [11–13]. The overall knee OA population-based course of muscle strength over time has not been reported.

Knowledge on predictors may contribute to the understanding of the mechanisms underlying change in muscle strength, and they may help clinicians to identify and treat subjects at risk for a decline in muscle strength. In the general older population, predictors for decline in muscle strength included older age, higher body mass, worse health status and medication use [18,19]. In persons with knee OA, cross-sectional studies reported that lower muscle quality, physical inactivity, more severe joint degeneration and more pain are associated with lower muscle strength [20]. Whether these factors also predict a decline in muscle strength over time in subjects with knee OA is unknown.

Given the lack of knowledge, the aims of the present study were (i) to describe the course of upper leg muscle strength over 48 months and (ii) identify baseline predictors for a decline in upper leg muscle strength over time in subjects with knee OA.

2. Subjects and methods

2.1. Subjects

Data were obtained from the Osteoarthritis Initiative (OAI) database (http://www.oai.ucsf.edu/) [17]. The OAI is a prospective cohort study focusing on studying biomarkers for the development or progression of knee OA. The OAI inclusion and exclusion criteria are described in Appendix I. The OAI cohort is divided in three subcohorts: healthy controls (reference control subcohort), subjects at risk of developing knee OA (incidence subcohort) and subjects with knee OA at baseline (progression subcohort). The progression cohort includes subjects with frequent knee symptoms and radiographic tibiofemoral knee OA at baseline. Frequent knee symptoms were defined as pain, aching or stiffness in or around the knee for most days for at least one month during the past 12 months. Radiographic tibiofemoral knee OA was defined as the presence of definite tibiofemoral osteophytes (equivalent to a score of ≥2 within the Kellgren and Lawrence (KL) grade) on the fixed flexion radiograph. In the present study, only data of the progression subcohort were used (specific datasets used are 0.2.2 and 0.2.3) [17].

2.2. Upper leg muscle strength of the index knee

In this study, an index knee (most affected knee) was determined for each participant. First, the index knee was determined based on KL grade. The knee with the highest KL grade was chosen as index knee. In case of an equal KL grade between the left and right knee, the knee with the highest score on the Western Ontario and McMaster Universities Osteoarthritis Index pain subscale (WOMAC pain) was chosen as index knee. In case of an equal score on both KL grade and WOMAC pain, the index knee was chosen randomly.

Upper leg muscle strength of each leg was measured, isometrically, for knee flexion and extension with the Good Strength chair (Mettitur Oy, Jyvaskyla, Finland) at baseline, 24 months and 48 months [17,21,22]. During the measurement, the subject was positioned in the Good Strength chair and the waist and the tested upper leg were fixed. After the measurement started, subjects performed a warming up exercise and practiced the measurements. Afterwards, at least three correct measurements were performed per leg with 30 s rest between trials. The maximum force in Newton (N) of the three measurements was used. During the measurements, subjects were vocally motivated. After each measurement subjects were encouraged to move, stretch or shake their legs in order to reduce muscular pain and stiffness after the test. The presence and severity of knee pain (e.g., mild, moderate, severe) during the measurements were assessed for each repetition [17]. In addition, data were reported on whether the pain prevented participants from pushing as hard as possible, to make it possible to correct this in the statistical analyses. The sum of flexion and extension strength of the knee was calculated for each leg to obtain a measure of upper leg muscle strength in Newton (N). For each patient upper leg muscle strength for the leg that corresponded with the index knee (the most affected knee) was determined. In addition, we have corrected upper leg muscle strength for body mass [1]. This is a recommended method to correct for the association of muscle strength with body size (which affects muscle size and the moment arm length), which has also been reported in patients with OA [1]. Upper leg muscle strength of the index knee was expressed as the sum of both flexion and extension strength adjusted for bodyweight (N/kg bodyweight) [1].

2.3. Baseline predictors

A set of the baseline measurements was selected as potential predictors for muscle strength over time. Potential predictors were categorized into three sub-categories: demographic factors, OA-specific and health and lifestyle related factors [20].

