

# The Relationship between Quadriceps Thickness, Radiological Staging, and Clinical Parameters in Knee Osteoarthritis

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**Abstract.** [Purpose] The aim of this study was to investigate the relationship between clinical parameters, radiological staging and evaluated ultrasound results of quadriceps muscle thickness in knee osteoarthritis. [Subjects] The current study comprised 75 patients (51 female, 24 male) with a mean age of  $57.9 \pm 5.2$  years (range 40–65 years) and a diagnosis of osteoarthritis in both knees. [Methods] Knee radiographs were evaluated according to the Kellgren-Lawrence grading system. Clinical evaluation performed with the visual analog scale (VAS), Western Ontario and McMaster Osteoarthritis Index (WOMAC), the 50-meter walking test, and the 10-step stair test. The thickness of the muscle layer of the quadriceps femoris (M. vastus intermedius and M. rectus femoris) was measured with high-resolution real-time ultrasonography. [Results] The results of this study showed a significant negative correlation between quadriceps thickness and age, duration of disease, stage of knee OA, and VAS, WOMAC, 50-m walking test, and 10-step stair test scores. [Conclusion] The evaluation of quadriceps muscle thickness with ultrasound can be considered a practical and economical method in the diagnosis and follow-up of knee osteoarthritis.

**Key words:** Knee osteoarthritis, Quadriceps femoris, Ultrasonography

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## INTRODUCTION

Osteoarthritis (OA) is a noninflammatory chronic degenerative disease characterized by progressively occurring cartilage destruction, osteophyte formation, and subchondral sclerosis especially in the load-bearing joints. Symptomatically, the knee is the most frequently affected joint in osteoarthritis<sup>1, 2)</sup>. With the current decrease in mortality of infectious, nutritional, and cardiovascular diseases and increasing lifespan, OA has become an increasingly significant disease in terms of public health<sup>3–5)</sup>.

An increase in weightbearing of the knee joint and weakness in the stabilizing muscles around the joint are important factors accelerating degeneration of the joint. Therefore, education about protecting the joint from mechanical trauma, the use of assistive Devices, and a strengthening program for the surrounding muscles to increase stability are important in conservative treatment of knee osteoarthritis<sup>6, 7)</sup>. The extensor effect in the knee and the flexor effect in the hip of the quadriceps muscle play an important role

in mobilization. A significant relationship has been shown between quadriceps muscle thickness and strength<sup>8–10)</sup>. However, the degree of atrophy in the quadriceps muscle has not, as yet, been used in OA diagnosis, staging, and evaluation of treatment efficacy or follow-up. The use of ultrasound (US) in the diagnosis and follow-up of musculoskeletal system diseases has recently become widespread as a noninvasive, cheap, easy to apply, reliable diagnostic method. US can easily differentiate muscle tissue, bone, fat, and vascular structures and has been reported to be a cheap, practical, valid, and safe choice in valuation of the quadriceps femoris muscle<sup>11)</sup>. Several reliable methods have been defined related to evaluation of the quadriceps femoris muscle mass with US. One of these evaluation methods is measuring of the quadriceps femoris muscle layer thickness by US<sup>10–14)</sup>. In the present work, the relationship between quadriceps muscle thickness measured by US, clinical parameters, and radiological staging in knee osteoarthritis was investigated.

## SUBJECTS AND METHODS

The study included a total of 75 patients (51 female, 24 male) aged 40–65 years who were admitted to the Physical Medicine and Rehabilitation Polyclinic between February 2013 and June 2013 with complaints of bilateral knee pain and were diagnosed with bilateral knee osteoarthritis ac-

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according to American College of Rheumatology (ACR) criteria<sup>15</sup>). The study was approved by the Local Ethics Committee, and informed consent was obtained from all the study participants.

