Clinic Rev Bone Miner Metab (2016) 14:77–104
DOI 10.1007/s12018-016-9212-6

LOCOMOTIVE SYNDROME

Osteoarthritis as a Cause of Locomotive Syndrome: Its Influence on Functional Mobility and Activities of Daily Living

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Published online: 27 May 2016

Abstract "Locomotive syndrome" is defined as a condition associated with restriction in one's ability to walk or lead a normal life due to a dysfunction in one or more of the parts of the locomotion system, including the muscles, bones, joints, cartilage or intervertebral discs. This syndrome especially refers to individuals who have come to need nursing care services because of problems with the locomotive organs, or those who have conditions which may require them to need such services in the near future. Recent epidemiological studies revealed that the one-fourth of elderly individuals who require special assistance or nursing care have locomotive disorders in Japan. Osteoarthritis of the knee (knee OA) and hip (hip OA), and osteoporosis and spinal canal stenosis due to spondylosis are three major locomotive disorders that cause elderly individuals require special assistance or nursing care. In this review, we focus on the effects of knee and hip OA on the lives of elderly individuals and the recent advantages in clinical research on the pathophysiology and management of these diseases.

Keywords Locomotive syndrome · Osteoarthritis of the knee and hip · Synovitis · Disability of daily living · Biomarkers · Magnetic resonance imaging (MRI)

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Locomotive Syndrome

Japan has evolved into a leading country in both the average life span and healthy life expectancy worldwide. A healthy life expectancy refers to the number of years an individual can expect to live in good health without any special assistance or nursing care. The global healthy life expectancy in Japan (73.4 years of age) is currently no. 1 worldwide in both females (75.6 years of age) and males (71.1 years of age) [1]. Therefore, Japan faces a future as the most elderly society humankind has ever known.

The Japanese Orthopaedic Association proposed the concept of "locomotive syndrome" in 2007 [2]. It is defined as a condition associated with being restricted in one's ability to walk or lead a normal life due to a dysfunction in one or more of the parts of the locomotion system, including the muscles, bones, joints, cartilage or intervertebral discs. This syndrome especially refers to elderly individuals who have come to need nursing care services because of problems with the locomotive organs, or those who have conditions which may require them to need such services in the near future.

Recent epidemiological studies revealed that one-fourth of the elderly individuals require special assistance or

nursing care have locomotive disorders in Japan [2] (Fig. 1). The three major locomotive disorders related to the requirement of special assistance or nursing care in elderly individuals are osteoporotic fragility fractures, knee and hip OA, and spinal canal stenosis due to spondylosis (Fig. 2). The prevalence of these disorders is increased with aging. In addition, it has also been revealed that many elderly individuals concomitantly suffer from two or all of these disorders, and the complication rate of these three locomotive disorders in elderly individuals increases with aging (Fig. 3) [3]. These locomotive organ disorders worsen as signs go unheeded. Thus, steps must be taken today to prevent locomotive syndrome and extend the healthy life expectancy of people living today, so that individuals can continue to be mobile for life (Fig. 4).

Osteoarthritis of the Knee

Knee OA is one of the representative age-related chronic motor organ diseases responsible for locomotive syndrome. OA is an age-related progressive joint disease, which is primarily characterized by cartilage degradation [4]. OA is an increasingly important public health concern, as the prevalence of the disease has increased with aging of the society. Knee OA is more common in women than in men. While knee OA can be a part of a generalized diathesis, obesity, knee injury, occupational bending and lifting, and previous knee surgery are the risk factors for knee OA [5]. Although knee OA is a slowly progressive disease, the natural history of knee OA is highly variable: While the disease improves in some patients, it is stable or gradually worsens in others. In Japan, although it has been estimated that there are 25 million people with radiographic knee OA, it has been speculated that only eight million have knee pain [6].

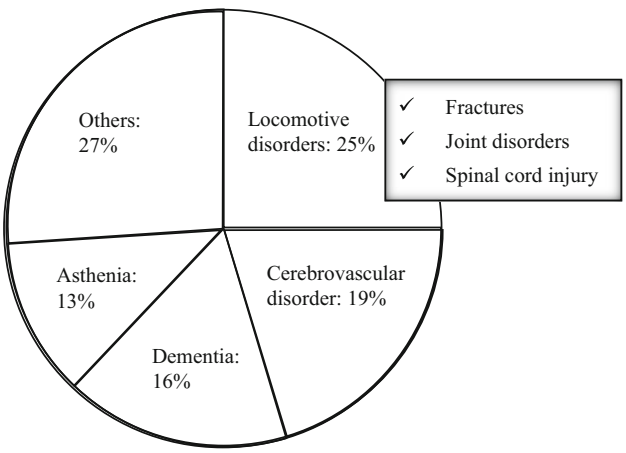


Fig. 1 Causes for nursing care in elderly patients in Japan [2]

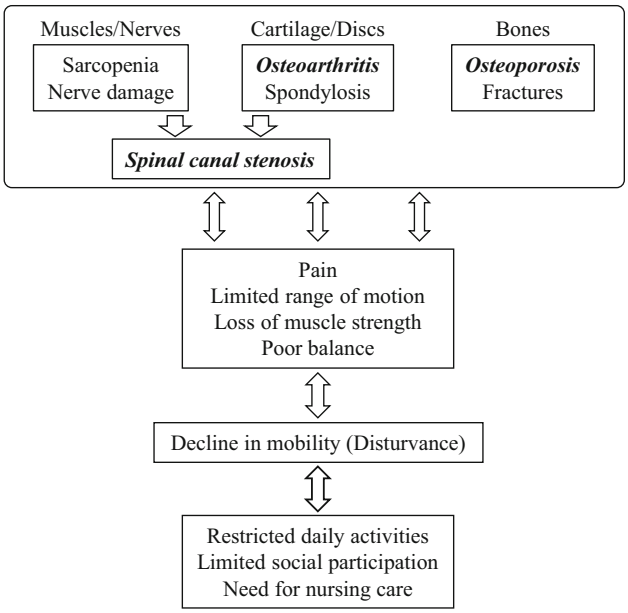
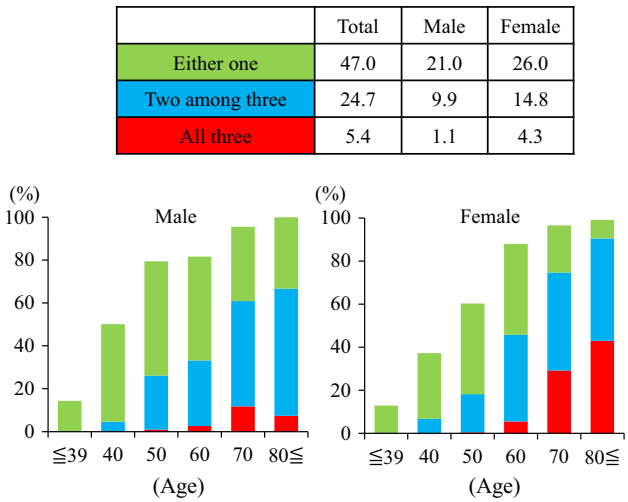


Fig. 2 Locomotive syndrome: a conceptual diagram [2]



	Total	Male	Female
Either one	47.0	21.0	26.0
Two among three	24.7	9.9	14.8
All three	5.4	1.1	4.3

Fig. 3 Prevalence of OA, lumbar spondylosis, and osteoporosis in Japanese men and women [3]

Knee OA is a leading cause of impaired mobility in the elderly [7]. The ideal management of knee OA is illustrated as a sequential, pyramidal approach (Fig. 5) [8]. Established surgical techniques, such as total knee arthroplasty (TKA), unicompartmental knee arthroplasty (UKA), and high tibial osteotomy (HTO), have been developed to improve the symptom, activity of daily life (ADL), and presumably, quality of life of patients with end-stage knee OA [5]. However, only a small population among the patients proceeds to end-stage knee OA. Actually, among patients with painful knee OA, 85,000 cases of TKA are currently being performed annually in Japan. However,

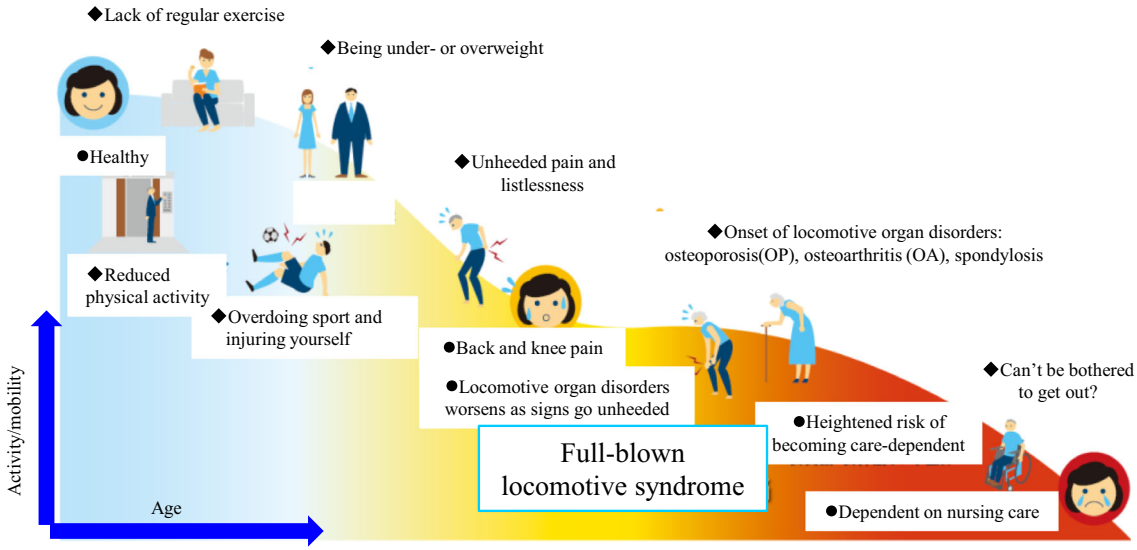


Fig. 4 Relationship between the development of locomotive syndrome and the mobility of people [2]

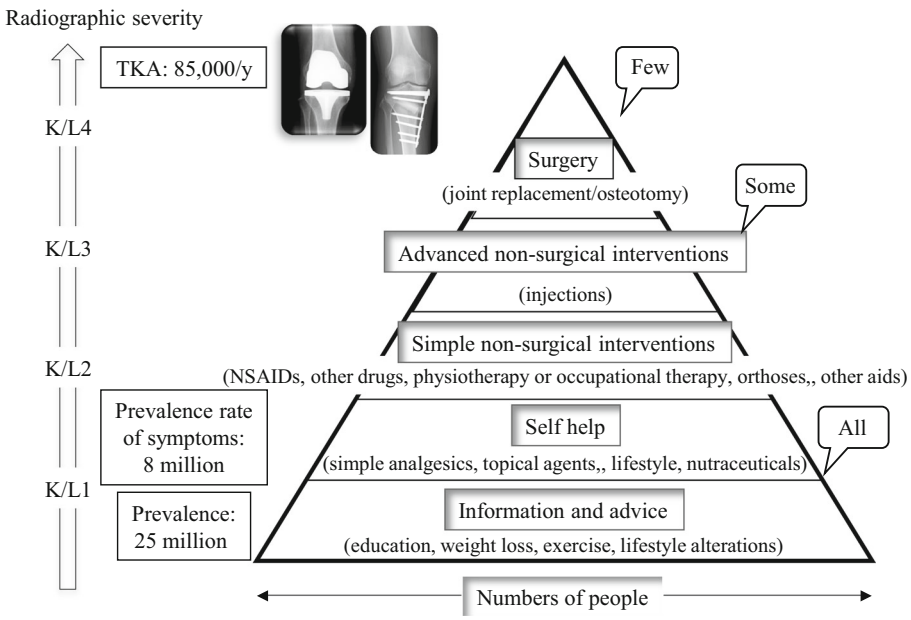


Fig. 5 Principles of the management of knee OA [8]. A suggested sequential, pyramidal approach for disease management

many persons with knee pain, even if they do not present with end-stage knee OA, have limitations in function that prevent them from engaging in activities [9]. Therefore, a complete management system that is applicable for both end-stage knee OA patients and early- and moderate-stage knee OA patients has to be developed under the concept of "locomotive syndrome." For instance, patients with knee OA who do or do not require TKA should be readily identified from the perspective of locomotive syndrome, and earlier identification of patients with symptomatic knee OA is necessary to prevent the development of locomotive syndrome by providing adequate pain relief. In this review, we focus on the current status, problems to be improved, and future directions for knee OA.

Classically Defined Knee OA: Knee OA as an "Illness"

OA is a common disease of the synovial joints and primarily characterized by focal areas of damage to the articular cartilage [8]. Although plain radiographs are commonly used to detect OA in the clinical practice, it is hard to detect the essentials of the disease using plain radiographs. The most common severity classification of

the disease is that defined by Kellgren and Lawrence in 1957 (K/L classification) [10]. A prevalence of knee OA is classically defined if the subject shows K/L grade 2 or greater. According to this definition, it is estimated that there are 25 million people with radiographic knee OA (Fig. 5) [3]. In patients with OA, radiographic findings correlated poorly with the severity of pain [4]. Reflecting this, it has been speculated that only eight million of 25 million people with radiographic knee OA actually have knee pain [3].

"Disease" is defined as abnormalities of the structure and function of body organs systems that can be specifically identified and described by reference to certain biological, chemical, or other evidence [11]. An "illness" is defined as the human response to disease [12]. Similar to osteoporosis, OA may potentially be preceded by a prolonged period of musculoskeletal tissue abnormalities at a molecular, but clinically silent level that can precede anatomic organ system disease [12]. In knee OA, disease does not always induce illness and radiographic-defined knee OA is often found in the joints without any symptoms. The present guideline for the treatment for knee OA is shown in Table 1, which is modified from the guideline defined by Osteoarthritis Research Society International (OARSI) [13]. There are currently no disease-modifying OA treatments, including both non-surgical and surgical treatments, available for knee OA, and symptom-modifying therapy is the only available treatment for knee OA [14]. Therefore, OA must be treated simultaneously as "illness" and "disease" at present. Despite the importance of the symptoms of OA, much remains unknown regarding the nature, causes, and natural history of OA symptoms.

End-Stage Knee OA

Knee OA is a progressive disease. In general, many patients with end-stage knee OA show severe refractory knee pain, which generally occurs at night, and substantial disability, such as reduced walking distance and speed, substantially leading to an inability to work. When the extended trial of non-surgical interventions cannot improve the symptoms and disabilities of the patients, surgical treatment is a potential option. Surgical treatment, such as TKA, UKA, and HTO, is considered to be an effective treatment for end-stage knee OA. The number of annual TKA performed in Japan has dramatically increased, similar to that in the USA [15]. In 2014, approximately 85,000 TKA and UKA were performed in Japan. Surgical treatment for knee OA, especially joint replacement surgery, can relieve pain and improve the knee function in patients with end-stage knee OA. At the same time, as knee OA is a slowly progressive disease, not all patients with knee OA will need to undergo such surgical treatments (Fig. 5).

