

Factors affecting pain and physical functions in patients with knee osteoarthritis

An observational study

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Abstract

Knee osteoarthritis (KOA) is more common as people age and have a higher body mass index (BMI). We must know the role of various factors in pain and physical functions in patients with KOA. Therefore, the present study sought to examine the factors associated with pain and physical functions in individuals with KOA. This cross-sectional observational study included patients with KOA ($n = 125$; 57 men, 68 women; mean age 52.9 years). Using the visual analogue scale and a reduced version of the Western Ontario McMaster Universities Osteoarthritis Index, pain severity and physical functions were assessed. Demographic factors such as age, BMI, sex, and Kellgren-Lawrence (K/L) radiographic grade of KOA were analyzed. Age ($R = 0.263$, $P < .001$), BMI ($R = 0.379$, $P < .001$), and K/L grade ($R = 0.844$, $P < .001$) were significantly associated with knee pain. Similarly, age ($R = 0.310$, $P < .001$), BMI ($R = 0.374$, $P < .001$), and K/L grade ($R = 0.862$, $P < .001$) were associated with physical functions. No significant association of sex with pain ($R = 0.071$, $P = .440$) and physical functions ($R = 0.055$, $P = .545$) was observed. Age, BMI, and K/L grade explained 71% and 74% of knee pain and physical functions, respectively. Age, BMI, and radiographic (K/L) grades were associated with pain and physical functions in patients with KOA. K/L grade was the most significant predictor of pain and physical functions in KOA.

Abbreviations: BMI = body mass index, K/L = Kellgren-Lawrence radiographic grade, KOA = Knee osteoarthritis, OA = osteoarthritis, VAS = visual analogue scale, WOMAC = Western Ontario McMaster Universities Osteoarthritis Index.

Keywords: age, body mass index, disability, gender, pain

1. Introduction

Knee osteoarthritis (KOA) is a prevalent degenerative musculoskeletal disease that affects men and women around the world.^[1,2] Increased prevalence of KOA is linked to a high body mass index (BMI) and advancing age.^[3–5] Obesity is the most significant modifiable risk factor for developing KOA.^[6] Degeneration of the cartilage and underlying bone causes KOA, a kind of degenerative arthritis.^[7] An increased body weight causes greater articular pressure resulting in osteophyte formation, subchondral bone sclerosis, and cartilage degeneration.^[8] The obese are 3 times more prone to develop KOA than those with a healthy weight.^[8] Furthermore, obesity and female sex negatively affect gait variables^[9] and post-surgical outcomes.^[10,11] KOA often causes pain, reduced physical functions, and impaired quality of life.^[12,13]

The radiographic grade of KOA is 1 of the important factors influencing post-surgical outcomes. Cushnaghan et al^[14]

indicated that patients with a higher Kellgren and Lawrence (K/L) grade at baseline showed greater improvement in functions after KOA surgery. Valdes et al^[15] reported that a lower K/L grade was related to an increased risk of post-surgical pain after knee and hip replacement surgery. Similarly, Dowsey et al^[16] found that a lower grade of radiographic osteoarthritis (OA) was associated with more pain and poor functions following total knee replacement surgery. Furthermore, Keurentjes et al^[17] reported that patients with severe radiographic OA showed greater improvement in physical functions after knee or hip replacement surgery than patients with mild radiographic OA.

Although age, BMI, and sex are the most significant risk factor for developing KOA, the role of these factors on pain and physical functions was not adequately reported. It is important to know the role of various factors in pain and physical functions in these patients. The current study aimed to identify factors influencing pain and physical functions in patients with KOA. We

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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hypothesized that age, BMI, and radiographic grades (K/L) are associated with pain and physical functions in patients with KOA.

2. Methods

2.1. Participants

A similar previous study on hip OA patients^[18] recruited 118 patients; therefore, 125 patients with KOA were recruited in the present study. The Physicians diagnosed these patients (aged 40 years and older) according to the American College of Rheumatology criteria participated in this cross-sectional study from November 2018 to March 2019.^[19] Data was collected in the medical hospital of King Saud University. Participants with a history of knee surgery, systemic arthritis, or impaired lower extremity functions due to any other muscular, joint, or neurological disorder were excluded from the study. King Saud University's institutional ethics committee (ID: RRC-2018-010) approved the study. Before data collection, each participant signed a written informed consent form.