Examination and evaluation of all the patients were performed by the same doctor. The age, gender, height (cm), weight (kg), and body mass index (BMI, kg/m<sup>2</sup>) of the patients were recorded. Each patient was questioned about their complaints, history, occupation, and family history. In the physical examination, posture, gait, range of movement of the joint, knee deformities, swelling, increased temperature, instability, crepitation, and patellar shock were evaluated. Standing anterior-posterior and lateral knee radiographs were evaluated for each patient using the Kellgren-Lawrence Grading Scale<sup>16</sup>). For patients that had different grades of OA in the two knees, the more advanced grade was taken as the basis for evaluation. Patients included in their study were chosen according to normal limits for full blood count, fasting blood sugar, liver and kidney function tests, erythrocyte sedimentation rate, C-reactive protein, rheumatoid factors, and full urine tests. Patients were excluded from the study if they had a history of knee trauma, surgery, injection in the knee within the previous six months, findings of active synovitis, rheumatoid arthritis, seronegative spondyloarthropathy, gout, pseudogout, osteoporosis, osteomalacia, diabetes mellitus, radiculopathy, coxarthrosis, or any neuromuscular disease, had used any steroid or nonsteroid anti-inflammatory medication within the previous month, or had performed exercise for the quadriceps within the previous month. Patients were clinically evaluated using a visual analog scale (VAS), the Western Ontario and McMaster Osteoarthritis Index (WOMAC), a 50-meter walking test, and a 10-step stair test. A VAS is used to evaluate the intensity of subjective pain. The patient scores the pain on a scale of 0–10 (0= no pain, 10= the most severe pain)<sup>17</sup>). The WOMAC is a widely-used, valid, and reliable method of evaluating hip and knee OA. The WOMAC OA index consists of 24 questions in 3 sections regarding pain, stiffness, and physical function. All the questions are scored on a scale of 0–4 (0=none, 1=mild, 2=moderate, 3=severe, 4=very severe)<sup>18</sup>). In the 50-meter walking test and 10-step stair test, the patients were required to walk a distance of 50 meters if possible and to go up and down 10 stairs if possible, as quickly as possible. The walking and stair tests were repeated three times with rest intervals of at least 5 minutes. The mean times for the walking and stair tests were recorded in seconds. Measurements of the muscle layer of the quadriceps femoris muscle (M. vastus intermedius and M. rectus femoris) were made from specified points as described in previous studies<sup>8, 19, 20</sup>). The patient was laid supine with their legs in full extension for bilateral assessment of the muscle layer thickness of the M. vastus intermedius and M. rectus femoris from the points (a) at the border between the upper and lower two-thirds and point (b) at the center of the line between the anterior superior iliac spine and the upper pole of the patella. Measurements from points (a) and (b) were made on both legs, and the mean of those 4 measurements was calculated as the mean muscle layer thickness (MLT). All the ultrasound examinations



**Fig. 1.** Transverse image of the anterior aspect of the M. vastus intermedius and M. rectus femoris.

**Table 1.** Demographic characteristics of the patients with knee osteoarthritis

	Mean $\pm$ SD (%)
Age (years)	57.9 $\pm$ 5.2
Sex (female/male)	41/19
BMI (kg/m <sup>2</sup> )	27.6 $\pm$ 2.2
Duration of Disease (months)	76.9 $\pm$ 15.2
Education $\pm$ SD (years)	5.4 $\pm$ 6.5
Employment status n (%)	
Employed	25 (33)
Official	13 (17)
Homemaker	27 (36)
Others	10 (14)

BMI, Body mass index; SD, Standard deviation

were performed on a portable Siemens Acuson Antares ultrasound (Siemens, Erlangen, Germany) device, equipped with 9–4 MHz linear array transducers (Siemens Acuson Antares VFX 9-4) by a single operator who was oblivious to the randomization and not involved in any further data analysis (Fig. 1). Statistical Evaluation obtained data were evaluated using the SPSS for Windows 16 software. According to the distribution characteristics in the definition and level of the relationship between variables, Pearson's or Spearman's correlation analysis was used. In the comparison of quantitative data between groups, the Mann Whitney U test and the Kruskal-Wallis test were used. A value of  $p < 0.05$  was accepted as statistically significant.