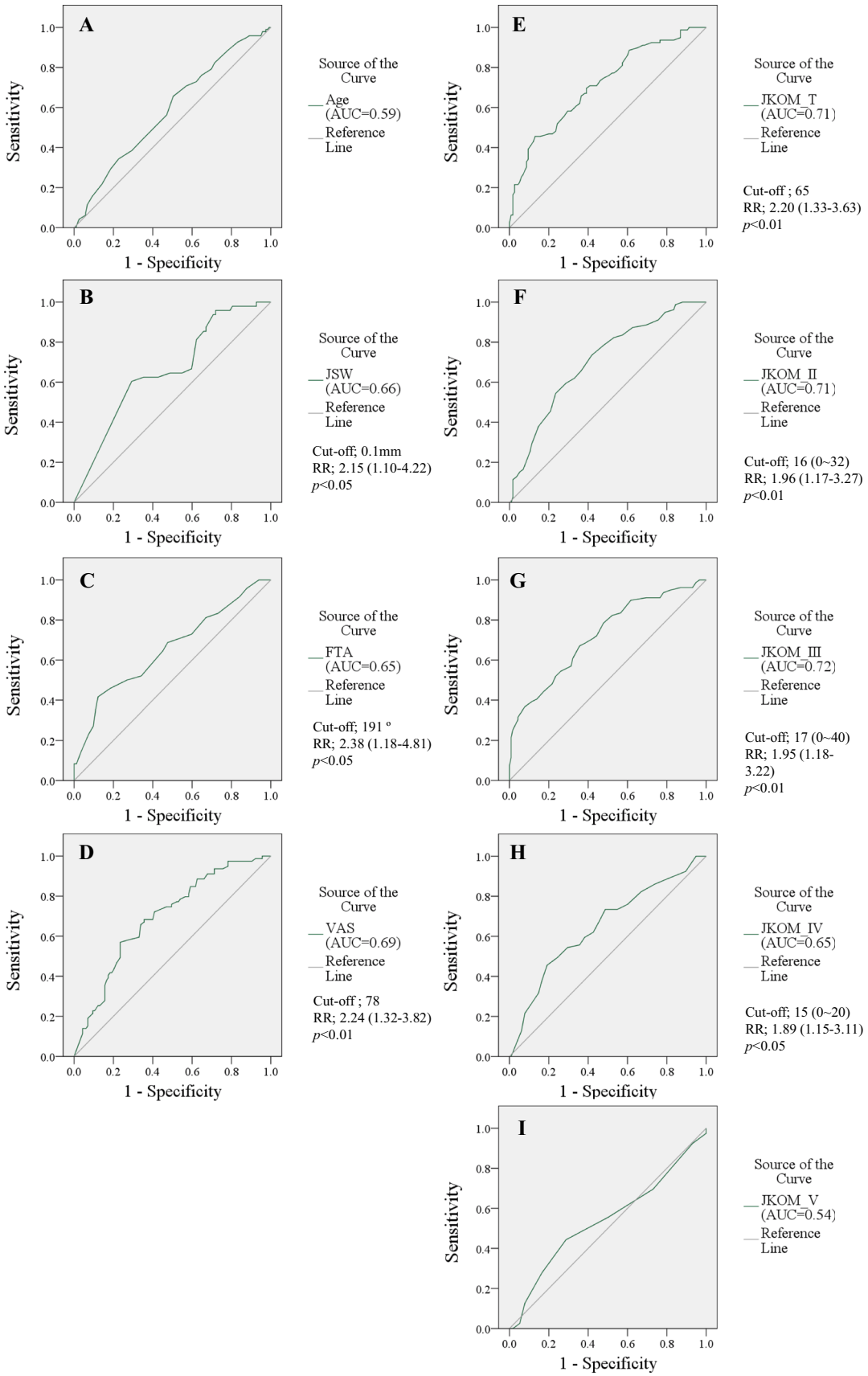
The indications for joint replacement surgery include pain, functional impairment, and structural changes [16], and disability and participation restriction are the main features to consider. However, there are no current symptoms which clearly indicate a need to perform joint replacement surgery [5, 17]. Setting objective indications for joint replacement surgery in patients with knee OA has long been a goal of researchers [18–24]. However, the decision whether to undergo joint replacement for patients with age-related chronic diseases, such as OA, is often difficult, with no clear-cut indications for the procedure [25, 26].

Whether a patient should undergo surgical treatment is determined by the physician and the patient working together [25]. For physicians, the development of such indications based on the past results of patients who have already undergone surgical treatment or selected an alternate approach to treatment is helpful to discuss with patients who are considering surgical treatment. We previously investigated which patients with end-stage OA physicians recommended undergo surgical treatment, and why these patients decided on that procedure. We examined whether it was possible to determine which patients would undergo surgical treatment within the next 6 months, and those who would not, according to their baseline data [27]. Two-hundred and forty end-stage medial-type knee OA patients were enrolled and followed up for 6 months. Radiographic findings, visual analog scale (VAS) for pain and a patient-oriented outcome measure, and the Japanese Knee Osteoarthritis Measure (JKOM) were recorded at baseline. Relative risks (RRs) using the area under the curve (AUC) for a receiver operating characteristic (ROC) curve analysis were calculated to evaluate several scores for receiving joint replacement surgery. While 119 patients (55.3 %) did not undergo TKA, the remaining 96 patients (44.7 %) underwent TKA during this period. The AUCs of the ROC curve for the JKOM total score [0.71 (95 % CI 0.64–0.79)] were higher than those for radiographic parameters (Fig. 6). Among the JKOM subcategories, JKOM category III, which indicates the condition in daily life, showed the highest AUC of 0.72 (95 % CI 0.65–0.80). The JKOM total score (65/100) and JKOM category III score (17/40) showed RRs of 2.20 (95 % CI 1.33–3.63) and 1.95 (95 % CI 1.18–3.22) for receiving TKA, respectively. This study showed that, among the patient-oriented outcome measures for patients with end-stage knee OA, disability for daily living was one of the indications for undergoing joint replacement surgery, while radiographic OA severity was not due to its low sensitivity and specificity [27].

In addition to TKA, the long-term results of UKA and HTO have been recently improved [5, 28]. In contrast, it is well known that any surgical treatment has a risk of complications. Surgical treatment for knee and hip OA is

Table 1 Guideline for knee OA defied by the Japanese Orthopaedic Association (JOA), which is modified by the OARSI recommendation [13] and adapted for Japanese patients with knee OA

			JOA recommendation
General	1	Optimal management of OA requires a combination of non-pharmacological and pharmacological modalities	A
Non-pharmacological modalities of treatment	2	All patients with hip and knee OA should be given information access and education about the objectives of treatment and the importance of changes in lifestyle, exercise, acing of activities, weight reduction, and other measures to unload the damaged joint(s). The initial focus should be on self-help and patient-driven treatments rather than on passive therapies delivered by health professionals. Subsequently, emphasis should be placed in encouraging adherence to the regimen of non-pharmacological therapy	A
	5	Patients with hip and knee OA should be encouraged to undertake, and continue to undertake, regular aerobic, muscle strengthening and range of motion exercises. For patients with symptomatic hip OA, exercises in water can be effective	A
	6	Patients with hip and knee OA, who are overweight, should be encouraged to lose weight and maintain their weight at a lower levels	A
	7	Walking aids can reduce pain in patients with hip and knee OA. Patients should be given instruction in the optimal use of a cane or crutch in the contralateral hand. Frames or wheeled walkers are often preferable for those with bilateral diseases	A
Pharmacological modalities of treatment	12	Acetaminophen (up to 4 g/day)	B
	13	In patients with symptomatic hip or knee OA, nonsteroidal anti-inflammatory drugs (NSAIDs) should be used at the lowest effective dose, but their long-term use should be avoided if possible. In patients with increased GI risk, either a COX-w selective agent for gastroprotection may be considered, but NSAIDs, including both non-selective and COX-2 selective agents, should be used with caution in patients with CV risk factors	A
	15	IA injections with corticosteroids can be used in the treatment for hip or knee OA and should be considered particularly when patients have moderate-to-severe pain not responding satisfactorily to oral analgesic/anti-inflammatory agents and in patients with symptomatic knee OA with effusion or other physical signs of local inflammation	C
	16	Injections of IA hyaluronate may be useful in patients with knee OA. They are characterized by delayed onset, but prolonged duration, of symptomatic benefit when compared to IA injections of corticosteroids	B
	19	The use of weak opioids and narcotic analgesics can be considered for the treatment for refractory pain in patients with hip or knee OA, where other pharmacological opioids should only be used for the management of severe pain in exceptional circumstances. Non-pharmacological therapies should be continued in such patients and surgical treatments should be considered	C
Surgical modalities of treatment	20	Patients with hip or knee OA who are not obtaining adequate pain relief and functional improvement from a combination of non-pharmacological and pharmacological treatment should be considered for joint replacement surgery. Replacement arthroplasties are effective and cost-effective interventions for patients with significant symptoms, and/or functional limitations associated with a reduced health-related quality od life, despite conservative therapy	A
	21	Unicompartmental knee replacement is effective in patients with knee OA restricted to a single compartment	C
	22	Osteotomy and joint preserving surgical procedures should be considered in young adults with symptomatic hip OA, especially in the presence of dysplasia. For the young and physically active patient with significant symptoms from unicompartmental knee OA, high tibial osteotomy may offer an alternative intervention that delays the need for joint replacement some 10 years	B
	23	The role of joint lavage and arthroscopic debridement in knee OA is controversial. Although some studies have demonstrated short-term symptom relief, and others suggest that improvement in symptoms could be attributable to a placebo effect	C


A
Sensitivity
1 - Specificity
Source of the Curve
Age (AUC=0.59)
Reference Line
B
Sensitivity
1 - Specificity
Source of the Curve
JSW (AUC=0.66)
Reference Line
Cut-off; 0.1mm
RR; 2.15 (1.10-4.22)
p<0.05
C
Sensitivity
1 - Specificity
Source of the Curve
FTA (AUC=0.65)
Reference Line
Cut-off; 191 °
RR; 2.38 (1.18-4.81)
p<0.05
D
Sensitivity
1 - Specificity
Source of the Curve
VAS (AUC=0.69)
Reference Line
Cut-off ; 78
RR; 2.24 (1.32-3.82)
p<0.01
E
Sensitivity
1 - Specificity
Source of the Curve
JKOM_T (AUC=0.71)
Reference Line
Cut-off ; 65
RR; 2.20 (1.33-3.63)
p<0.01
F
Sensitivity
1 - Specificity
Source of the Curve
JKOM_II (AUC=0.71)
Reference Line
Cut-off; 16 (0~32)
RR; 1.96 (1.17-3.27)
p<0.01
G
Sensitivity
1 - Specificity
Source of the Curve
JKOM_III (AUC=0.72)
Reference Line
Cut-off; 17 (0~40)
RR; 1.95 (1.18-3.22)
p<0.01
H
Sensitivity
1 - Specificity
Source of the Curve
JKOM_IV (AUC=0.65)
Reference Line
Cut-off; 15 (0~20)
RR; 1.89 (1.15-3.11)
p<0.05
I
Sensitivity
1 - Specificity
Source of the Curve
JKOM_V (AUC=0.54)
Reference Line

◀**Fig. 6** Receiver operating characteristic (ROC) curves of the basal characteristics and the Japanese Knee Osteoarthritis Measure (JKOM) category scores demonstrating the ability to discriminate between patients with total knee joint arthroplasty (TKA) and those without TKA [27]. The ROC curve identifying the sensitivity and (1 - specificity) for the basal characteristics [**a** age; **b** medial knee joint space width (JSW); **c** femorotibial angle (FTA); **d** visual analog scale (VAS); **e** total score of the Japanese Knee Osteoarthritis Measure (JKOM_T); **f** JKOM sub-category II (JKOM_II); **g** JKOM sub-category III (JKOM_III); **h** JKOM sub-category IV (JKOM_IV); **i** JKOM sub-category V (JKOM_V)]. AUC: area under the curve in predicting patients with and without TKA. *RR* relative risk, *AUC* area under the curve. AUC and RR indicate the data (95 % CI)

not an exception. For instance, early death after joint replacement surgery is one of the critical complications of joint replacement surgery. A recent study reported that 467,779 primary knee replacement surgeries were performed to treat knee OA during a 9-year period in England and Wales; 1183 patients died within 45 days of surgery, although a substantial secular decrease in mortality from 0.37 % in 2003 to 0.20 % in 2011 was observed (Fig. 7a) [29]. Moreover, 409,096 primary hip replacement surgeries were performed to treat hip OA during a 9-year period in England and Wales; 1743 patients died within 90 days of surgery, although a substantial secular decrease in mortality from 0.56 % in 2003 to 0.29 % in 2011 was observed (Fig. 7b) [30]. UKA has also a risk for early death after surgery. A recent study compared patients who underwent UKA with those who underwent TKA using a propensity score-matching technique [28]. 25,334 patients who underwent UKA were matched to 75,996 who underwent TKA, and UKA showed a worse implant survival for revision and revision/reoperation than TKA. In contrast, the mortality was significantly lower after UKA at all time points than TKA (30 day: hazard ratio: 0.23, 95 % CI 0.11–0.50; 8 year: 0.85, 95 % CI 0.79–0.92) (Fig. 8). The length of hospitalization, complications (such as thromboembolism, myocardial infarction, and stroke), and rate of readmission were all lower for UKA than TKA. As mentioned above, there are currently no disease-modifying treatments including surgical treatment for knee OA. In