2.2. Dependent (Outcome) variables

2.2.1. Pain. A visual analogue scale (VAS) was used to measure the severity of the pain.^[20] VAS is frequently used to assess pain intensity and has good reliability and validity.^[20] VAS consists of a bidirectional 10-cm straight line with “no pain” and “worst possible pain” at either end of the line. The participants were asked to make a vertical mark on the line indicating the intensity of their pain.

2.2.2. Physical functions. The Arabic version of the Reduced Western Ontario and McMaster Universities Arthritis Index (WOMAC) was used to assess physical functionality.^[21] The reduced WOMAC includes 12 questions, each scored using 5 response options designed to evaluate patients' perceptions of pain and physical functions. High scores indicate poor functions.^[21,22]

2.3. Independent (Explanatory) variables

Age, sex, BMI, and radiographic grades of KOA were considered independent factors affecting pain and physical functions in patients with KOA. The participants were asked to wear simple clothing and to remove footwear to measure height and weight. Height and weight were measured using a fixed stadiometer and a Beurer glass diagnostic scale. Height and weight were used to calculate the BMI, which was then categorized in accordance with previously published literature.^[23] Radiographic grades of KOA were classified according to K/L rating criteria by the physician.^[24]

2.4. Statistical analysis

All the statistical analysis was done using SPSS version 22 for Windows. Descriptive statistics were presented as mean and standard deviation, continuous data as ranges and categorical data as frequencies. The Pearson correlation coefficient was used to calculate the bivariate correlations between the independent (age, BMI, sex, K/L grades) and the dependent (pain and physical functions) variables. The self-reported pain and physical functions were modeled using the analysis of covariance (ANCOVA). The independent variables indicating a statistically significant correlation ($P < .01$) with the dependent variables were included in the ANCOVA.

3. Results

3.1. Participant characteristics

The participants' characteristics and clinical data are presented in Table 1. A total of 125 patients participated in the current

study. Of these participants, 57 were men, and 68 were women (mean age, 52.9 ± 9.3 years). As per the BMI category, 52% ($n = 65$) of the participants were in the overweight category (BMI, 25–30), followed by 26.4% ($n = 33$) of the participants in the obesity class I category (BMI, 30–35). According to K/L radiographic grade, the distribution of patients was as follows: 14.4% ($n = 18$) of the patients had K/L grade 1, 44.8% ($n = 56$) had K/L grade 2, 31.2% ($n = 39$) had K/L grade 3 and 9.6% ($n = 12$) of the patients had K/L grade 4 radiographic severity of KOA.

3.2. Bivariate correlations

The bivariate correlations between independent (age, BMI, sex, and K/L grade) and dependent (pain and physical functions) variables are shown in Table 2. Age ($R = 0.263$, $P < .001$), BMI ($R = 0.379$, $P < .001$), and K/L grade ($R = 0.844$, $P < .001$) were significantly associated with knee pain. Similarly, age ($R = 0.310$, $P < .001$), BMI ($R = 0.374$, $P < .001$), and K/L grade ($R = 0.862$, $P < .001$) were significantly associated with

Table 1
Participants' characteristics and clinical data.

Characteristics	n = 125
Age, years	
Mean (SD)	52.9 (9.3)
Range	40–80
Age group, N (%)	
40 to 50	55 (44)
50 to 60	40 (32)
60 to 70	25 (20)
70 to 80	5 (4)
Sex, N (%)	
Men	57 (45.6)
Women	68 (54.4)
Height, m	
Mean (SD)	1.7 (0.1)
Range	1.5–1.9
Weight, Kg	
Mean (SD)	85.3 (11.9)
Range	55 - 105
BMI, Kg/m ²	
Mean (SD)	30.1 (4.2)
Range	21.4–41.4
Weight category, N (%)	
Normal Weight (BMI, 18.5–25)	9 (7.2)
Over weight (BMI, 25–30)	65 (52)
Obesity class I (BMI, 30–35)	33 (26.4)
Obesity class II (BMI, 35–40)	17 (13.6)
Obesity Class III (BMI, > 40)	1 (0.8)
OA Grade (K/L rating score), no. (%)	
Grade 1	18 (14.4)
Grade 2	56 (44.8)
Grade 3	39 (31.2)
Grade 4	12 (9.6)
VAS, 0 to 10 cm	
Mean (SD)	5.8 (2.3)
Range	0.5–10
WOMAC pain score	
Mean (SD)	8.9 (4.1)
Range	1–16
WOMAC function score	
Mean (SD)	12.5 (5.9)
Range	1–27
WOMAC total score	
Mean (SD)	21.5 (9.9)
Range	2 - 43

BMI = body mass index, K/L = Kellgren-Lawrence scale, OA = osteoarthritis, SD = standard deviation, VAS = visual analogue scale, WOMAC = Western Ontario McMaster Universities Osteoarthritis Index.