## RESULTS

The mean age and BMI of the patients included in the study were 57.9  $\pm$  5.1 years and 27.6  $\pm$  2.2 kg/m<sup>2</sup> respectively. The patient gender ratio (male:female) was approximately 2:3 (Table 1). In examination of the relationship between the thickness of the quadriceps muscle layer and various clinical parameters, a statistically significant negative cor-

**Table 2.** Variations in the thickness of the quadriceps muscle layer according to various demographic and clinical characteristics in knee osteoarthritis

Characteristics	n (%)	Quadriceps Thickness (mm) (mean± SD)
Age		-0.449**
Gender		
Women	51 (68)	27.88
Men	24 (32)	25.15
BMI		-0.449
Educate years		0.215
Disease duration		-0.563**
OA Grade**		
I	15 (20)	42.6
II	18 (24)	31.0
III	27 (36)	21.6
IV	15 (20)	13.0
VAS- rest		-0.285*
VAS- active		-0.342*
WOMAC-pain		-0.473**
WOMAC-stiffness		-0.496**
WOMAC-function		-0.357**
WOMAC-total		-0.502**
50 meters walking time		-0.470**
10-step stair time		-0.418**

\* $p < 0.05$ ; \*\* $p < 0.01$ . OA, osteoarthritis; WOMAC, Western Ontario and McMaster Osteoarthritis Index; VAS, visual analog scale

relation was determined between patient age and duration of knee OA and quadriceps thickness ( $p < 0.001$ ). However, no significant correlation was determined between gender, BMI or educational level and quadriceps thickness ( $p > 0.05$ ) (Table 2). When the relationship between the grade of knee OA and quadriceps muscle layer thickness was examined, a statistically significant negative correlation was determined, as quadriceps thickness decreased from Grade I to Grade IV ( $p = 0.001$ ) (Table 2). However, in the post hoc test (Dunn multiple comparison), no significant difference was determined in terms of quadriceps thickness between knee OA Grades I and II, II and III, or III and IV ( $p > 0.05$ ) (Table 2). A statistically significant negative correlation was determined between the quadriceps muscle layer thickness of the patients with knee OA and VAS scores at rest and while active (respectively;  $p = 0.038$ ,  $p = 0.012$ ). The WOMAC scores (pain, stiffness, function, total) showed a statistically significant negative correlation (respectively;  $p < 0.001$ ,  $p < 0.001$ ,  $p = 0.009$ ,  $p < 0.001$ ). There was also a statistically significant negative correlation in the 50-m walking test and the 10-step stair test (respectively;  $p < 0.001$ ,  $p = 0.002$ ). Variations in quadriceps muscle layer thickness according to various demographic and clinical characteristics are shown in Table 2. A statistically significant positive correlation was determined between the age of the patients with knee OA and the duration of the disease and the VAS,

WOMAC, walking test, and stair test scores ( $p < 0.05$ ). BMI was determined as statistically significantly positively correlated with VAS-active (during patient walking), WOMAC-pain and the 10-step stair test scores ( $p < 0.05$ ) (Table 3). No significant difference was determined between the genders in terms of VAS, WOMAC, 50-m walking, and 10-step stair test scores (Table 4). No significant difference was determined between the quadriceps thickness of the genders when compared in terms of VAS, WOMAC, 50-m walking, and 10-step stair test scores (Tables 2 and 4).