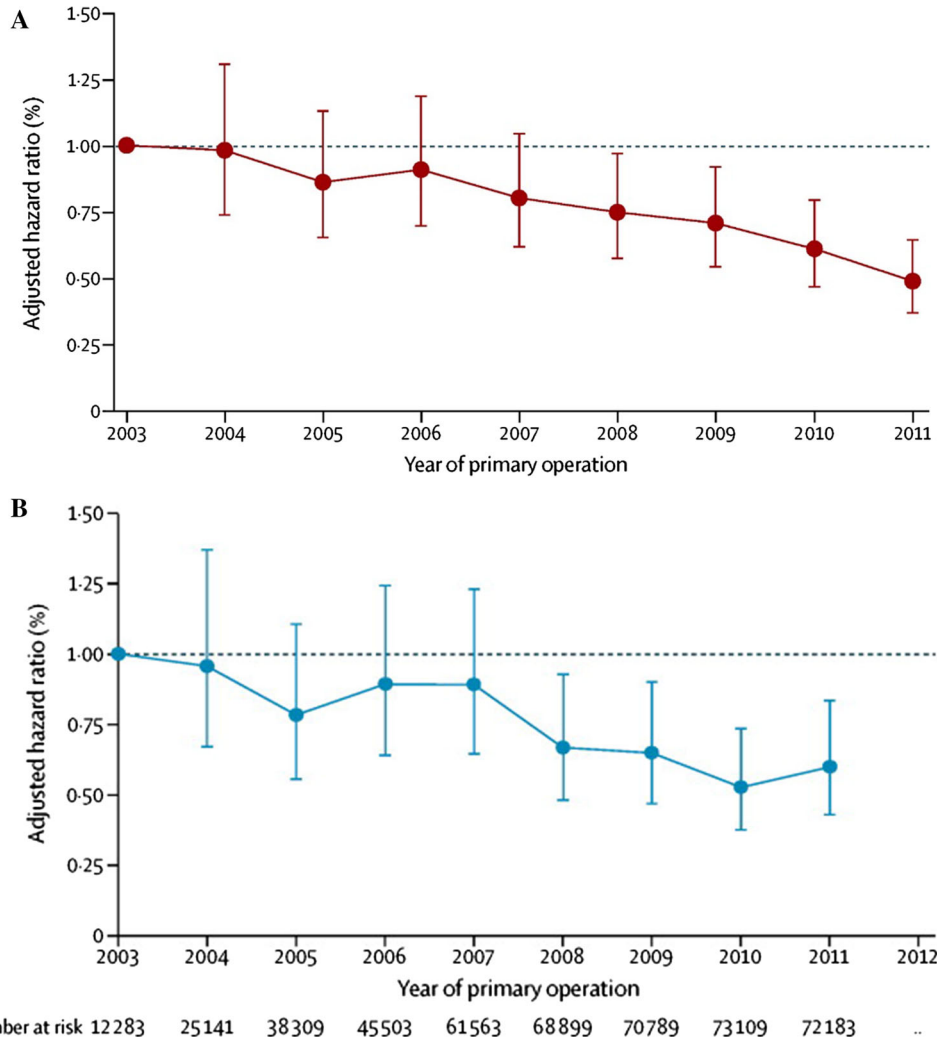


Fig. 7 **a** Changes in 90-day mortality after total hip arthroplasty (THA) over time [30]. Annual hazard ratios with 95 % CI of primary THA after adjusting for sex and age. **b** Changes in 45-day mortality after TKA with time [29]. Annual hazard ratios with 95 % CI of primary TKA after adjusting for sex and age. *Numbers shown underneath the plotted values are the number of primary operations performed that year

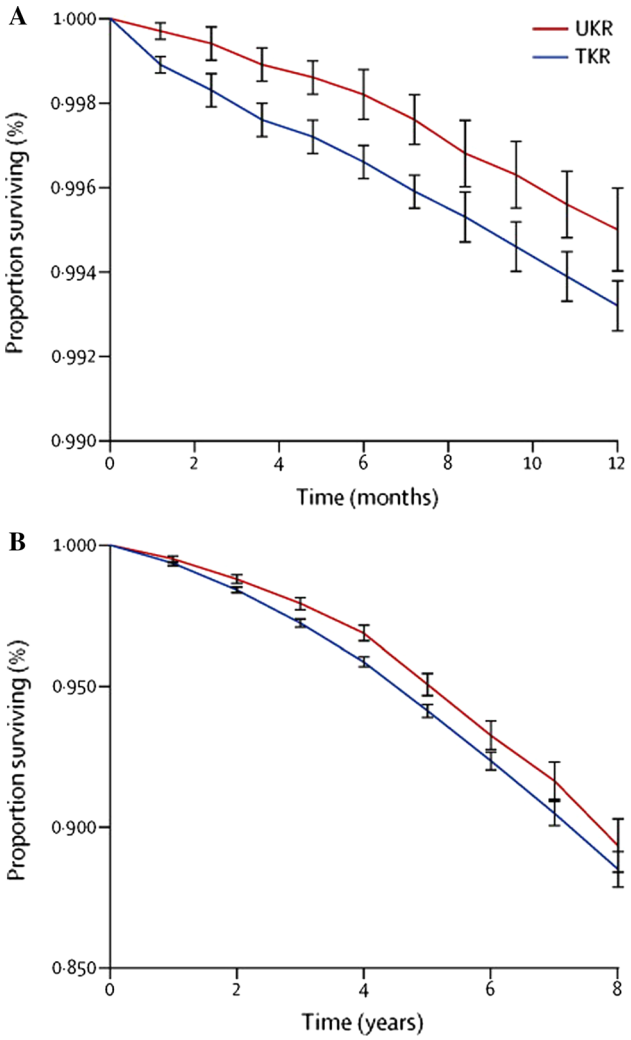


Fig. 8 Survival curves showing the comparison of mortality at 1 year (**a**) and 8 years (**b**). *UKR* unicompartmental knee replacement, *TKR* total knee replacement. *Error bars* show 95 % CI [28]

addition determining whether a patient should undergo surgical treatment, the timing for surgical treatment and choice of procedure for patients with end-stage knee OA should be discussed under the concept of "locomotive syndrome," which aims to contribute to the extension of a healthy life expectancy. Specifically, we should pay more attention to the impairment of mobility and pain due to knee OA, especially from advanced to end-stage knee OA, and prevent worsening of the mobility and recover mobility promptly by performing various surgical treatments.

Early- to Middle-Stage Knee OA

Pain in Knee OA

Importance of Pain in Knee OA Pain is the most prominent and disabling symptom of knee OA. The pain in knee OA is a type of nociceptive pain [31]. Pain is the major reason why individuals seek medical attention from early- through end-stage knee OA, and it is also a major determinant for the loss of joint function. Furthermore, there are currently no disease-modifying osteoarthritis drugs (DMOADs) available for OA, and symptom-modifying therapy is the only available treatment for knee OA. As it is also currently impossible to predict who will progress to OA and whose OA will progress from mild to severe, it is not possible to prevent the progression of the disease. Thus, the treatments for knee OA are essentially treatments for knee pain. Despite its importance, much remains unknown about the nature, causes, and natural history of OA joint pain. Therefore, the factors associated with pain and the pathogenesis of pain must be investigated in terms of the severity of joint damage [32].

It has recently been reported that in patients with knee OA, the avoidance of activity leads to the deterioration of the knee extensor muscle strength and, consequently, greater limitations in activities (Fig. 9) [33]. In a 5-year prospective cohort study, 288 patients with knee and hip OA were recruited. In patients with knee OA, reduced knee extensor muscle strength mediated the relationship between the avoidance of activity and limitations in activities. In patients with hip OA, reduced hip abductor muscle strength mediated the relationship between avoidance of activity and limitations in activities [33]. As pain is a major cause of avoidance of activity in patients with knee and hip OA (Table 2), it is necessary to better understand the pain in OA and develop strategies to prevent or at least provide better relief of this pain.

A recent epidemiological study in Japan suggested the association between knee pain and lumbar pain [34]. In the

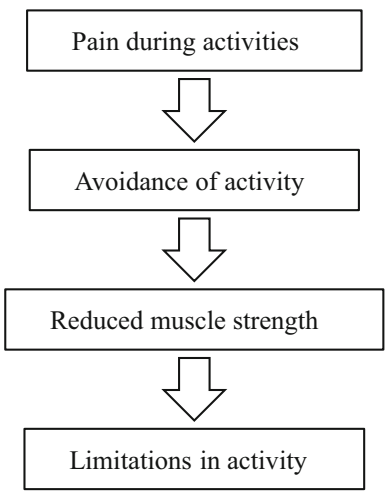


Fig. 9 A hypothetical model of the associations among pain, the avoidance of activities, reduced muscle strength, and limitation in activity [33]

Table 2 Mediating effects of muscle strength on the relationship between the avoidance of activity and performance-based limitations in activities [33]

Dependent variables	Independent variables	Regression coefficient (95 % CI)	*p*
1. Limitations in activities	Avoidance of activity	1.68 (0.98 to 2.39)	<0.001*
2. Knee extensor muscle strength	Avoidance of activity	−0.24 (−0.35 to −0.12)	<0.001*
3. Limitations in activities	Knee extensor muscle strength	−0.52 (−1.02 to −0.02)	0.043*
	Avoidance of activity	1.55 (0.84 to 2.26)	<0.001*

* Potential confounders included age, gender, the duration of complaints, the BMI, education level, and comorbidities

Longitudinal Cohorts of Motor System Organ (LOCOMO) study, in which 12,019 participants were registered, the prevalence of knee pain was 32.7 %, lumbar pain was 37.7 %, and both knee and lumbar pain was 12.2 % of the total population. It was clarified that the factors associated with knee or lumbar pain were age, sex, body build, and residential characteristics. In addition, the presence of knee pain affected the lumbar pain, and vice versa (Table 3). These results suggest that knee pain may affect other motor organs, although the etiology for the association between knee pain and lumbar pain is still unclear.

A comparative assessment of the preventable risk factors for adult mortality from non-communicable diseases in Japan showed that physical inactivity, subsequent to tobacco smoking and high blood pressure, was the third most common determinant of adult mortality from non-communicable diseases in 2007 (Fig. 10) [35]. Cardiovascular diseases (CVDs) were the most prominent diseases that induced physical inactivity. It has been suggested that knee and hip OA is associated with an increased risk of CVDs [36]. In population-based administrative data from British Columbia, Canada, the medical history of a random sample of 600,000 individuals from 1991 to 2009 was analyzed, and knee and hip OA was an independent predictor of CVD. The adjusted RRs for CVDs were 1.15 (95 % CI 1.04–1.27), 1.26 (95 % CI 1.13–1.42), and 1.17 (95 % CI 1.07–1.26) among older males (age ≥65 years), younger females (age <65 years), and older females, respectively. OA patients who underwent joint replacement surgery had a 26 % increased risk of CVD in comparison with non-OA cases (Table 4).

In a population-based cohort study in southwest England, all-cause and disease-specific mortality with knee and hip OA was examined [37]. In this study, individuals with symptoms and radiographic confirmation of knee or hip OA had an excessive all-cause mortality compared with the general population (standardized mortality ratio 1.55, 95 % CI 1.41–1.70). The excess was particularly pronounced for death from CVD (standardized mortality ratio 1.71, 95 % CI 1.49–1.98)- and dementia (standardized mortality ratio 1.99, 95 % CI 1.22–3.25)-associated mortality (Table 5). Mortality increases with increasing age (*p* for trend <0.001), male sex (adjusted hazard ratio 1.59, 95 % CI 1.30–1.96), self-reported history of diabetes (1.95, 95 % CI 1.31–2.90), cancer (2.28, 95 % CI 1.50–3.47), CVD (1.38, 95 % CI 1.12–1.71), and walking disability (1.48, 95 % CI 1.17–1.86) (Fig. 11). The more severe the walking disability, the higher the risk of death (*p* for trend <0.001) (Fig. 12). These results indicate that the risk of death from cardiovascular causes was increased in patients with walking

Table 3 Odds ratios (OR) of potentiality associated factors for the presence of knee pain/lumbar pain versus the absence of pain [34]

Explanatory variables	Reference	OR	95 % confident interval	*p*
Knee pain (presence vs. absence)				
Age (years)	+1 year	1.045	1.039–1.051	<0.001***
Gender	0: men, 1: women	1.602	1.441–1.780	<0.001***
Region	0: urban area, 1: rural area	2.419	2.152–2.720	<0.001***
BMI (kg/m^2)	+1 kg/m^2	1.141	1.124–1.158	<0.001***
Lumbar pain	0: absence, 1: presence	1.373	1.243–1.515	<0.001***
Lumbar pain (presence vs. absence)				
Age (years)	+1 year	1.018	1.013–1.023	<0.001***
Gender	0: men, 1: women	1.130	1.023–1.248	0.016*
Region	0: urban area, 1: rural area	2.016	1.801–2.256	<0.001***
BMI (kg/m^2)	+1 kg/m^2	1.020	1.003–1.031	0.021*
Knee pain	0: absence, 1: presence	1.375	1.246–1.518	<0.001***

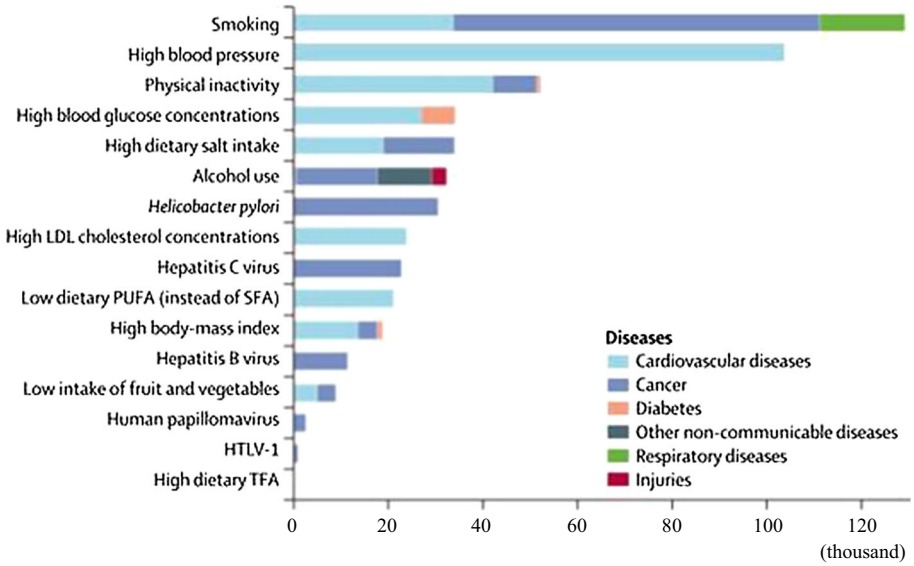


Fig. 10 Deaths from non-communicable diseases and injuries in females and males, and the deaths attributable to various risk factors in Japan in 2007 [35]

Table 4 RRs and 95 % CIs of cardiovascular diseases for OA patients according to the OA diagnosis and TJR [36]

Exposure	RR (95 % CI)
CVD	
OA diagnosis	1.11 (1.05–1.17)[a]
TJR	1.26 (1.12–1.41)[a]
IHD	
OA diagnosis	1.30 (1.18–1.43)[a]
TJR	1.44 (1.16–1.79)[a]
CHF	
OA diagnosis	1.09 (0.97–1.23)
TJR	1.46 (1.16–1.83)[a]

[a] In all cases, non-OA was the reference category

RR relative risk, *95 % CI* 95 % confidence interval, *TJR* total joint replacement, *CVD* cardiovascular disease, *IHD* ischemic heart disease other than myocardial infarction, *CHF* congestive heart failure

Table 5 Age- and sex-standardized mortality ratios [37]

Cause of death	All patients ($n = 1163$)		
	No of deaths		
	Observed	Expected	SMR (95 % CI)
All causes	438	283	1.55 (1.41–1.70)
Cardiovascular disease	188	110	1.71 (1.49–1.98)
Cancer-related	123	93	1.32 (1.10–1.57)
Respiratory disease	43	33	1.29 (0.96–1.74)
Gastrointestinal disease	19	13	1.47 (0.94–2.30)
Dementia-associated	16	8	1.99 (1.22–3.25)

All-cause mortality in patients with radiographically confirmed OA of the knee and hip compared with the general population was found

SMR standardized mortality ratio

disability, suggesting that the management of patients with knee or hip OA and walking disability may become an effective treatment for cardiovascular risk factors and comorbidities, as well as on increasing physical activity.