Table 2
Pearson correlation coefficients between dependent (outcome) and independent (explanatory) variables.

Variables	WOMAC Pain	WOMAC Function	WOMAC Total	VAS
Age, years	0.326*	0.310*	0.320*	0.263*
BMI, kg/m ²	0.326*	0.374*	0.360*	0.379*
K/L grade	0.854*	0.862*	0.877*	0.844*
Sex	0.056	0.055	0.058	0.071

*significant at $P < .001$.

BMI = Body mass index, K/L = Kellgren-Lawrence scale, VAS = visual analogue scale, WOMAC = Western Ontario McMaster Universities Osteoarthritis Index.

physical functions. No significant association of sex with pain ($R = 0.071, P = .440$) and physical functions ($R = 0.055, P = .545$) was observed.

3.3. Analysis of covariance

The factors for self-reported pain and physical functions are given in Table 3. Age, BMI, Sex, and K/L grades explained 71% and 74% of knee pain and physical functions, respectively.

4. Discussion

The current study aimed to examine the factors associated with pain and physical functions in patients with KOA. In the present study, independent factors such as age, BMI, and radiographic severity of OA were found to be associated with increased knee pain and poor physical functions in patients with KOA.

In the general population, KOA can be detected radiologically in up to one-third of older adults and is highly correlated with age.^[25-27] Previous studies have reported an association between higher BMI and poor physical functions.^[28,29] Another study reported lower physical functions and higher pain intensity in individuals with high BMI than those with a normal BMI.^[30] More recently, Alfieri et al^[31] reported that being overweight was negatively associated with increased knee pain in OA. However, they did not report any negative effects on physical functions.^[31] In another study, Connelly et al^[32] reported increased knee pain associated with a higher BMI category in patients with KOA. In previous studies, the correlation between BMI and pain levels has been established,^[33-35] and a weight reduction program

is 1 of the important treatment strategies to reduce pain and improve physical functions in patients with KOA.^[36]

In the current study, the sex of the patients was not found to be associated with the severity of pain and physical disability in KOA. Similarly, a previous study reported no association between sex and pain levels in patients with KOA.^[32] Other studies did not report significant sex differences in symptomatic KOA.^[37-39] In contrast, Elbaz et al^[33] reported that women with KOA had higher pain levels and poor functions.

In the current study, the radiographic (K/L) grade of KOA was observed to be a better predictor of pain and physical functions than other factors (age and BMI). A recent study reported a significant association between the severity of radiographic OA indicated by K/L grade and the severity of knee pain in patients with KOA.^[40] Similarly, Pereira et al^[41] reported that the severity of radiographic OA was significantly associated with higher pain levels, reduced quality of life, and increased disability in patients with KOA. In contrast, few studies reported an insignificant association between the severity of radiographic OA and physical functions in patients with KOA.^[42-44]

Several pathophysiological changes in the human body, including age and obesity-related, contribute to OA development. Decreased muscle mass and increased fat mass are related to increase in cytokine and adipokine production, which results in low-grade systemic inflammation.^[45] Also, decreased muscle mass and increased fat mass affect joint loading.^[45] The extracellular matrix undergoes changes that affect the mechanical properties of cartilage and increase its susceptibility to degeneration.^[46] These changes include the buildup of advanced glycation end-products, decreased aggrecan size, decreased hydration, and increased collagen cleavage.^[46] Degeneration and potential alteration in joint mechanics is accelerated by decreased cell density in the ligaments and meniscus and extracellular matrix disruption.^[47,48] Subchondral bone functions are also affected due to impaired mineral composition and decreased osteophyte numbers.^[49]

According to Coggon et al,^[50] people with a BMI of more than 30 kg/m² had a 6.8 times higher risk of developing KOA than people of normal weight. Obesity-related OA is thought to have multifactorial pathophysiology. In obesity, structural damage to joints is thought to occur due to mechanical as well as metabolic factors. Mechanical factors include impaired biomechanics, reduced muscle strength, and higher forces on the joints during activities of daily living.^[51,52] Although the exact metabolic mechanisms by which obesity causes joint structural damage are not yet established, it is believed to include

Table 3
Predictors of Pain and Function in knee osteoarthritis: The analysis of covariance.