## DISCUSSION

In this study, an evaluation of the relationship between the thickness of the quadriceps muscle layer in patients with knee OA and radiological grade and clinical factors was performed. The results of the study showed a significant negative correlation between quadriceps muscle thickness and age, duration of the disease, grade of knee OA, and VAS, WOMAC, 50-m walking test, and 10-step stair test scores. The muscles surrounding joints play an important role in fulfilling the joint function by powering the normal biomechanics of the joint with shock-absorbing effects<sup>21</sup>. The quadriceps femoris muscle, as a basic stabilizer of the knee joint, is important for mobilization with extensor function in the knee and flexor function in the hip. According to data from health check-ups, quadriceps muscle strength and thickness in patients with knee OA are significantly reduced and have been reported to be two of the primary risk factors in the development of knee OA<sup>10, 22-25</sup>. In addition, it has also been determined that quadriceps muscle atrophy and weakness seen from the early stages of knee OA have a significant role in pain and functional loss<sup>21, 26</sup>. Our study results confirmed the findings in the literature in terms of the significant negative correlation between quadriceps thickness and pain and functional scores. The most frequently used method to evaluate joint damage and diagnose OA is measurement of the width of the gap in the joint on direct radiographs. When joint degeneration is first determined radiologically and the time of diagnosis of OA, is actually the phase when cartilage damage is considerably advanced at the molecular level<sup>27, 28</sup>. It has been reported that methods such as computed tomography (CT), magnetic resonance imaging (MRI), and bone scintigraphy can be used in the diagnosis of OA<sup>29</sup>. As these diagnostic methods are not practical or economical, they are rarely used in the diagnosis or follow-up of OA. In the current study, we found a significant negative correlation between quadriceps thickness and the grade of knee OA, pain, and function scores. Therefore, early determination of knee OA via a quadriceps thickness evaluation can be considered a diagnostic method that will be able to contribute to follow-up of the effectiveness of a treatment program applied for knee OA. Age is one of the most important risk factors in the development of OA. The incidence of OA increases after 45 years of age. This increase in OA incidence at older ages has been reported to be due to reasons such as inadequate muscle function and peripheral neurological response, joint instability associated with increased ligament laxity, reduced anabolic

**Table 3.** Correlation analysis of the demographic and clinical characteristics of the patients with knee osteoarthritis

	Age	BMI	Educate years	Disease duration	VAS-rest	VAS-active	WOMAC-pain	WOMAC-stiffness	WOMAC-function	WOMAC-total	50 meters walking time	10-step stair time
Knee OA Grade (KW)	18.09**	1.24	2.96	16.43**	17.19**	18.39**	13.90*	24.24**	16.49*	22.69**	12.87*	11.98*
Age		0.066	-0.061	0.787**	0.422*	0.511**	0.516**	0.626**	0.513**	0.628**	0.490**	0.532**
BMI			-0.453*	0.169	0.215	0.305*	0.337*	0.240	0.129	0.269	0.222	0.303*
Educate years				-0.065	-0.175	-0.244	-0.051	-0.096	-0.064	-0.109	-0.028	-0.103
Disease duration					0.419*	0.560**	0.628**	0.617**	0.416*	0.605**	0.589**	0.555**
VAS-rest						0.699**	0.506**	0.743**	0.323*	0.528**	0.622**	0.561**
VAS-active							0.695**	0.732**	0.536**	0.741**	0.558**	0.573**
WOMAC-pain								0.713**	0.304*	0.676**	0.643**	0.634**
WOMAC-stiffness									0.608**	0.839**	0.819**	0.744**
WOMAC-function										0.892**	0.396*	0.442*
WOMAC-total											0.634**	0.664**
50 meters walking time												0.864**

\* p<0.05;\*\* p<0.001. KW, Kruskal-Wallis test; OA, osteoarthritis; WOMAC, Western Ontario and McMaster Osteoarthritis Index; VAS, visual analog scale

**Table 4.** Comparison of the clinical parameters according to gender

	Women (n=51) (mean rank)	Men (n=24) (mean rank)
VAS-rest	26.60	27.85
VAS-active	28.13	24.62
WOMAC-pain	26.22	28.65
WOMAC-stiffness	25.29	30.62
WOMAC-function	26.49	28.09
WOMAC-total	26.06	29.00
50 meters walking time (sn)	25.10	31.03
10-step stair time (sn)	26.71	27.62
GRADE	n (%)	n (%)
Grade I	10 (19)	5 (21)
Grade II	12 (24)	6 (25)
Grade III	18 (35)	9 (37)
Grade IV	11 (22)	4 (17)

No significant differences between groups at the 0.05 alpha level

response to growth factors, chondrocyte loss, and thinning of the cartilage plate<sup>30</sup>). The results of the current study showed a significant negative correlation between age and quadriceps thickness and a significant positive correlation between age and pain and functional scores. Thus, it can be considered that together with ageing, the atrophy in the quadriceps muscle occurring with age contributes to the lower pain and functional scores in knee OA. OA has been reported to be seen more frequently in females than males with more severe pain and function loss. This has been associated with the hormonal changes that occur with age in