Demographic predictors included age, sex, body mass index (BMI) and race. Age (years) and sex (male as reference category) were assessed by questionnaire. During a screening visit height (m) and bodyweight (kg) were measured and were used to calculate BMI (kg/m²). Race was assessed by questionnaire during the screening visit. Due to limited numbers across the different races included in the present study, we dichotomized race into ‘Caucasian’ (reference category) and ‘non Caucasian’.

OA-specific predictors included KL grade, knee alignment and knee pain. The radiographic features of the index knee (joint space narrowing, osteophyte formation, sclerosis, cysts) within the tibiofemoral joints were scored according to the Osteoarthritis Research Society International (OARSI) atlas in KL grades. Scoring of the KL grades was in five categories (0–4). In this study only participants of the progression cohort are included which all have KL grades of ≥2. Knee alignment was measured during the screening visit and was classified as ‘no malalignment’ (reference category), ‘valgus malalignment (>5°)’ and ‘varus malalignment (>5°)’. Knee pain was assessed by the WOMAC pain subscale. The WOMAC pain subscale was scored from 0 to 20; higher scores represent more pain.

Health and lifestyle related predictors included dietary protein intake, dietary energy intake, alcohol consumption, smoking, vitamin D use, physical activity, comorbidities and depression. Dietary protein (g/day) and energy intake (kcal) was measured by the Block Brief 2000 Food Frequency (Block 2000 FFQ) Questionnaire (Nutritionquest©) [23]. The Block 2000 FFQ has 102 items and measures participants’ usual eating habits focusing on the past 12 months. Subjects were asked ‘how often, on average, did you eat the food during the past 12 months?’. In addition, portion sizes, per serving, were asked. Based on the information collected with the questionnaire, daily intake of energy and numerous nutrients, including protein, were calculated. Unlikely values for caloric intake were excluded based on commonly used methods to exclude records in food frequency questionnaires [17]. These include: kilocalories (kcal) less than 500, or greater than 5000 per day and when more than 15% of the questions were missing.

Alcohol consumption was assessed by questionnaire and categorized into ‘no alcoholic drinks’ (reference category), ‘less than one alcoholic drink per week up to 7 alcoholic drinks per week’ and ‘eight or more alcoholic drinks per week’. Smoking habits were assessed by questionnaire and categorized into ‘never smoked’ (reference category), ‘former smoker’ and ‘current smoker’. Vitamin D usage was assessed by questionnaire and expressed in the frequency in which supplementation of vitamin D was used: ‘none’ (reference category), ‘less than 3 days per week’ or ‘4 or more days per week’. Physical activity was measured by the physical scale for elderly (PASE) [24]. The PASE score ranges from 0 to 400. Higher scores indicate; higher level of physical activity. A self-reported questionnaire based on the Charlson index was used to collect information about comorbidities [25]. The Charlson index scores comorbidities based on the mortality risk: a high score represents a high...
number of comorbidities. The Charlson index score has been dichotomized into “no comorbidities” (score = 0, reference category) and “1 or more comorbidities” (score > 0). Depression was assessed by the Center of Epidemiological Studies Depression Scale (CES-D), which was included in the questionnaire of the screening visit[26]. The CES-D score ranges from 0 to 60; a score greater than 16 indicates the presence of a depression. The CES-D score has been dichotomized into “no depression” (reference category) for scores of 16 and lower, and “depression” for scores greater than 16.

2.4. Statistical analyses

Descriptive values were calculated for all baseline variables. Independent T-tests were performed to detect differences in characteristics between subjects with complete and non-complete data for muscle strength over time. Mixed model analyses were performed to analyze the course of muscle strength over time, i.e. the model consisted of muscle strength as the dependent variable and time (in dummy variables) as the independent variable. The overall effect of time on muscle strength and separate regression coefficients for each time point were calculated. To identify predictors of a decline in muscle strength over time, first, univariable mixed model analyses were performed for each potential predictor variable as the independent variable and muscle strength over time as the dependent variable. Third, a multivariable mixed model analyses was performed. To model the change in muscle strength over time baseline muscle strength was added as a covariate in all models. Random intercept were added in the analyses. All variables that were identified as predictors of muscle strength over time in the univariable model according to a level of significance of p < 0.10 were entered into this multivariable model. The final model was developed with a backward selection procedure with a cut-off p-value of 0.05. Additionally, in the final model interaction terms with time were added for each of the included variables, in order to identify different predictive values over time for each variable. For the final multivariable model, the explained variance was estimated. SPSS version 18.0 (SPSS Inc., 2009) was used to perform the analyses.