Establishment of a better management system of early, middle, and end stage of knee and hip OA, which are diseases that induce walking disability, is required. Pain remains a prominent symptom in knee and hip OA. However, individuals with pain due to knee or hip OA reduce their physical activity to avoid pain. These individuals do not have severe pain, but the impairment of their mobility remains, causing them to become physically inactive. We should pay more attention to the physical inactivity of patients with knee or hip OA and the systemic effect of physical inactivity of patients with knee or hip OA. We should also focus on the pathophysiology of pain in knee and hip OA to avoid this vicious cycle induced by pain.

Pathophysiology of Pain in Knee OA: The Role of Synovitis OA is primarily characterized by cartilage degradation. This may be associated with pain and the pathogenesis of knee OA. However, as cartilage is aneural, it is not a tissue that can directly generate pain [31]. Nevertheless, changes in articulation caused by structural changes and associated changes in extracellular matrix turnover in the articular cartilage, reflected by cartilage biomarkers [38], may result in the manifestation of pain in other joint tissues. This may be a consequence of alterations in joint mechanics, resulting in structural changes elsewhere, and/or the generation of joint debris that may cause synovitis [39]. Synovitis and osteophyte formation are considered to be secondary phenomena in OA, as degenerated articular cartilage affects the subchondral bone and the synovium [40–42]. In synovitis, the synovial

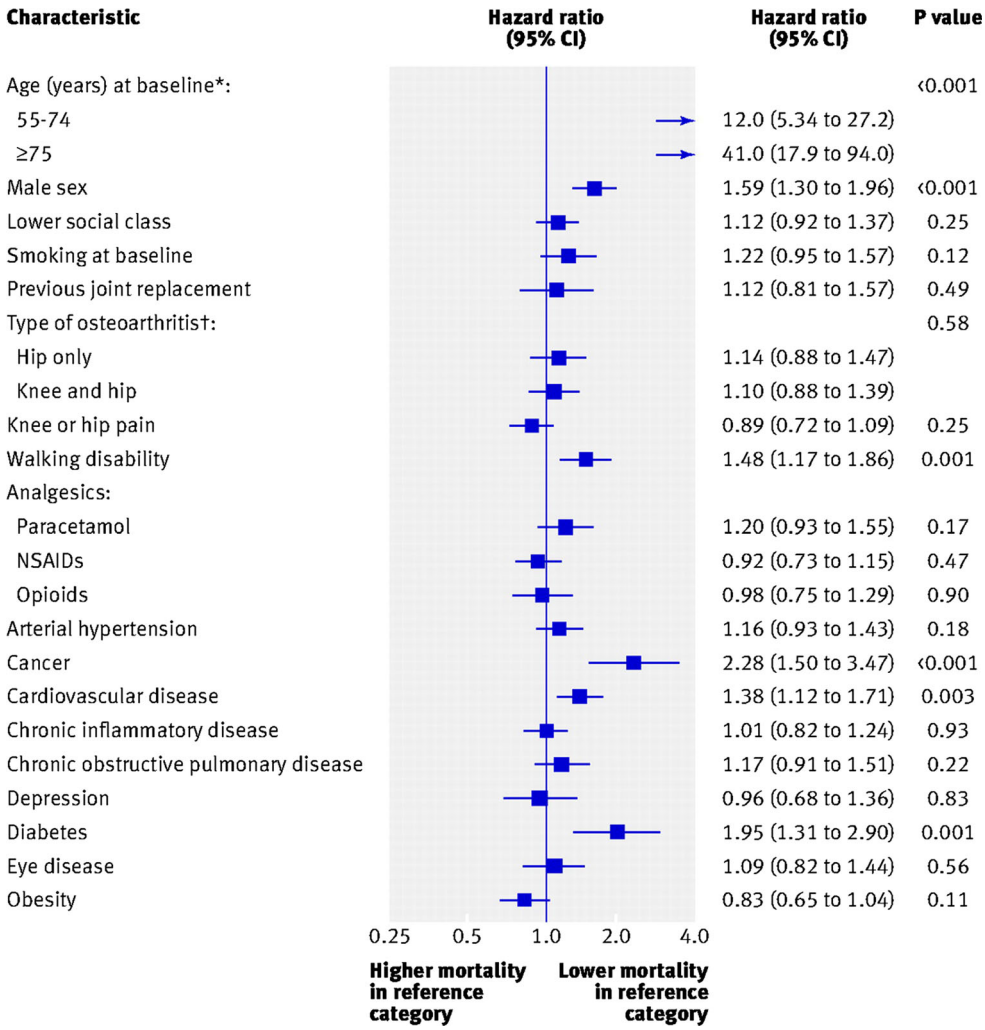


Fig. 11 Associations between characteristics at baseline and all-cause mortality up to 15 years thereafter [37]. The figure shows hazard ratios with corresponding 95 % CI from multivariable Cox proportional hazards models after multiple imputation of missing values in covariates. *p* values were calculated using two-sided Wald tests. *NSAIDs* nonsteroidal anti-inflammatory drugs. *Age 35–44 is set as the reference category

membrane produces proteases and cytokines, which enhance cartilage degradation [43]. Although synovitis occurs throughout the affected joint in rheumatic arthritis, synovitis occurs locally and more mildly in OA [44]. Biomarkers, in addition to the use of imaging technologies such as magnetic resonance imaging (MRI), are now being used to detect and monitor cartilage and bone turnover and synovial metabolism for the critical assessment of the pathophysiological processes that lead to joint failure and pain in OA patients [45–47].

We previously showed that there are interrelationships between the presence or absence of knee pain and the changes in skeletal tissue and synovitis biomarkers in early-stage knee OA [38]. Five commercial biomarker assays were used in these analyses, which evaluated the serum cartilage type II collagen cleavage by collagenase (sC2C); urinary cartilage type II collagen C-telopeptide (uCTX-II); serum cartilage type II procollagen carboxy propeptide (sCP II), which is cleaved from cartilage type II procollagen following the release of newly synthesized procollagen into the matrix; urinary bone N-terminal cross-linking telopeptide of type I collagen (uNTx), a biomarker of bone resorption; and serum hyaluronic acid (sHA), a marker of synovitis [48], all of which have been used to study the pathology of OA. Patients with a K/L grade of 1 or 2 were divided into two groups according to the presence or absence of knee pain, and these two groups were evaluated by biomarker analyses. The levels of cartilage biomarkers, including sC2C, uCTX-II and sCP II, and the synovitis biomarker, sHA, were all significantly increased in patients with knee pain compared to those without knee pain, irrespective of the K/L grade (Fig. 13). These results suggest that synovitis is related to early chondral lesions in knee OA and can be detected by biomarkers such as C2C, CTX-II, CPII, and HA, which are associated with knee pain in early-stage knee OA [38].

Detrimental mechanical loading across the knee joint is speculated to be one of the main factors underlying the pathophysiology of knee OA [39]. The malalignment of the lower limb, as well as excess body mass, has been

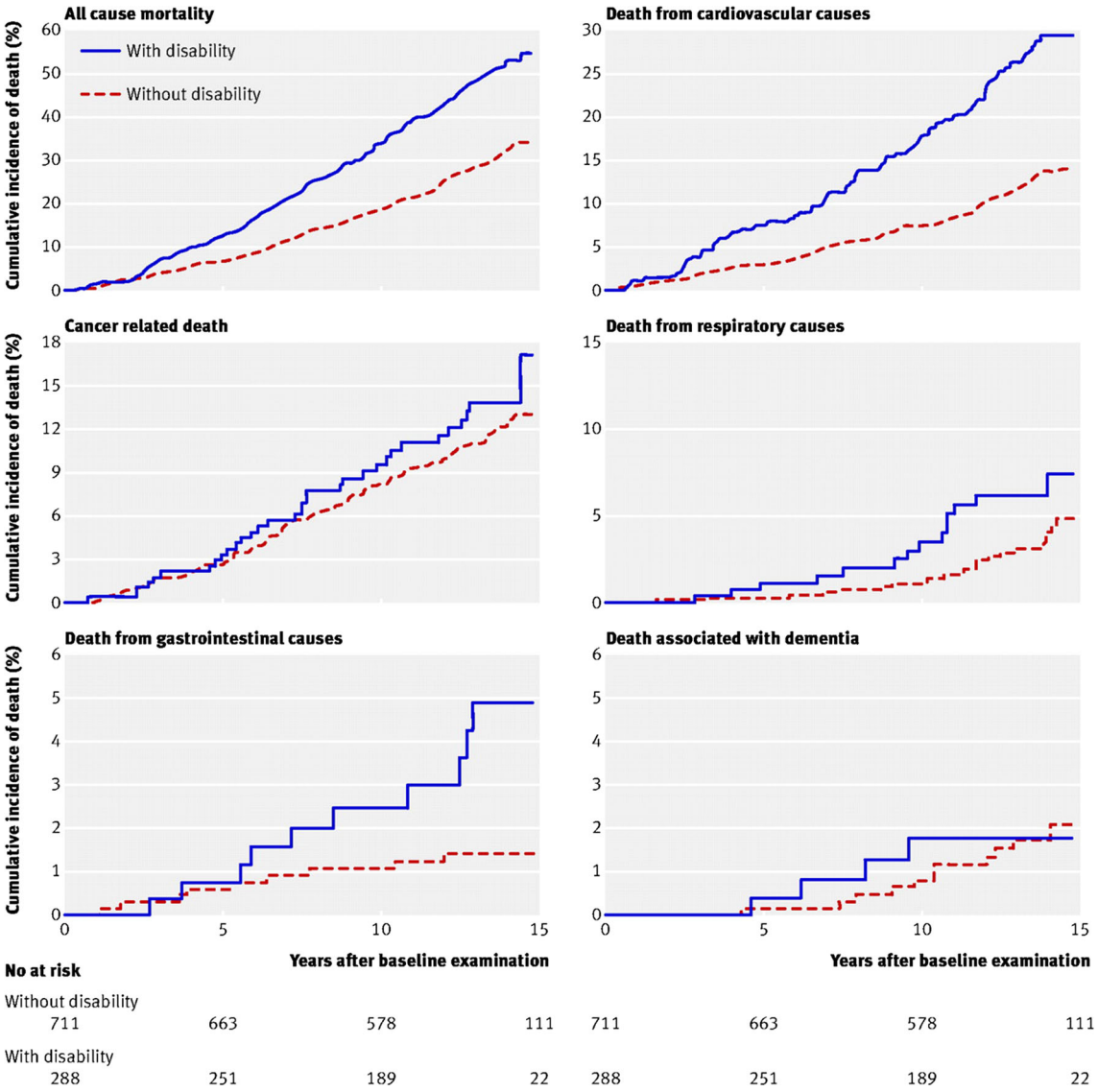


Fig. 12 All-cause and disease-specific mortalities in patients with and without walking disability at the baseline examination [37]. Kaplan–Meier curves show the cumulative incidence of all-cause mortality, death from cardiovascular causes, cancer-related death, death from respiratory causes, death from gastrointestinal causes, and death associated with dementia up to 15 years

considered to be a risk factor for the progression of knee OA, due to the association between this factor and the joint load [49–51]. As pain associated with knee OA is a type of nociceptive pain [31], it has been speculated that detrimental mechanical loading across the joint and inflammation, especially synovitis, may be the main factors associated with the severity of pain [8, 39]. While detrimental mechanical loading across the joint and synovitis were both speculated to be involved in the pain severity in knee OA, it was unclear how the pain components varied according to the progression of the disease.

We previously showed that the factors associated with pain in knee OA varied according to the disease progression [32]. In this study, the patients were divided into two groups according to the radiographic severity of knee OA and the pain severity, serum interleukin (IL)-6 levels, and alignment of the lower limb in patients with knee OA was investigated to examine whether the factors associated with pain in knee OA varied according to the radiographic disease severity. Early- to end-stage knee OA [67 (41.9 %) with a K/L grade of 2, 51 (31.9 %) with a K/L grade of 3, and 42 (26.2 %) with a K/L grade of 4] patients were included, and a multiple linear regression analysis indicated that the serum IL-6 levels and the anatomic alignment angle (AAA) were both associated with the pain severity, as evaluated by the pain VAS score in the overall cohort (Table 6). On the other hand, the serum levels of IL-6 were solely associated with pain VAS score in the

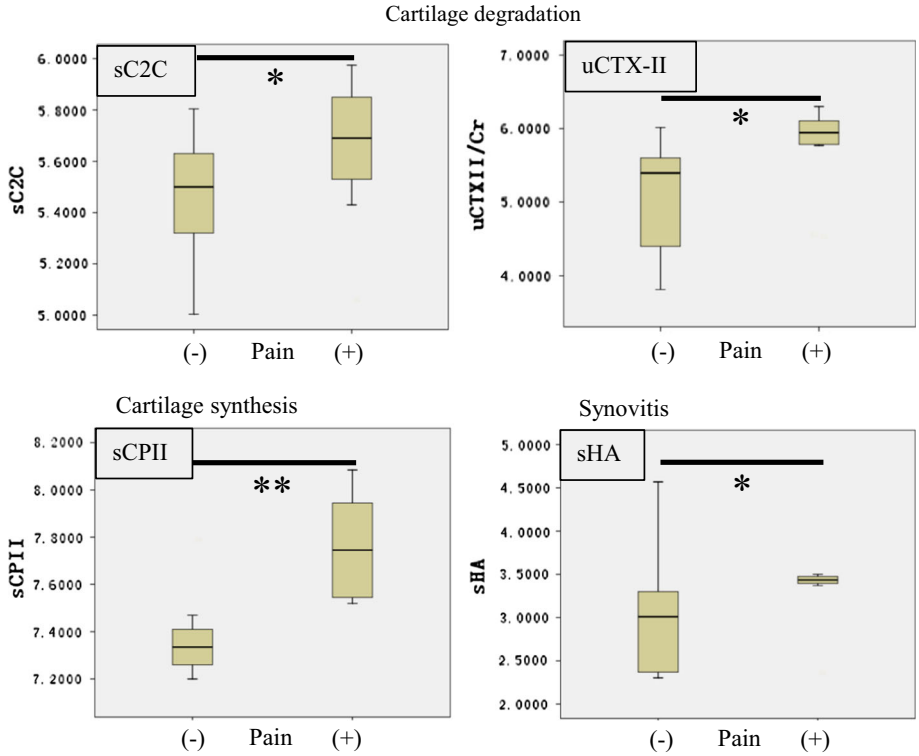


Fig. 13 Biomarker levels of the subjects with early-stage knee OA according to the presence or absence of knee pain [38]. All analyses were adjusted for age, gender, and the body mass index. Urinary biomarkers were corrected using the creatinine level. *Values of $p \leq 0.05$ were considered to be statistically significant. *s* serum, *u* urine, *C2C* cartilage collagen type II cleavage, *CPII* cartilage type II collagen carboxy propeptide, *CTX-II* type II collagen C-telopeptide, *NTx* N-terminal cross-linking telopeptide of type I collagen, *HA* hyaluronic acid

Table 6 Factors associated with the pain VAS score in patients with knee OA [32]

Pain VAS score	β (95 % CI) (crude)	*p*	β (95 % CI) (adjusted)	*p*
Total				
IL-6	5.87 (1.57 to 10.18)	<0.01	5.92 (1.48 to 10.35)	<0.01[#]
AAA	−1.03 (−1.95 to −0.115)	0.03	−1.04 (−2.03 to −0.06)	0.04[#]
Early				
IL-6	10.65 (4.16 to 17.15)	<0.01	10.77 (4.14 to 17.40)	<0.01[#]
AAA	−0.004 (−2.683 to 2.68)	0.99	−0.03 (−2.74 to 2.69)	0.99
Advanced				
IL-6	0.895 (−4.87 to 6.66)	0.76	0.64 (−5.44 to 6.72)	0.86
AAA	−1.36 (−2.45 to −0.27)	0.02	−1.29 (−2.51 to −0.08)	0.04[#]

A multiple linear regression analysis. Adjusted: adjusted for age and the BMI

[#] *p* values <0.05 were considered to be statistically significant. Early: early-stage knee OA [Kellgren–Lawrence (K/L) grade 2], advanced: advanced-stage knee OA (K/L grade 3 or 4)

IL-6 interleukin 6, *AAA* anatomic axis angle, *95 % CI* 95 % confidence interval

patients with early-stage knee OA, while the AAA was solely associated with the pain VAS score in the patients with advanced-stage knee OA (Table 6). Although it remains unclear precisely how joint loading induces pain in patients with knee OA, and because such joint loading was not measured in the present study, the results of this study suggest that the pain in advanced-stage knee OA is associated with mechanical loading across the knee joint, which

is associated with a deterioration in lower limb alignment [52]. A higher level of serum IL-6 is thus considered to be associated with pain in early-stage knee OA, while the varus alignment of the joint was found to be associated with pain in advanced-stage knee OA patients. Therefore, it has clearly been suggested that pain components in knee OA vary depending on the disease progression (Table 6).