females resulting in a change in the bone build-destroy balance and failure to develop appropriate coping strategies<sup>31</sup>). The majority of the patient group in the current study consisted of females. However, no significant difference was observed in quadriceps thickness between male and female patients in terms of pain and functional scores. It has been known for many years that obesity is a risk factor for OA. High BMI scores of healthy people have been shown to be a significant risk factor for the development of radiographic knee OA in later life<sup>32</sup>). This is due to the mechanical loading, particularly on the lower extremities, of obesity<sup>33</sup>). It has also been reported that the various adipokines expressed in adipose tissue, such as leptin, adiponectin, resistin, and visfatin, have shown a catabolic effect on articular cartilage<sup>34, 35</sup>). Furthermore, sarcopenia has been reported to play an important role in accounting for obesity as a risk factor for the development of OA<sup>35</sup>). In the current study, there was a significant positive correlation among BMI and pain scores and the 10-step stair test scores. However, no significant relationship was determined among BMI and radiological grade of knee OA and quadriceps thickness. On this point, in order to better understand the relationship between BMI and knee OA, it is thought that a more appropriate approach may be to evaluate separately whether general sarcopenia was present or not. It has been reported in previous studies that individuals with a low educational level have a higher risk of developing degenerative joint diseases<sup>36</sup>). A low level of education is thought to be the reason for inadequacy in commenting on feelings of pain and coping with pain and disability. In addition, a low educational level is thought to engender negative aspects such as a tendency to obesity, incorrect use of joints, a sedentary lifestyle, and not being accustomed to regular exercise. However, in the

current study, no significant relationship was determined between educational level and quadriceps thickness and other clinical characteristics of knee OA. As the mean educational level of the patients included in the current study was generally low, it may not have been a sufficient level to demonstrate a relationship between knee OA and education. Conflicting results have been reported regarding the relationship between the radiological grade of knee OA, pain, and function loss. Reasons have been suggested for this, such as radiographs being taken at different times, interpretation by different researchers, and the use of different methods for grading<sup>31, 33</sup>). In the current study, a significant positive correlation was determined between the grade of knee OA and the pain and functional evaluation scores. In addition, it was significant that as the knee OA grade went from Grade I to IV, the thickness of the quadriceps muscle layer showed a significant reduction. When no precautions are taken by patients with knee OA, atrophy occurs with gradual inactivation of the quadriceps muscle. Joint stabilization was impaired because of inactivation, and the knee was more easily traumatized. Thus, irritation and effusion increase the pain. The continuation of this vicious cycle leads to advanced function loss and atrophy in the quadriceps femoris muscle<sup>7</sup>). It has been reported that exercise programs applied to prevent quadriceps muscle strength loss and atrophy, have been successful in terms of recovery from pain and recovery of functional parameters<sup>26–28</sup>). Provision of patient with timely information about the factors that may constitute risks for quadriceps atrophy and knee OA is important in terms of preventing physical deficiencies and disruption to social adaptation. Preventative measures before the disease occurs, such as maintaining an ideal weight without causing sarcopenia, avoiding incorrect movements that force the joint, prompt treatment of painful conditions that may cause immobilization, and becoming accustomed to regular exercise, will make a positive contribution to knee OA treatment and prognosis. There are some limitations to the current study in that it was cross-sectional, knee OA was only evaluated by plain radiography of the knee, and quadriceps muscle strength was not evaluated. The results of the current study showed that there was a significant correlation between the thickness of the quadriceps muscle layer and the grade of knee OA, pain scores, and functional scores. In this context, the evaluation of quadriceps thickness with US can be considered a practical, economical, and reliable method in the diagnosis and follow-up of knee OA. However, there is a need for further studies with wider patient groups of different demographic and cultural characteristics to evaluate all the factors that may affect the thickness of the quadriceps muscle layer.