3. Results

A total of 1390 subjects (progression cohort) were included from the OAI cohort. Baseline characteristics of the study population are summarized in Table 1. The mean observed values for muscle strength over time are represented in Fig. 1. Subjects with incomplete (missing) data for muscle strength were found to have a higher BMI, report more pain (WOMAC-pain), are less active (PASE score) and have lower baseline muscle strength than subjects with complete data for muscle strength over time.

Estimated total knee strength at baseline (5.43 ± 0.06 N/kg) was significantly higher compared to the estimated total knee strength at 24 months (5.24 ± 0.07 N/kg) or 48 months (5.25 ± 0.07 N/kg). No significant change in total knee strength between 24 and 48 months was observed. On average subjects lost 3.2% of muscle strength over 48 months.

In Table 2, the univariable relations to identify potential predictors for change in muscle strength over time are presented. The potential predictors that were significantly associated with total knee strength over time were age, sex, BMI, race, KL grade, dietary protein intake and alcohol consumption.

In Table 3, the multivariable prediction model is presented. Demographic predictors for a decline in muscle strength over time were older age, being female and higher BMI. With respect to lifestyle related factors, dietary protein intake was found to be significant in the multivariate model (p = 0.046). Higher dietary protein intake was found to be a predictor for an increase in muscle strength over time. With regard to the OA-specific factors, radiographic severity only was found to be significant OA-specific predictor for the change of muscle strength over time. A KL grade of 2 or 4 was found to be a predictor of a decline in muscle strength over time in comparison to a KL grade of 3. For all variables in the final multivariable model, no significant interactions with time were detected, indicating that the predictive value of the baseline predictors were stable over time. The predictors in the final multivariable model explained 8.6% of the variance of in decline of muscle strength over time.

![Fig. 1. Observed mean values with 95%CI for knee muscle strength at baseline (n = 1201), 24 months (n = 1002) and 48 months (n = 859).](image-url)
In subjects with knee OA, muscle strength was found to decrease over time. The highest decline in muscle strength was observed in the first 24 months in this study population. On average, a decrease of 3.4% was reported in older adults [18,19]. Interestingly, between 24 and 48 months muscle strength remained stable. A potential explanation is that subjects with knee OA have a more pronounced decline in muscle strength in the earlier stages of the disease, which stabilizes over time to the minimum level of muscle strength needed to perform daily activities. Further research, i.e. cohort studies following healthy patients which develop knee OA over time, is needed to confirm this hypothesis.

Predictors for a decline in muscle strength included demographic factors (older age, being female, higher BMI) a lifestyle predictor (lower dietary protein intake) and one OA-specific factor (radiographic severity: KL grade 2, 4 vs 3). The identified demographic predictors (older age, being female, higher BMI) are in line with predictors identified for a decline in muscle strength over time in the general population [19]. Similarly, inadequate dietary protein intake has been found to be associated with lower muscle strength in both older adults and in patients with knee OA [27–30]. In addition, radiographic severity was found to be a predictor, however, the direction was inconsistent across the KL grade. KL grades of 2 and 4 were found to predict a significant decline in comparison to KL grade 3. Since this finding was unexpected and inconsistent with previous cross-sectional studies, we believe this finding should be interpreted with caution [20].

Also unexpectedly, pain and physical activity, which were found to be strongly linked to muscle strength in cross-sectional studies [20], did not predict a decline in muscle strength over time in the present study. This may be explained by the fact that the variance in change of muscle strength is rather small, which makes it more difficult to detect predictors, compared to the variance in muscle strength at one point in time [20]. Regarding physical activity, it could also be that the measurement used in the present study, i.e. the PASE questionnaire, is not sensitive enough to be detected as a predictor. The use of physical activity trackers to quantify the amount, intensity and pattern of physical activity has been suggested to better capture the concept of physical activity [31].