While synovitis is suggested to be associated with pain in early-stage knee OA (Fig. 13), we also showed that synovitis is associated with symptoms in advanced- to end-stage knee OA [53]. We examined whether synovitis in knee OA assessed by histological examinations and enhanced MRI correlated with the disability of patients with end-stage knee OA who underwent joint replacement surgery. The symptoms of the patients, which were evaluated using the patient-oriented outcome score (total JKOM score), showed a significant positive correlation with both the mean total synovitis score evaluated by the histological analysis and that evaluated by Gd-MRI (Fig. 14). The results of this study suggest that synovitis may play a crucial role in the current functional impairment and disability in patients with end-stage knee OA who underwent joint replacement surgery.

As synovitis is associated with pain and symptom of patients with early- to end-stage knee OA, it is easy to speculate that inflammatory mediators, such as cyclooxygenase (COX)-2 and IL-1β, and proteinases, such as metalloproteinases (MMPs), are associated with patients with early- to end-stage knee OA. However, it has been recently revealed that the expression levels of these inflammatory mediators are not increased according to the severity of knee OA [54]. An immunohistochemical analysis of the synovial tissue of patients with medial knee OA who underwent either joint replacement ($n = 19$) or arthroscopic surgery ($n = 4$) revealed that the expression levels of MMP-1 and IL-1β in both the lining and sublining layers of the medial perimeniscal synovial tissue showed significant correlations with the radiographic severity (Fig. 15) [54]. For instance, the joint space width (JSW) of the medial tibiofemoral joint was positively correlated with the expression levels, while the femorotibial angle (FTA) was negatively associated with the expression levels in patients with medial knee OA. On the other hand, the expression levels of TGF-β in the sibling layer of the medial perimeniscal synovial tissue in the patients showed a significant negative correlation with the JSW and a significant positive correlation with the FTA. As the JSW and FTA reflect the historical view of OA, we next examined whether the expression levels of the inflammatory mediators and growth factor also correlated with the current levels of physical disability of the patients as evaluated by the JKOM score. The expression levels of MMP-1, COX-2, and IL-1β in both the lining and sublining layers of the medial perimeniscal synovial tissue showed a significant negative correlation with the JKOM score of the patients. The expression levels of TGF-β in the sublining layer of the medial perimeniscal synovial tissue in the patients

Table 7 Correlation between the total histological synovitis score (HSS) and the whole-organ magnetic resonance imaging score (WORMS) in patients with end-stage knee OA receiving TKA [55]

MRI-detected OA pathologies	HSS	
	r	*p*
Cartilage morphology	−0.006	0.97
BML	0.325	0.04*
SBC	0.350	0.03*
SBA	0.482	<0.01*
Osteophyte	−0.100	0.54
Menisci		
Medial	0.155	0.34
Lateral	0.266	0.10
Synovitis	0.358	0.02*

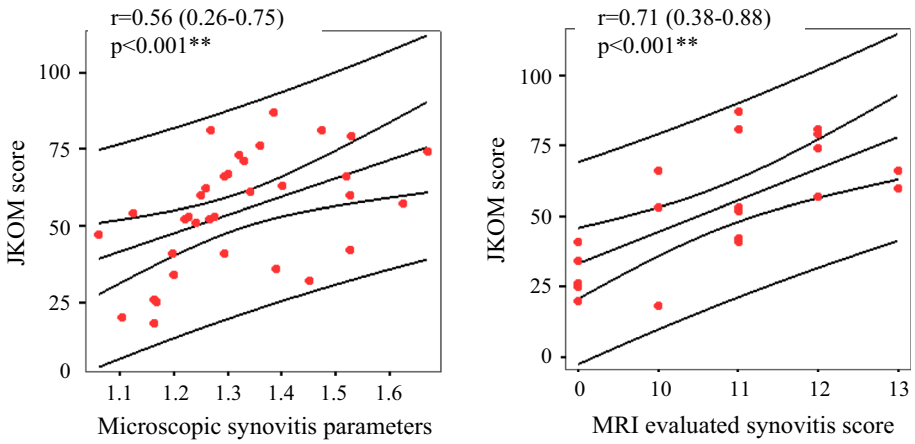


Fig. 14 A simple regression analysis comparing the histological and enhanced MRI-evaluated synovitis score with the JKOM score in patients with end-stage knee OA [53]. *MRI* magnetic resonance imaging, *ROI* region of interest, *JKOM* Japanese Knee Osteoarthritis Measure. The data are presented as *r* (95 % CI for *r*) and *p* values. *$p < 0.05$; **$p < 0.01$

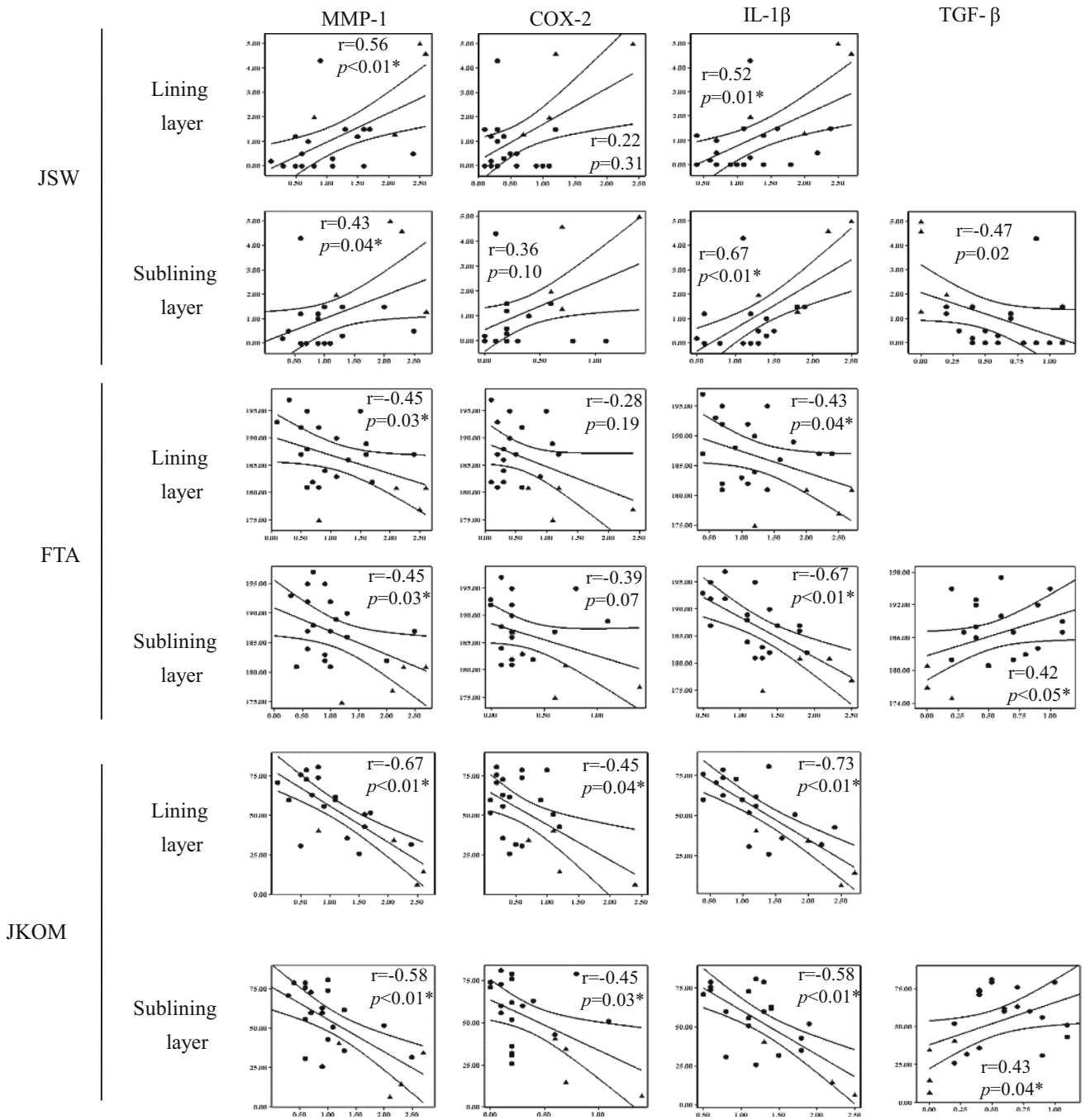


Fig. 15 Correlation between the expression levels of inflammatory mediators and growth factor in the medial perimeniscal synovial tissue and the radiographic parameters and patient-oriented outcome measures for knee OA in patients [54]. *Circles* and *triangles* indicate the data from patients with K/L grade 4 and those with K/L grade 2 or 3, respectively ($n = 23$). *JSW* joint space width, *FTA* femorotibial angle, *JKOM* Japanese Knee Osteoarthritis Measure

showed a significant positive correlation with the JKOM score (Fig. 15) [54]. This study suggested that the expression levels of MMP-1, COX-2, and IL-1β in the medial perimeniscal synovium were decreased, while the levels of TGF-β were increased, according to the severity of the disease in patients with medial knee OA. As the expression of MMP-1, COX2, and IL-1β in synovial tissues is thought to be induced by degenerated articular cartilage, the expression of these inflammatory mediators might be enhanced in the synovial tissues of patients with either K/L grade 2 or 3 knee OA in comparison with those with K/L grade 4 knee OA.

According to our results, we further examined the OA-related structural changes associated with histological synovitis in end-stage knee OA patients [55]. Among the seven OA-related structural changes evaluated using the whole-organ MRI scoring (WORMS) method, such as cartilage morphology, subchondral bone marrow lesion (BML), subchondral bone cyst (SBC), subchondral bone attrition (SBA), osteophytes, meniscal lesion, and synovitis, the BML, SBC, SBA, and synovitis were significantly associated with the histological synovitis score (HSS) ($r = 0.33$, 0.35, 0.48, and 0.36, respectively), while other morphological changes were not (Table 7, Fig. 16) [55]. Although synovial COX-2, IL-1β or IL-6 expression levels were not associated with the HSS, the synovial TGF-β