## REFERENCES

- Felson DT: Epidemiology of hip and knee osteoarthritis. *Epidemiol Rev*, 1988, 10: 1–28. [Medline]
- Lawrence RC, Hochberg MC, Kelsey JL, et al.: Estimates of the prevalence of selected arthritic and musculoskeletal diseases in the United States. *J Rheumatol*, 1989, 16: 427–441. [Medline]
- van Saase JL, van Romunde LK, Cats A, et al.: Epidemiology of osteoarthritis: Zoetermeer survey. Comparison of radiological osteoarthritis in a Dutch population with that in 10 other populations. *Ann Rheum Dis*, 1989, 48: 271–280. [Medline] [CrossRef]
- McAlindon TE, Wilson PW, Aliabadi P, et al.: Level of physical activity and the risk of radiographic and symptomatic knee osteoarthritis in the elderly: the Framingham study. *Am J Med*, 1999, 106: 151–157. [Medline] [CrossRef]
- Goldberg VM, Kettelkamp DM, Colyer RA, et al.: Osteoarthritis of the knee. In: Moskowitz RW, Howell DS, Goldbery VM, Monkin HJ (Eds). *Osteoarthritis. Diagnosis and Medical/Surgical Management*. Philadelphia: WB Saunders, 1992, pp 599–620.
- Sharma L, Pai YC: Impaired proprioception and osteoarthritis. *Curr Opin Rheumatol*, 1997, 9: 253–258. [Medline] [CrossRef]
- Liikavainio T, Lyytinen T, Tyrväinen E, et al.: Physical function and properties of quadriceps femoris muscle in men with knee osteoarthritis. *Arch Phys Med Rehabil*, 2004, 85: 980–986. [Medline]
- Chi-Fishman G, Hicks JE, Cintas HM, et al.: Ultrasound imaging distinguishes between normal and weak muscle. *Arch Phys Med Rehabil*, 1995, 5: 415–422. [Medline]
- Freilich RJ, Kirsner RL, Byrne E: Isometric strength and thickness relationships in human quadriceps muscle. *Neuromuscul Disord*, 1995, 5: 415–422. [Medline] [CrossRef]
- Seymour JM, Ward K, Sidhu PS, et al.: Ultrasound measurement of rectus femoris cross-sectional area and the relationship with quadriceps strength in COPD. *Thorax*, 2009, 64: 418–423. [Medline] [CrossRef]
- Noorkoiv M, Nosaka K, Blazevich AJ: Assessment of quadriceps muscle cross-sectional area by ultrasound extended-field-of-view imaging. *Eur J Appl Physiol*, 2010, 109: 631–639. [Medline] [CrossRef]
- Gruther W, Benesch T, Zorn C, et al.: Muscle wasting in intensive care patients: ultrasound observation of the M. quadriceps femoris muscle layer. *J Rehabil Med*, 2008, 40: 185–189. [Medline] [CrossRef]
- Bleakney R, Maffulli N: Ultrasound changes to intramuscular architecture of the quadriceps following intramedullary nailing. *J Sports Med Phys Fitness*, 2002, 42: 120–125. [Medline]
- Uremović M, Pasić MB, Serić V, et al.: Ultrasound measurement of the volume of musculus quadriceps after knee joint injury. *Coll Antropol*, 2004, 28: 227–233. [Medline]
- Altman R, Alarcón G, Appelrouth D, et al.: The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. *Arthritis Rheum*, 1991, 34: 505–514. [Medline] [CrossRef]
- Kellgren JH, Lawrence JS: Radiological assessment of osteoarthrosis. *Ann Rheum Dis*, 1957, 16: 494–502. [Medline] [CrossRef]
- Price DD, McGrath PA, Rafii A, et al.: The validation of visual analogue scales as ratio scale measures for chronic and experimental pain. *Pain*, 1983, 17: 45–56. [Medline] [CrossRef]
- Bellamy N, Buchanan WW, Goldsmith CH, et al.: Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip or knee. *J Rheumatol*, 1988, 15: 1833–1840. [Medline]
- Gruther W, Kainberger F, Fialka-Moser V, et al.: Effects of neuromuscular electrical stimulation on muscle layer thickness of knee extensor muscles in intensive care unit patients: a pilot study. *J Rehabil Med*, 2010, 42: 593–597. [Medline] [CrossRef]
- Reid CL, Campbell IT, Little RA: Muscle wasting and energy balance in critical illness. *Clin Nutr*, 2004, 23: 273–280. [Medline] [CrossRef]
- McAlindon TE, Cooper C, Kirwan JR, et al.: Determinants of disability in osteoarthritis of the knee. *Ann Rheum Dis*, 1993, 52: 258–262. [Medline] [CrossRef]
- Tan J, Balci N, Sepici V, et al.: Isokinetic and isometric strength in osteoarthritis of the knee. A comparative study with healthy women. *Am J Phys Med Rehabil*, 1995, 74: 364–369. [Medline] [CrossRef]
- Fisher NM, Pendergast DR, Gresham GE, et al.: Muscle rehabilitation: its effect on muscular and functional performance of patients with knee osteoarthritis. *Arch Phys Med Rehabil*, 1991, 72: 367–374. [Medline]
- Gür H, Cakin N, Akova B, et al.: Concentric versus combined concentric-eccentric isokinetic training: effects on functional capacity and symptoms in patients with osteoarthritis of the knee. *Arch Phys Med Rehabil*, 2002, 83: 308–316. [Medline] [CrossRef]
- Fitzgerald GK, Piva SR, Irrgang JJ, et al.: Quadriceps activation failure as a moderator of the relationship between quadriceps strength and physical function in individuals with knee osteoarthritis. *Arthritis Rheum*, 2004, 51: 40–48. [Medline] [CrossRef]
- Lankhorst GJ, Van de Stadt RJ, Van der Korst JK: The relationships of functional capacity, pain, and isometric and isokinetic torque in osteoarthritis of the knee. *Scand J Rehabil Med*, 1985, 17: 167–172. [Medline]
- Ravaud P, Giraudeau B, Auleley GR, et al.: Variability in knee radiographing: implication for definition of radiological progression in medial knee