From a clinical point of view it is important to identify those patients with knee OA who are at risk for a decline in muscle strength. Especially, since in patients with knee OA lower muscle strength is strongly related to more pain and activity limitations, and has been associated with symptomatic progression of the disease [2–7]. Therefore, risk of low muscle strength needs early identification and targeted treatment in order to optimize muscle strength, for which is consistent scientific evidence [10,32]. This may lower the burden of knee osteoarthritis on health care. It should be taken into account that it is unclear what amplitude of decline in muscle strength is also clinically relevant in patients with knee OA. Although, Ruhdorfer and colleagues have studied the minimal clinically important difference in relation to the WOMAC functional disability score, however, this was performed in a cross-sectional study. Therefore more longitudinal studies (with and without interventions) are needed to support their findings.

Beside more general predictors for a decline in muscle strength over time that cannot be influenced (i.e. age, sex and radiographic severity), BMI is modifiable and should be targeted via treatment in subjects with knee OA. Weight management can be effective to lower the BMI in obese knee OA subjects and therefore optimize relative muscle strength (i.e., the force a person can generate per unit of bodyweight) [1,34]. In addition, increasing the level of physical activity with an emphasis on muscle strengthening exercises is an important target in knee OA management [35]. Adequate dietary protein intake may be of importance to counteract the decline in muscle strength in patients with knee OA, especially, in combination with strength training. Hence, patients with low muscle strength or at risk for a decline in muscle strength should focus on strength training, weight management and adequate dietary protein intake in order to preserve or optimize muscle strength.

As expected, baseline muscle strength was strongly related to muscle strength at 24 and 48 months, and may be an important predictor for change in muscle strength. In the present study, we adjusted for baseline muscle strength in order to model change. Also, other factors that were
not measured in this study may predict a change in muscle strength as our set of predictors explained only 8.6% of the variance of muscle strength over time. Future research is needed to further improve our knowledge on predictors for change in muscle strength in patients with knee OA.

Strengths of the present study are the large number of subjects and the large number of potential predictors available in the OAI database. The present study has also a follow-up period of 48 months which is relatively long for studies in knee OA populations. Missing data in baseline predictors, especially in food intake, and for muscle strength during the 48 months period of the study is a limitation of this study. It was shown that those patients with missing data for muscle strength had higher BMI, report more pain, are less active and have lower baseline muscle strength. Hence, the data of the more severe group within this study population is incomplete and the course presented in this study may therefore be an overestimation of the reality. We performed mixed model analyses to address the problem with missing data as best as possible. Mixed model analyses are a well-tested and adequate method to analyze datasets that include missing data [35]. Finally, external validation of the identified predictors is recommended, allowing for the development of a prediction rule for use in clinical practice. Future studies are needed to validate our findings and develop a prediction rule for identifying knee OA patients at risk for a decline in muscle strength.

In conclusion, muscle strength decreased over a period of 48 months in subjects with knee OA. Demographic factors (older age, being female, higher BMI) and an OA-specific factor (radiographic severity) were found to predict a decline in muscle strength. These predictors may help clinicians to identify and treat subjects with knee OA at risk of decline of muscle strength.

Declaration of Competing Interest

The authors declare that they have no conflict of interest.

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1. The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. This manuscript was prepared using an OAI public use data set and does not necessarily reflect the opinions or views of the OAI investigators, the NIH, or the private funding partners.

2. This study was funded by the Dutch Arthritis Association.

Appendix I

OAI is a prospective cohort study focusing on studying biomarkers for the progression or development of knee OA. On entry, all included participants were aged 45–79 years old. Participants were excluded from the study in case of rheumatoid arthritis or inflammatory arthritis, unlikely to demonstrate measurable loss of joint space, bilateral total knee joint replacement or planned bilateral knee replacement in the next 3 years, unable to undergo a 3.0 T MRI exam, positive pregnancy test, unable to provide a blood sample for any reason, use of ambulatory aids other than single straight cane, Co-morbid condition that might interfere with the ability to participate in a 4-year study, unlikely to reside in the clinical area for at least 3 years, current participation in a double-blind randomized controlled trial or unwilling to sign informed consent (1). References.

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