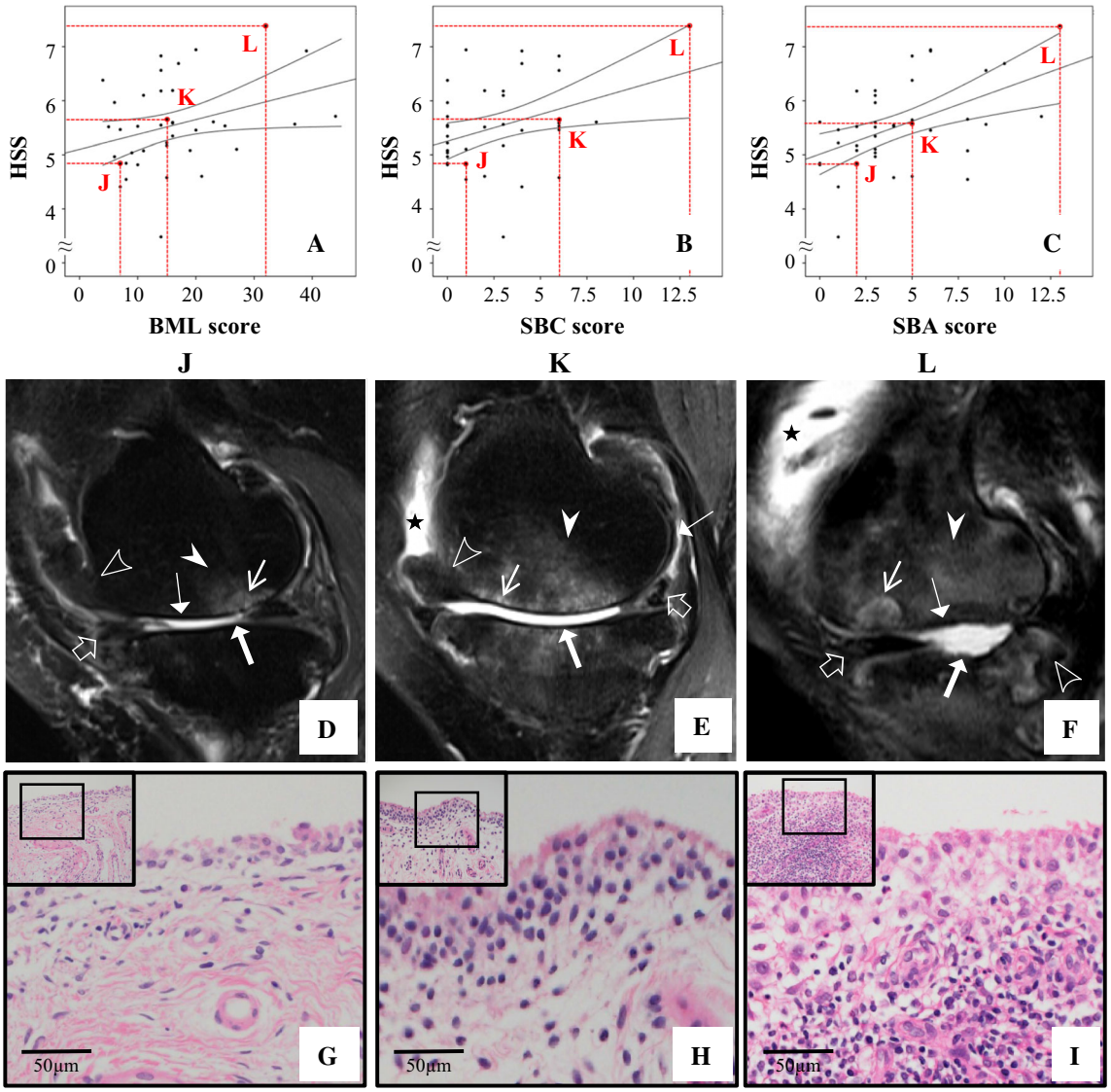


Fig. 16 Association between the HSS and the BML score (**a**), SBC score (**b**), and SBA score (**c**) in patients with end-stage knee OA receiving TKA [55]. The sagittal T2-weighted MR image (**d**–**f**) and the histological sections (**g**–**i**) of three representative cases (*J*, *K* and *L*, respectively) show the presence of BML, SBC, and SBA. *J* Cartilage loss in MFc (*arrow with head*), MTc, MFa, MTa, MFp, and MTp, BML in MTa and MFc (*arrowhead*), SBC in MFc (*thin arrow*), SBA in MTc (*thick arrow*), osteophyte in MFa (*open arrow head*), MFp, MTa, and MTp, meniscus in the medial meniscus (*open arrow*). *K* Cartilage loss in MFa, MFc, MTa, MTc, MFp (*arrow with head*) and MTp, BML in MFa, MFc (*arrowhead*), MTa, MTc, MTp, SBC in MFa and MFc (*thin arrow*), SBA: in MTc (*thick arrow*), osteophyte in MFa (*open arrow head*), MFp, MTa and MTp, meniscus in the medial meniscus (*open arrow*), and effusion (*star*). **l** Cartilage loss in MFc (*arrow with head*), MFp, MTc, MFa and MTa, BML in MFa, MFc (*arrowhead*), MFp, MTa, MTc and MTp, SBC: grade 3 in MFc (*thin arrow*), grade 2 in MFp, SBA: grade 3 in MFc and MTc (*thick arrow*), osteophyte in MTa (*open arrow head*), MTp and MFa, meniscus in the medial meniscus (*open arrow*), effusion (*star*). *BML* bone marrow lesion, *SBC* subchondral bone cyst, *SBA* subchondral bone attrition, *HSS* histological synovitis score, *TKA* total knee arthroplasty, *MF* medial femoral plateau, *MT* medial tibial plateau, *a* anterior, *c* central, *p* posterior

expression levels were associated with the HSS (data not shown) [55]. These data suggest that synovitis is present not only in early-stage, but also end-stage knee OA and is possibly induced by articular cartilage destruction and, at least in part, subchondral pathologies.

While synovitis and osteophyte formation are considered to be secondary phenomena in OA, it has gradually been revealed that synovitis may play a more important role in the initiation, progression, pain, and disability of the disease. Chronic inflammation occurred by synovitis with increased levels of inflammatory mediators and growth factors and may be causally involved in various chronic conditions (such as cardiovascular and diabetes) or cancer, as shown in the previous study [37], although further study is needed. In addition, although OA is primarily characterized by cartilage degradation, we should pay more attention to pain as a prominent symptom for the treatment for knee OA and should therefore treat OA as a whole-organ disease.

Sedentary Behavior in Knee OA A recent epidemiological study in Japan revealed that the accumulation of metabolic components is significantly related to both the occurrence and progression of knee OA [56]. Although mechanistic insight into the association between metabolic components and knee OA remained unclear, the occurrence and progression of knee OA were associated with higher systolic blood pressure, lower HDL cholesterol levels, and higher serum HbA1c levels, as well as body mass index (BMI) (Fig. 17).

It is widely recognized that physical inactivity increases the risk of many adverse health conditions, including major non-communicable diseases, such as CVDs, type 2 diabetes, and shortens the life expectancy [57]. Patients with knee OA are also known to be physically inactive. In a study of participants enrolled in the Osteoarthritis Initiative (OAI), almost half (48.9 %) of participants with knee OA were physically inactive. Being overweight [odds ratio (OR) 1.8, 95 % CI 1.2–2.5] or obese (OR 3.9, 95 % CI 2.6–5.7) and having inadequate dietary fiber intake (OR 1.6, 95 % CI 1.2–2.2), severe knee dysfunction (OR 1.9, 95 % CI 1.3–2.8), or severe pain (OR 1.7, 95 % CI 1.1–2.5) were significantly related to inactivity. Modifiable factors with significant average attributable fractions (AFs) were being overweight or obese (AF 23.8 %, 95 % CI 10.5–38.6 %) and inadequate dietary fiber (AF 12.1 %, 95 % CI 0.1–24.5 %) (Fig. 18).

In modern society, prolonged sitting has been engineered into our lives across many setting, including transportation, the workplace, and the home. There is new evidence that too much sitting, referred to as "sedentary behavior" that involves very low energy expenditure, is adversely associated with health outcomes, including CVDs and type 2 diabetes, and premature mortality [58]. In the study, which investigated the relationship between sedentary behavior and physical function in adults with knee OA, knee OA patients spent two-thirds of their daily time in sedentary behavior [59]. The average gait speed among the most sedentary quartile was 3.88 feet/second, which was significantly slower than the speed of the less

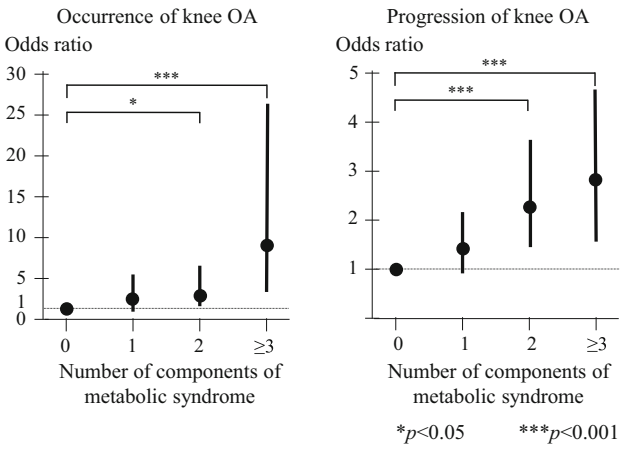


Fig. 17 Odds ratios (ORs) for the occurrence and progression of knee OA during the 3-year follow-up period versus number of risk factors for metabolic syndrome (MS) [56]

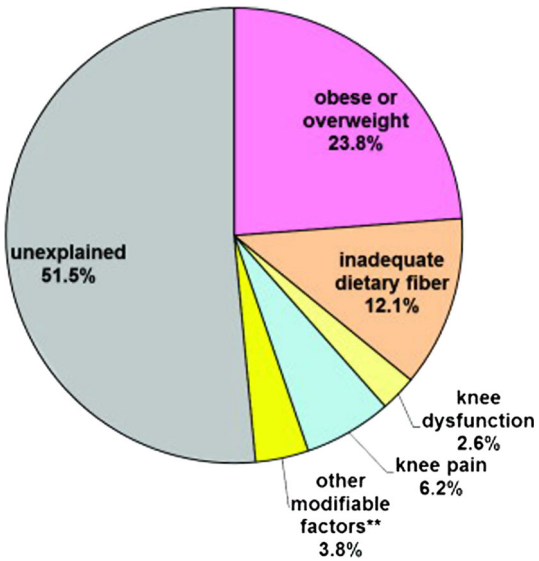


Fig. 18 Adjusted average attributable fraction of inactivity for modifiable factors adjusted for descriptive factors (age, sex, race, living status, education, employment, chronic knee pain, total knee replacement, comorbidities) and all modifiable factors (obese/overweight, inadequate dietary fiber, knee dysfunction, knee pain, high-fat diet, smoking, high depressive symptoms, or being troubled by knee confidence). **, aggregated contribution or remaining modifiable risk factors (high-fat diet, smoking, high depressive symptoms, or being troubled by knee confidence [57]

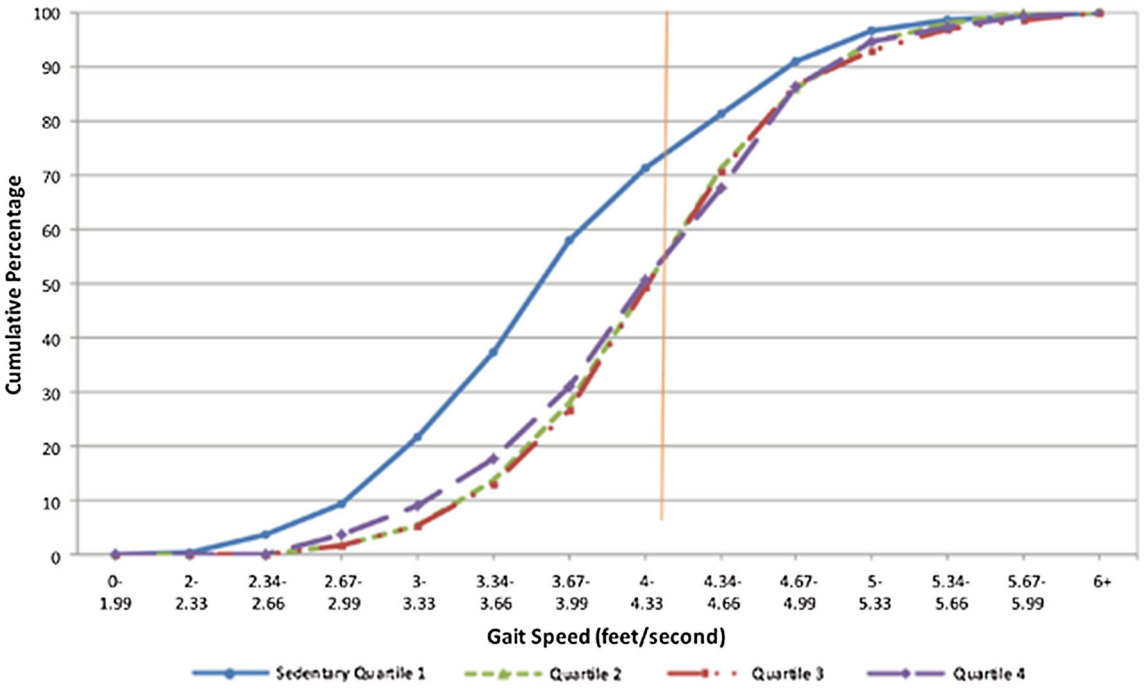


Fig. 19 Cumulative percentage of 1168 participants in each sedentary behavior quartile [quartile cutoff values (%): quartile $1 \geq 72.7$ %; 67.13 % $\leq$ quartile $2 < 72.7$ %; 61.1 % $\leq$ quartile $3 < 67.13$ %; and quartile $4 < 61.1$ %) with the indicated gait speed (feet/second) at the 48-month clinic visit. Participants in sedentary quartile 1 were the most sedentary, and those in quartile 4 were the least sedentary [59]

sedentary groups (4.23, 4.33, and 4.33 feet/second, respectively) (Fig. 19). Similar results were observed in terms of the average chair stand rate. In addition, it was also showed that sedentary behavior in patients with knee OA is associated with blood pressure (BP) [60]. In the OAI cohort, the mean BP was 121.4 (SD 15.6)/74.7 (9.5) mmHg and 33 % of the subjects had hypertension. The most sedentary quartile had 4.26 (95 % CI 0.69–7.82) mmHg higher systolic BP (SBP) than the least sedentary quartiles, after adjusting for several related factors ($p = 0.002$) (Fig. 20a). The probability of having hypertension significantly increased in higher sedentary quartiles (p for trend $= 0.046$) (Fig. 20b). These data indicate that patients with knee OA tended to be physically inactive. Moreover, similar to other non-communicable diseases, the sedentary behavior in patients with knee OA is associated with elevated BP. Therefore, the reducing daily sedentary time in patients with knee OA is related to a better physical function and may be important to improve BP and reduce cardiovascular risks. Under the concept of "locomotive syndrome," we should be more aware of sedentary behavior, as well as physical inactivity, in patients with knee OA, in addition to pain and impairment of mobility.

Trauma in Knee OA It has long been known that knee injury is one of the risk factors for knee OA [61]. In contrast to physical inactivity and sedentariness, the relationship between physical activity and the development of knee OA is an important clinical and public health issue. By the multicenter osteoarthritis (MOST) and OAI studies, the effect of physical activity on knee OA development in individuals without knee injury was investigated [62]. In these studies, 2073 subjects with a mean age of 61 years were enrolled and followed up for 30 months (in MOST) and 48 months (in OAI). The cumulative incidence of symptomatic knee OA was 1.12 % in the active group versus 1.82 % in the others [OR among active group 0.6 (95 % CI 0.3–1.3)]. Medial joint space narrowing occurred in 3.41 % of knees in the active group compared with 4.04 % in the others [OR among active group 0.9 (95 % CI 0.5–1.5)]. These results suggest that physical activity in the highest quartile did not affect the risk of developing knee OA [62].

While knee OA is typically a slowly progressing disorder, it has recently been appreciated that 5–17 % of knee OA have a rapid progression of structural damage. The OAI study investigated whether a recent knee injury was associated with accelerated knee OA progression [63]. A knee injury during the total observation period was associated with accelerated knee OA progression (OR 3.1). Furthermore, a more recent knee injury, which occurred within a year, was associated with accelerated (OR 8.5) and common knee OA progression (OR 3.1).