Model	Variables	β	SE	P-value	R ² -adjusted
WOMAC Pain	Age	0.038	0.023	.093	0.727
	BMI	-0.001	0.051	.970	
	K/L grade	4.052	0.256	<.001*	
	Sex	0.074	0.396	.851	
WOMAC Function	Age	0.035	0.032	.268	0.741
	BMI	0.079	0.072	.272	
	K/L grade	5.813	0.361	<.001*	
	Sex	0.073	0.557	.896	
WOMAC Total	Age	1.028	0.544	.061	0.771
	BMI	0.562	0.539	.300	
	K/L grade	9.827	0.558	<.001*	
	Sex	0.176	0.869	.840	
VAS	Age	0.001	0.013	.920	0.708
	BMI	0.044	0.029	.140	
	K/L grade	2.222	0.148	<.001*	
	Sex	0.095	0.229	.678	

*significant at $P < .001$.

BMI = body mass index, K/L = Kellgren-Lawrence scale, VAS = visual analogue scale, WOMAC = Western Ontario McMaster Universities Osteoarthritis Index.

abnormal adipokine expression with direct and downstream consequences causing the destruction and remodeling of joint tissue.^[53,54] Adipokines have an impact on the synovium, bone, and cartilage that makeup joints.

4.1. Strength and limitations

The main strength of this paper is a good literature review and extensive references. VAS and the WOMAC index are the most reliable and valid outcome measures in KOA studies. The current study acknowledged some potential limitations. In this study, a relatively small number of participants had severe radiographic grades assessed according to the K/L criteria. In addition, a body composition analysis could have been more helpful than BMI, as the latter does not provide information about fat and lean mass proportion. Using body composition analysis in future studies will help improve understanding of the role of overweight in KOA. The cross-sectional design of the current study is another significant limitation, which limits exploring how these differences have evolved and changed over time.

5. Conclusion

Age, BMI, and radiographic (K/L) grade were associated with pain and physical functions in patients with KOA. K/L grade was the most significant predictor of pain and physical functions in KOA. More longitudinal studies are warranted to assess these differences and their development over time.