- osteoarthritis. *Ann Rheum Dis*, 1998, 57: 624–629. [[Medline](#)] [[CrossRef](#)]
- 28) Garnero P, Piperno M, Gineyts E, et al.: Cross sectional evaluation of biochemical markers of bone, cartilage, and synovial tissue metabolism in patients with knee osteoarthritis: relations with disease activity and joint damage. *Ann Rheum Dis*, 2001, 60: 619–626. [[Medline](#)] [[CrossRef](#)]
- 29) Kiviranta P, Töyräs J, Nieminen MT, et al.: Comparison of novel clinically applicable methodology for sensitive diagnostics of cartilage degeneration. *Eur Cell Mater*, 2007, 13: 46–55, discussion 55. [[Medline](#)]
- 30) Arden N, Nevitt MC: Osteoarthritis: epidemiology. *Best Pract Res Clin Rheumatol*, 2006, 20: 3–25. [[Medline](#)] [[CrossRef](#)]
- 31) Creamer P, Lethbridge-Cejku M, Hochberg MC: Factors associated with functional impairment in symptomatic knee osteoarthritis. *Rheumatology (Oxford)*, 2000, 39: 490–496. [[Medline](#)] [[CrossRef](#)]
- 32) Felson DT, Zhang Y, Hannan MT, et al.: Risk factors for incident radiographic knee osteoarthritis in the elderly: the Framingham Study. *Arthritis Rheum*, 1997, 40: 728–733. [[Medline](#)] [[CrossRef](#)]
- 33) de Miguel Mendieta E, Cobo Ibáñez T, Usón Jaeger J, et al.: Clinical and ultrasonographic findings related to knee pain in osteoarthritis. *Osteoarthritis Cartilage*, 2006, 14: 540–544. [[Medline](#)] [[CrossRef](#)]
- 34) Hui W, Litherland GJ, Elias MS, et al.: Leptin produced by joint white adipose tissue induces cartilage degradation via upregulation and activation of matrix metalloproteinases. *Ann Rheum Dis*, 2012, 71: 455–462. [[Medline](#)] [[CrossRef](#)]
- 35) Hu PF, Bao JP, Wu LD: The emerging role of adipokines in osteoarthritis: a narrative review. *Mol Biol Rep*, 2011, 38: 873–878. [[Medline](#)] [[CrossRef](#)]
- 36) Leigh JP, Fries JF: Correlations between education and arthritis in the 1971–1975 NHANES I. *Soc Sci Med*, 1994, 38: 575–583. [[Medline](#)] [[CrossRef](#)]