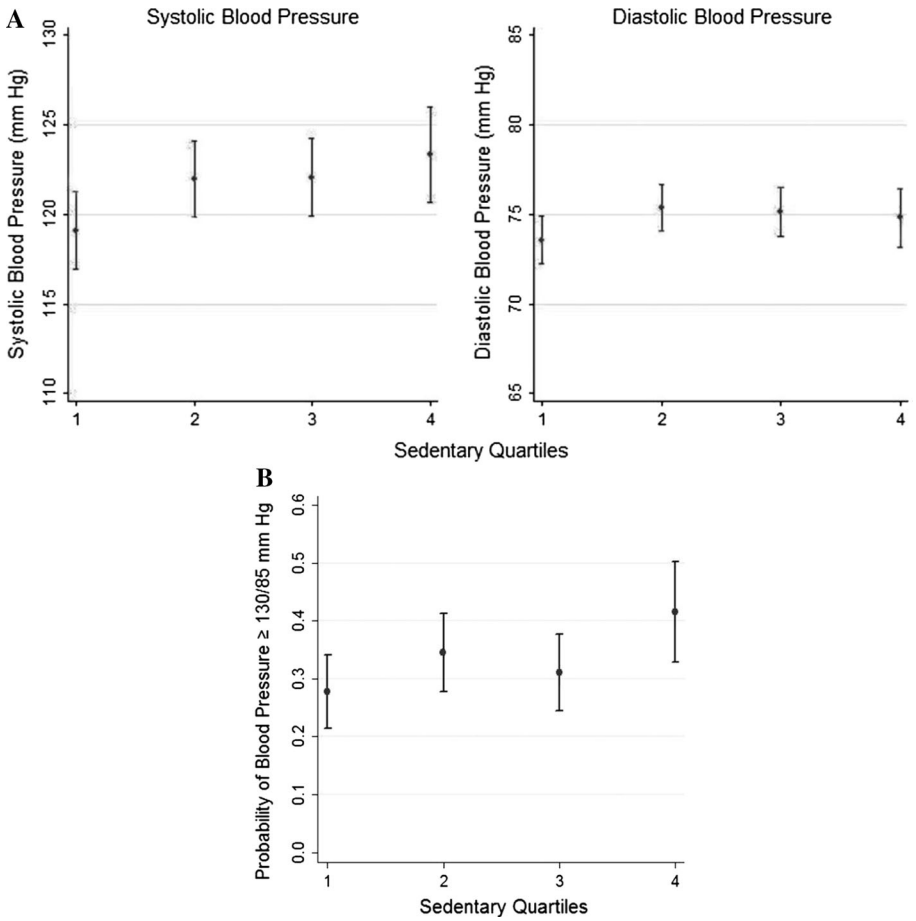


Fig. 20 Adjusted mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) (mmHg) (**a**) and adjusted probability of blood pressure (BP) ≥130/85 mmHg (**b**) by sedentary behavior quartiles in a cross-sectional analysis of the osteoarthritis initiative (OAI) 48-month visit participants [60]. The data were adjusted for moderate-to-vigorous (MV) physical activity, age, sex, race/ethnicity, abdominal circumference, Charlson comorbidities, alcohol drinking, past or current smoker, knee osteoarthritis, WOMAC score, and global pain

In another study, in which the association between self-reported OA and incident falls and fractures was studied in postmenopausal women, 20,409 of 51,386 women (40 %) with self-reported OA were followed up for a median of 2.9 years, and the adjusted RR for falls was 1.24 (95 % CI 1.22–1.26, $p < 0.0001$) [64]. Postmenopausal women with self-reported OA have an experience 25 % more falls than those without OA.

While individuals with knee OA have shown knee extensor muscle weakness compared with control subjects, individual studies have reported knee extensor muscle weakness to be a risk factor for knee OA [65]. As muscle strength is a potential modifiable risk factor for the incidence for knee OA, it is very important to determine whether knee extensor muscle weakness is a risk factor for knee OA. A recent systematic review identified 12 studies that were eligible for inclusion in the meta-analysis, and finally five cohort studies, with a follow-up time between 2.5 and 14 years and a total number of 5707 participants were included in this study. The meta-analysis showed that knee extensor muscle weakness was associated with an increased risk of developing knee OA (Fig. 21) [66]. Although the role of knee extensor muscle weakness as a risk factor for the development of knee OA is not fully understood, the knee extensors work as shock absorbers and stabilizers, and hence protect the joint surfaces during loading and movement. In addition, excessive mechanical stress on the articular cartilage due to muscle weakness has been suggested to induce a degenerative process of articular cartilage. Maintaining knee extensor muscle strength could be important as one of the controllable risk factors for knee OA.

Too much moving, which could be associated with trauma, and less moving, especially sedentariness, could become one of the risk factors for the occurrence and progression of knee OA. How we manage our mobility will be an important issue to determine future management strategies for knee OA.

Very Early-Stage Knee OA: Knee OA as a "Disease"

Clinical research for knee and hip OA has dramatically developed. Epidemiological, serum and urine biomarker, imaging biomarker, and pain research using a patient-oriented outcomes strategy have contributed to this

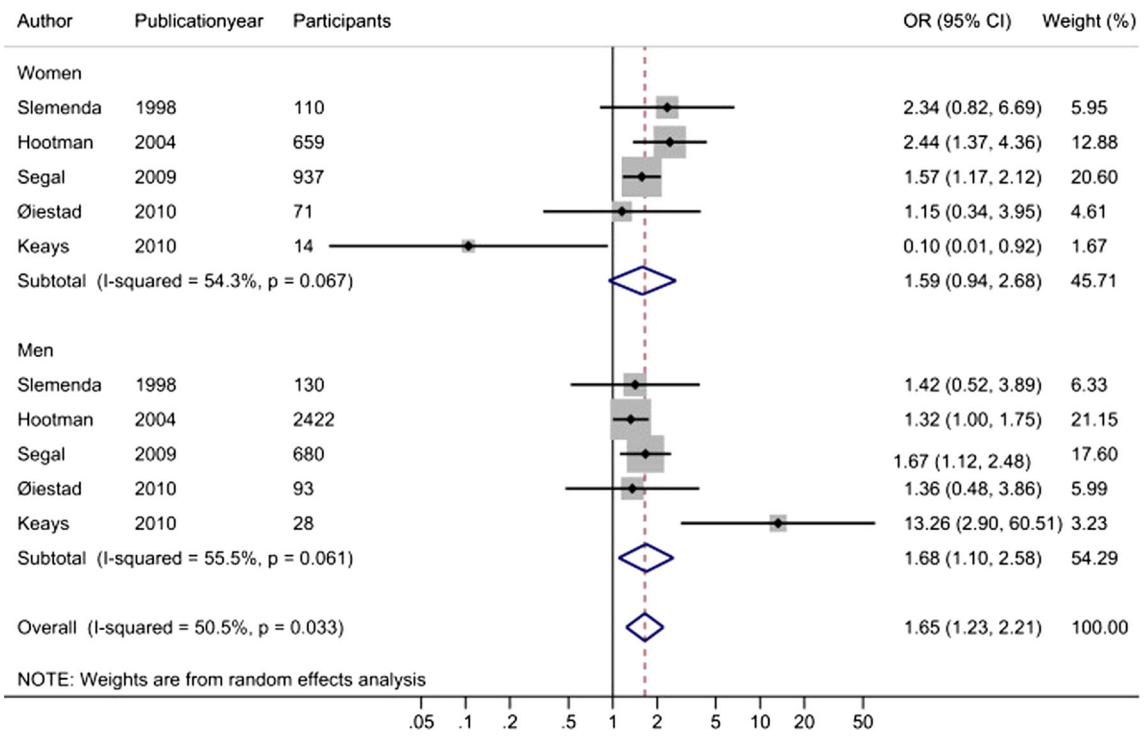


Fig. 21 Results of meta-analyses on knee extensor muscle weakness and the risk of knee OA [66]

development. Investigators in this field are currently interested in "very" early-stage knee OA. Similar to osteoporosis, OA may be a condition by which a prolonged period of musculoskeletal tissue abnormalities at a molecular, but clinically silent, level can precede anatomic organ system disease and illness by years or even decades [12] (Fig. 22). As shown in Fig. 22, a clinical threshold would be anticipated that would result in the transition from disease to illness. The hallmark of illness in OA is clearly joint pain. The articular cartilage is an organ that repeats metabolism by synthesis and degeneration, similar to the bone. As shown in our previous study [38], when the participants were divided into 4 groups according to the presence (K/L 2) or absence (K/L 1) of both radiographic knee OA and knee pain, sC2C (a cartilage degradation marker) in K/L grade 1 patients with knee pain was

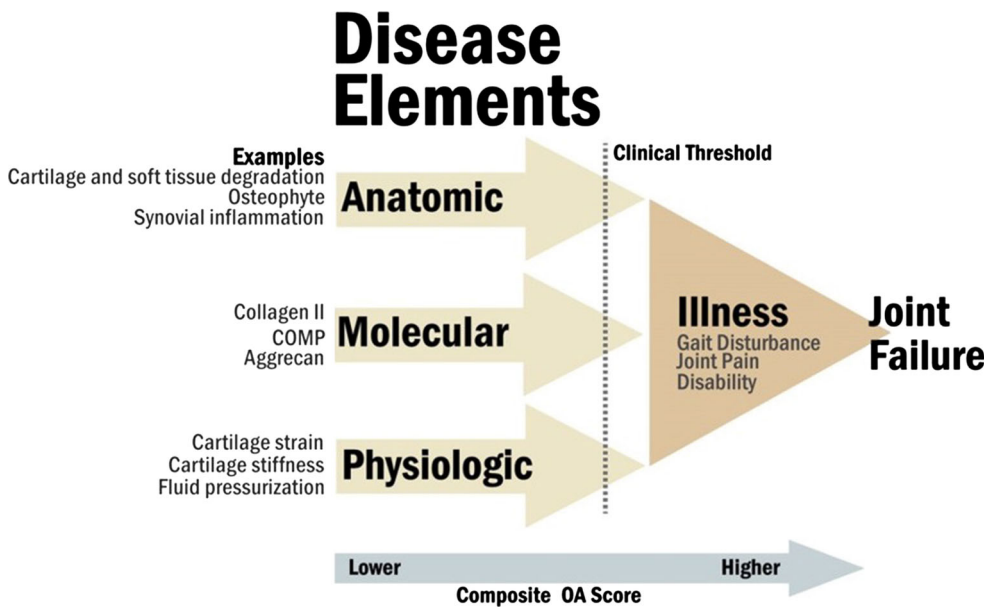


Fig. 22 Taxonomy of OA [12]. A clinical threshold would be anticipated that would result in the transition from disease to illness. The hallmark of illness in OA is joint pain

significantly increased in comparison with the same grade group without knee pain. uCTX-II, another cartilage degradation marker, in K/L grade 2 patients with knee pain was significantly increased in comparison with those in K/L grade 2 without knee pain. In contrast, while sCPII, a cartilage synthesis marker, in K/L grade 1 patients with knee pain was also significantly increased in comparison with those with no pain in this grade, such pain-related differences were not seen in K/L grade 2 patients (Fig. 23). Cartilage degradation is considered to induce synovitis, which can be monitored by serum levels of hyaluronan (HA). The serum levels of HA increased according to the severity of OA (Fig. 24) [48].

The validation of improved imaging biomarkers, in addition to chemical biomarkers, may make it possible to circumvent some of the problems in the OA field. MRI is more sensitive than radiography to detect bone and soft tissue changes, which are features of OA. In early-stage knee OA, OA changes begin at the molecular level of the articular cartilage, such as a loss of proteoglycan, an increased water content, and the disorganization of the collagen network, likely before any morphologic changes occur in the articular cartilage.

The morphologic changes, such as cartilage lesions, bone attritions, cysts, bone marrow abnormalities (BMAs), osteophytes, meniscal pathology, synovitis, and ligament changes, can be visualized and semiquantified by MRI. The T2 mapping sequence on MRI is a technique that can sensitively detect early biochemical changes in the water content and any disorganization of the collagen network in the articular cartilage. In addition, we can also evaluate the

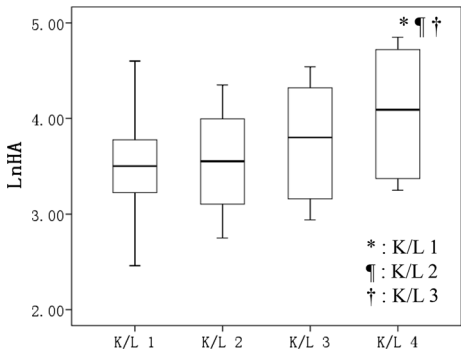


Fig. 24 Reference intervals of serum hyaluronic acid corresponding to the radiographic severity of knee OA in women [48]. The ln-sHA levels of subjects with K/L grade 4 were significantly increased in comparison with those with K/L grades 1, 2, and 3. On the other hand, no significant difference in the ln-sHA levels was observed between subjects with K/L grade 3 and those with K/L grades 1 and 2. There were no significant differences in the ln-sHA levels between subjects with K/L grades 1 and 2. *sHA* serum levels of hyaluronic acid, *ln-sHA* logarithmically transformed sHA. $n = 372$

OA-induced structural joint changes semiquantitatively by, for instance, using the WORMS method. These techniques may enable us to further understand very early-stage knee OA.

In a previous study, which determined age-dependent differences in cartilage T2 values in healthy asymptomatic women (Fig. 25a), there was little association between age and the T2 value of the articular cartilage of the patello-femoral joint in subjects aged 45 years and younger (Fig. 25b) [67]. However, there was an age-dependent elevation and greater variability in the T2 values of the

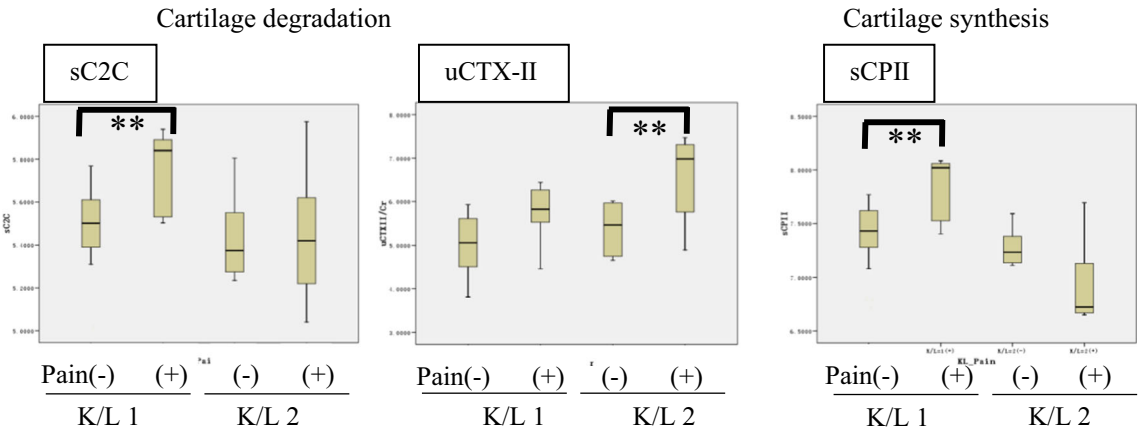


Fig. 23 Biomarker levels of subjects with early-stage knee OA according to the presence or absence of knee pain [47]. sC2C and sCPII in K/L grade 1 patients with knee pain was significantly increased in comparison with the same grade group without knee pain. No such differences were seen in K/L grade 2 patients. In contrast, uCTX-II with K/L grade 2 patients with knee pain was significantly increased in comparison with those in K/L grade 2 without knee pain. Such pain-related differences were not seen in K/L grade 1 patients. All analyses were adjusted for age, gender, and the body mass index. Urinary biomarkers were corrected using the creatinine level. *p values ≤ 0.05 were considered to be statistically significant. *K/L* Kellgren–Lawrence grade, *SE* standard error of the mean, *95 % CI* 95 % confidence interval, *s* serum, *u* urine, *C2C* cartilage collagen type II cleavage, *CPII* cartilage type II collagen carboxy propeptide, *CTX-II* type II collagen C-telopeptide