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References

- Jordan KP, Wilkie R, Muller S, et al. Measurement of change in function and disability in osteoarthritis: current approaches and future challenges. *Curr Opin Rheumatol*. 2009;21:525–30.
- Cross M, Smith E, Hoy D, et al. The global burden of hip and knee osteoarthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis*. 2014;73:1323–30.
- Gelber AC, Hochberg MC, Mead LA, et al. Body mass index in young men and the risk of subsequent knee and hip osteoarthritis. *Am J Med*. 1999;107:542–8.
- Jaul E, Barron J. Age-related diseases and clinical and public health implications for the 85 years old and over population. *Front Public Health*. 2017;5:335.
- Felson DT, Lawrence RC, Dieppe PA, et al. Osteoarthritis: new insights. Part 1: the disease and its risk factors. *Ann Intern Med*. 2000;133:635–46.
- Lee R, Kean WF. Obesity and knee osteoarthritis. *Inflammopharmacology*. 2012;20:53–8.
- Poornima S, Subramanyam K, Khan IA, et al. Role of SREBP2 gene polymorphism on knee osteoarthritis in the South Indian Hyderabad Population: A hospital based study with G595C variant. *J Orthopaedics*. 2019;16:293–7.
- Blagojevic M, Jinks C, Jeffery A, et al. Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthritis Cartilage*. 2010;18:24–33.
- Kumar D, Souza RB, Subburaj K, et al. Are there sex differences in knee cartilage composition and walking mechanics in healthy and osteoarthritis populations? *Clin Orthopaedics Related Res*. 2015;473:2548–58.
- Dowsey MM, Liew D, Stoney JD, et al. The impact of pre-operative obesity on weight change and outcome in total knee replacement: a prospective study of 529 consecutive patients. *J Bone Joint Surg Br*. 2010;92:513–20.
- Mehta S, Perruccio A, Palaganas M, et al. Do women have poorer outcomes following total knee replacement? *Osteoarthritis Cartilage*. 2015;23:1476–82.
- Hawker GA, Gignac MA, Badley E, et al. A longitudinal study to explain the pain-depression link in older adults with osteoarthritis. *Arthritis Care Res*. 2011;63:1382–90.
- Briggs A, Scott E, Steele K. Impact of osteoarthritis and analgesic treatment on quality of life of an elderly population. *Ann Pharmacother*. 1999;33:1154–9.
- Cushnaghan J, Bennett J, Reading I, et al. Long-term outcome following total knee arthroplasty: a controlled longitudinal study. *Ann Rheum Dis*. 2009;68:642–7.
- Valdes AM, Doherty SA, Zhang W, et al. Inverse relationship between preoperative radiographic severity and postoperative pain in patients with osteoarthritis who have undergone total joint arthroplasty. Paper presented at: Seminars in arthritis and rheumatism. 2012.
- Dowsey MM, Dieppe P, Lohmander S, et al. The association between radiographic severity and pre-operative function in patients undergoing primary knee replacement for osteoarthritis. *Knee*. 2012;19:860–5.
- Keurentjes J, Van Tol F, Fiocco M, et al. Minimal clinically important differences in health-related quality of life after total hip or knee replacement: a systematic review. *Bone Joint Res*. 2012;1:71–7.
- Juhakoski R, Tenhonen S, Anttonen T, et al. Factors affecting self-reported pain and physical function in patients with hip osteoarthritis. *Arch Phys Med Rehabil*. 2008;89:1066–73.
- Peat G, Thomas E, Duncan R, et al. Clinical classification criteria for knee osteoarthritis: performance in the general population and primary care. *Ann Rheum Dis*. 2006;65:1363–7.
- Hjermstad MJ, Fayers PM, Haugen DF, et al. Studies comparing numerical rating scales, verbal rating scales, and visual analogue scales for assessment of pain intensity in adults: a systematic literature review. *J Pain Symptom Manage*. 2011;41:1073–93.
- Alghadir A, Anwer S, Iqbal ZA, et al. Cross-cultural adaptation, reliability and validity of the Arabic version of the reduced Western Ontario and McMaster Universities osteoarthritis index in patients with knee osteoarthritis. *Disabil Rehabil*. 2016;38:689–94.
- Whitehouse S, Lingard E, Katz J, et al. Development and testing of a reduced WOMAC function scale. *J Bone Joint Surg Br*. 2003;85:706–11.
- World Health Organization. *Obesity: Preventing and Managing the Global Epidemic*. Singapore: World Health Organization. 2000.
- Kellgren JH, Lawrence J. Radiological assessment of osteoarthrosis. *Ann Rheum Dis*. 1957;16:494–502.
- Felson DT, Naimark A, Anderson J, et al. The prevalence of knee osteoarthritis in the elderly. The Framingham osteoarthritis study. *Arthritis Rheumatism*. 1987;30:914–8.
- Odding E, Valkenburg HA, Algra D, et al. Associations of radiological osteoarthritis of the hip and knee with locomotor disability in the Rotterdam Study. *Ann Rheum Dis*. 1998;57:203–8.
- Van Saase J, Van Romunde L, 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;48:271–80.
- Apovian CM, Frey CM, Wood GC, et al. Body mass index and physical function in older women. *Obesity Res*. 2002;10:740–7.
- Schoffman DE, Wilcox S, Baruth M. Association of body mass index with physical function and health-related quality of life in adults with arthritis. *Arthritis*. 2013;2013:1–10.
- Gomes-Neto M, Araujo AD, Junqueira IDA, et al. Comparative study of functional capacity and quality of life among obese and non-obese elderly people with knee osteoarthritis. *Revista brasileira de reumatologia*. 2016;56:126–30.

- [31] Alfieri FM, Silva NCOV, Battistella LR. Study of the relation between body weight and functional limitations and pain in patients with knee osteoarthritis. *Einstein (São Paulo)*. 2017;15:307–12.
- [32] Connelly AE, Tucker AJ, Kott LS, et al. Modifiable lifestyle factors are associated with lower pain levels in adults with knee osteoarthritis. *Pain Res Manag*. 2015;20:241–8.
- [33] Elbaz A, Debbi EM, Segal G, et al. Sex and body mass index correlate with Western Ontario and McMaster Universities Osteoarthritis Index and quality of life scores in knee osteoarthritis. *Arch Phys Med Rehabil*. 2011;92:1618–23.
- [34] Goulston LM, Kiran A, Javaid MK, et al. Does obesity predict knee pain over fourteen years in women, independently of radiographic changes? *Arthritis Care Res*. 2011;63:1398–406.
- [35] Felson DT, Zhang Y, Hannan MT, et al. Risk factors for incident radiographic knee osteoarthritis in the elderly. The Framingham study. *Arthritis Rheumatism*. 1997;40:728–33.
- [36] Riddle DL, Stratford PW. Body weight changes and corresponding changes in pain and function in persons with symptomatic knee osteoarthritis: a cohort study. *Arthritis Care Res*. 2013;65:15–22.
- [37] Dillon CF, Rasch EK, Gu Q, et al. Prevalence of knee osteoarthritis in the United States: arthritis data from the Third national health and nutrition examination survey 1991-94. *J Rheumatol*. 2006;33:2271–9.
- [38] Debi R, Mor A, Segal O, et al. Differences in gait patterns, pain, function and quality of life between males and females with knee osteoarthritis: a clinical trial. *BMC Musculoskelet Disord*. 2009;10:1–10.
- [39] Yoshimura N, Muraki S, Oka H, et al. Prevalence of knee osteoarthritis, lumbar spondylosis, and osteoporosis in Japanese men and women: the research on osteoarthritis/osteoporosis against disability study. *J Bone Miner Metab*. 2009;27:620–8.
- [40] Wang K, Kim HA, Felson DT, et al. Radiographic knee osteoarthritis and knee pain: cross-sectional study from five different racial/ethnic populations. *Sci Rep*. 2018;8:1–8.
- [41] Pereira D, Severo M, Santos RA, et al. Knee and hip radiographic osteoarthritis features: differences on pain, function and quality of life. *Clin Rheumatol*. 2016;35:1555–64.
- [42] McAlindon T, Cooper C, Kirwan J, et al. Determinants of disability in osteoarthritis of the knee. *Ann Rheum Dis*. 1993;52:258–62.
- [43] Creamer P, Lethbridge-Cejku M, Hochberg M. Factors associated with functional impairment in symptomatic knee osteoarthritis. *Rheumatology*. 2000;39:490–6.
- [44] Larsson AC, Petersson I, Ekdahl C. Functional capacity and early radiographic osteoarthritis in middle-aged people with chronic knee pain. *Physiother Res Int*. 1998;3:153–63.
- [45] Greene MA, Loeser RF. Aging-related inflammation in osteoarthritis. *Osteoarthritis Cartilage*. 2015;23:1966–71.
- [46] Lotz M, Loeser RF. Effects of aging on articular cartilage homeostasis. *Bone*. 2012;51:241–8.
- [47] Pauli C, Grogan S, Patil S, et al. Macroscopic and histopathologic analysis of human knee menisci in aging and osteoarthritis. *Osteoarthritis Cartilage*. 2011;19:S2021132–1141.
- [48] Hasegawa A, Otsuki S, Pauli C, et al. Anterior cruciate ligament changes in the human knee joint in aging and osteoarthritis. *Arthritis Rheumatism*. 2012;64:696–704.
- [49] Busse B, Djonic D, Milovanovic P, et al. Decrease in the osteocyte lacunar density accompanied by hypermineralized lacunar occlusion reveals failure and delay of remodeling in aged human bone. *Aging Cell*. 2010;9:1065–75.
- [50] Coggon D, Reading I, Croft P, et al. Knee osteoarthritis and obesity. *Int J Obes*. 2001;25:622–7.
- [51] Runhaar J, Koes B, Clockaerts S, et al. A systematic review on changed biomechanics of lower extremities in obese individuals: a possible role in development of osteoarthritis. *Obes Rev*. 2011;12:1071–82.
- [52] King L, Birmingham T, Kean C, et al. Resistance training for medial compartment knee osteoarthritis and malalignment. *Med Sci Sports Exercise*. 2008;40:1376.
- [53] Gómez R, Conde J, Scotecce M, et al. What's new in our understanding of the role of adipokines in rheumatic diseases? *Nat Rev Rheumatol*. 2011;7:528–36.
- [54] Garnero P, Rousseau JC, Delmas PD. Molecular basis and clinical use of biochemical markers of bone, cartilage, and synovium in joint diseases. *Arthritis Rheumatism*. 2000;43:953–68.