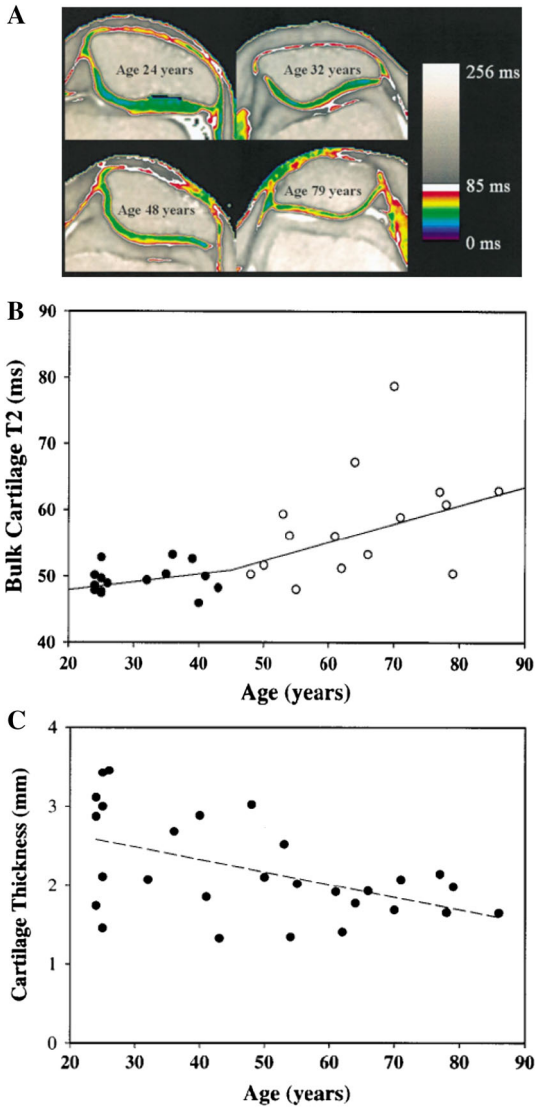


Fig. 25 Age-dependent cartilage MRI T2 relaxation times in asymptomatic women [67]. **a** Representative quantitative patellar cartilage T2 maps for four age cohorts of female study subjects. All groups demonstrated similar spatial variation in cartilage T2 times, with longer values (*red* and *yellow* areas) occurring near the articular surface. The T2 map of a 79-year-old subject demonstrates relatively thin cartilage with elevated T2 times compared with the T2 maps obtained for the younger subjects. **b** Bulk cartilage T2 values as a function of age in subjects 45 years and younger (*filled circle*) and those older than 45 years (*open circle*). The data of the two groups, which were analyzed using a single-change-point linear regression model, indicate a significant slope ($p < 0.05$) for subjects older than 45 years and a nonsignificant slope ($p > 0.05$) for subjects 45 years and younger. **c** Cartilage thickness as a function of age. There is an inverse correlation between the patellar cartilage thickness and increasing age ($r = -0.51$, $p = 0.006$) (Color figure online)

articular cartilage of the patellofemoral joint in subjects older than 45 years. There was a wide variation in the cartilage thickness in younger individuals, with the largest range observed in those aged 18–30 years. Additionally, there was a statistically significant inverse variation between cartilage thickness and age ($r = -0.51$, $p = 0.006$) (Fig. 25c).

It was uncertain whether the degeneration and destruction of the articular cartilage occurred simultaneously in the femoral, tibial, and patellar articular cartilage, or if some spatial and temporal differences exist in the degeneration and destruction of the articular cartilage. We showed that the degenerative changes, detected by T2 mapping on MRI, and the morphological changes, detected by a WORMS analysis on MRI, of the femoral articular cartilage showed a greater degree of deterioration than those of both the tibial and patellar articular cartilage in patients with early-stage knee OA (Fig. 26) [68].

However, when we focused on SBA (Fig. 27), the prevalence of SBA in non-advanced knee OA was substantial (Table 8) [69] and more frequently observed in the tibial plateau than in the femoral condyle (Table 8).

According to these imaging studies in knee OA, especially "very" early-stage-knee OA, it has been revealed that subchondral changes, in addition to the articular cartilage, are initiated much earlier than previously thought, shedding light on both the future OA research field and the development of novel treatment strategies.

Furthermore, recent studies have shown that meniscal extrusion may play a critical role in the progression of knee OA [70–76]. In knee OA subjects, increased medial meniscal extrusion on MRI correlated with the disease severity (Fig. 28) [70]. It was also showed through ultrasonography that the medial meniscus was significantly displaced radially by weight-bearing not only in knee OA patients but also healthy controls (Fig. 29). Medial meniscal extrusion was shown to be related to the structural progression of knee OA through an association with subsequent medial cartilage loss [77]. Although medial meniscal extrusion has been gradually suggested to be a critical role in the progression of knee OA, its precise mechanism remains unclear; thus, further studies are required [78].

A recent meta-analysis has suggested that knee extensor muscle weakness is a risk factor for the development of knee OA [66]. An accumulation of metabolic syndrome components is significantly related to both the occurrence and progression of knee OA, suggesting that the prevention of metabolic syndrome may be useful in reducing future knee OA risk (Fig. 17) [56]. In addition, therapies targeting metabolic-triggered inflammation and its components are also suggested to have potential for the treatment for knee OA [79]. Lifestyle factors, such as the avoidance of sedentary activities, may also be involved in the occurrence and/or progression of knee OA; however, further studies are needed.

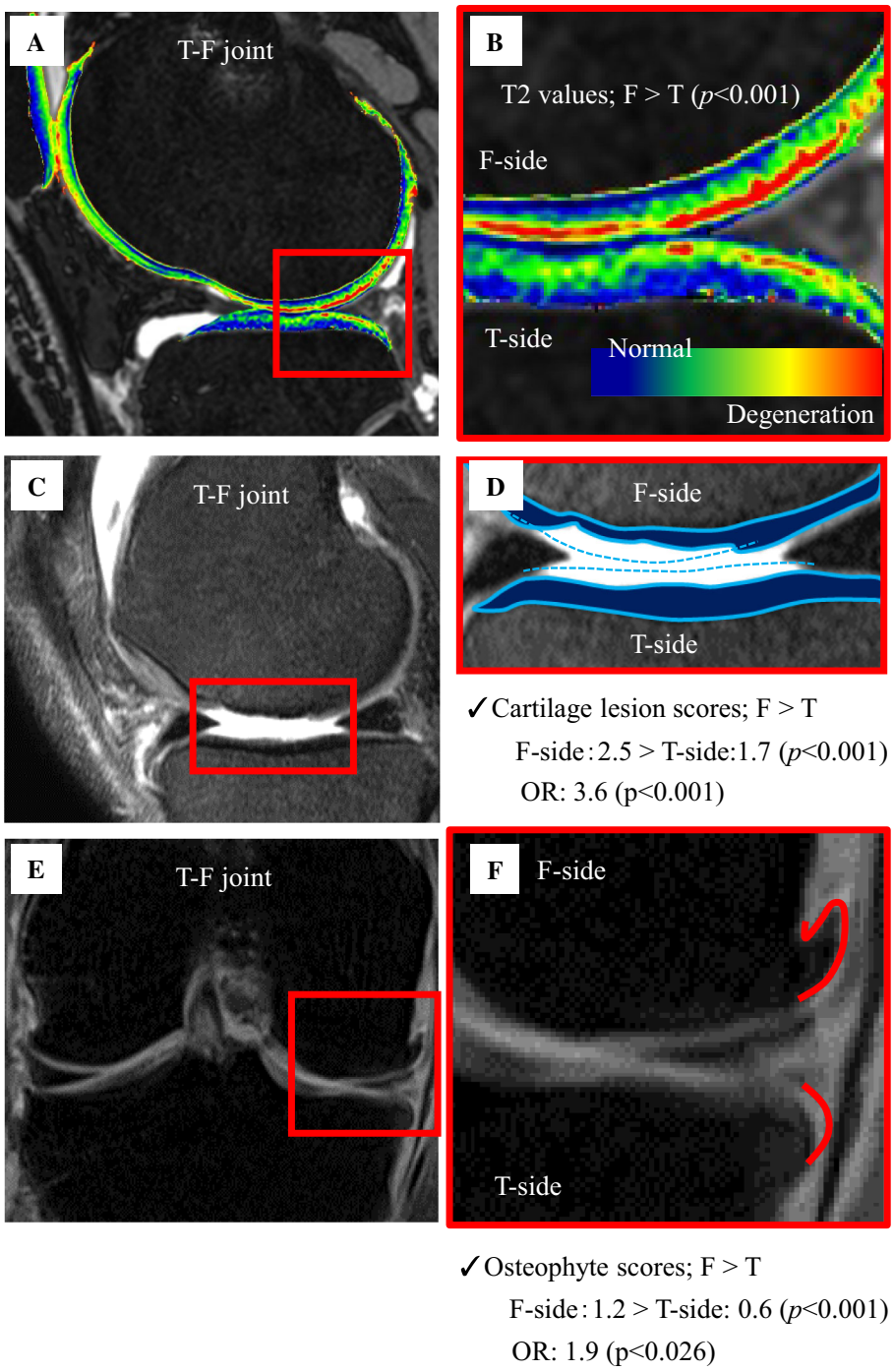


Fig. 26 Early-stage OA-induced degenerative and morphological changes between the femoral side and the confronting tibial or patellar sides within the knee join were not the same [68]. **a** A T2 mapping image of the sagittal section of the knee joint. **b** Enlargement of the articular cartilage of **a**. The T2 values in the femoral articular cartilage (F) were significantly higher in comparison with those in the tibial articular cartilage (T) in patients with early-stage knee OA. **c** A 3T MRI image of the sagittal section of the knee joint. **d** Enlargement of the articular cartilage of **c**. Comparison of the cartilage lesions of the articular cartilage in early-stage knee OA; femoral (F) side > tibial (T) side ($p < 0.001$), odds ratio (OR): 3.6 (95 % CI 1.8–6.9, $p < 0.0001$). **e** A 3T MRI image of the coronal section of the knee joint. **f** Enlargement of the articular cartilage of **e**. Comparison of the osteophyte score in early-stage knee OA: femoral side > tibial side ($p < 0.001$), OR: 1.9 (95 % CI 1.0–3.5, $p = 0.026$)

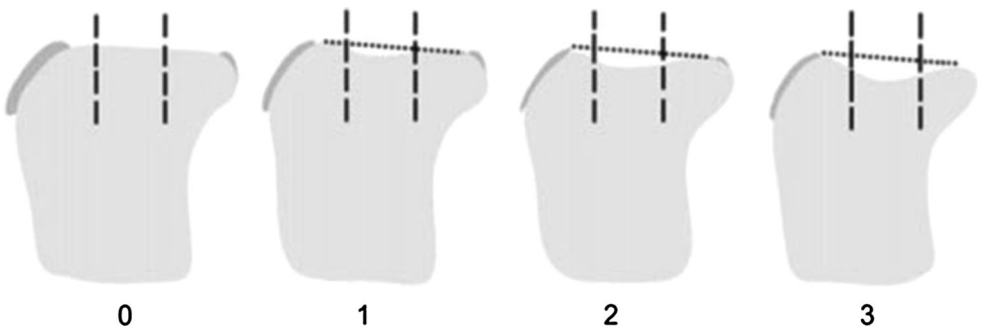


Fig. 27 A diagram showing the subchondral bone attrition (SBA) score by WORMS. SBA is scored according to the basis of the degree or depression of the articular surface compared with the normal articular surface [69]

Table 8 Prevalence of subchondral bone attrition (SBA) in radiographs (score ≥1) and MRI (score ≥1) in 964 knees of 964 subjects for the tibiofemoral joint and different compartments of the knee according to the K/L score [69]

SBA	K/L 0 ($n = 747$)		K/L 1 ($n = 44$)		K/L 2 ($n = 88$)		K/L 3 ($n = 56$)		K/L 4 ($n = 29$)	
	Radiograph	MRI	Radiograph	MRI	Radiograph	MRI	Radiograph	MRI	Radiograph	MRI
Tibiofemoral joint (%)	0.0	14.3	0.0	18.2	8.0	47.7	33.9	75.0	100	100
Medial femoral condyle (%)	0.0	3.2	0.0	9.1	0	21.6	3.6	46.4	79.3	79.3
Medial tibial condyle (%)	0.0	11.4	0.0	15.9	8.0	35.2	35.2	55.4	82.8	79.3

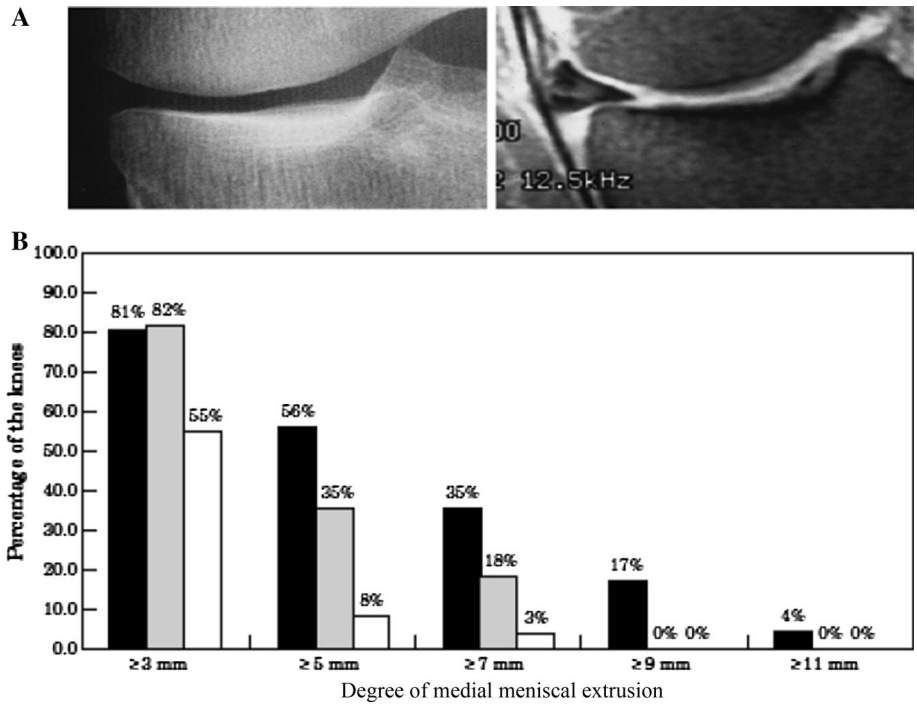


Fig. 28 Increasing medial meniscal extrusion correlates with the severity of knee OA [70]. **a** (*Left*) An AP view of the knee demonstrates grade I medial narrowing and (*right*) the corresponding proton density-weighted fat saturation MRI demonstrates 4 mm of medial meniscal extrusion beyond a vertical line through the medial border of the tibia. **b** Prevalence of medial meniscal extrusion in cases and controls with and without joint space narrowing (JSN). *Black bar*, case; *gray bar*, control with JSN; *white bar*, control without JSN

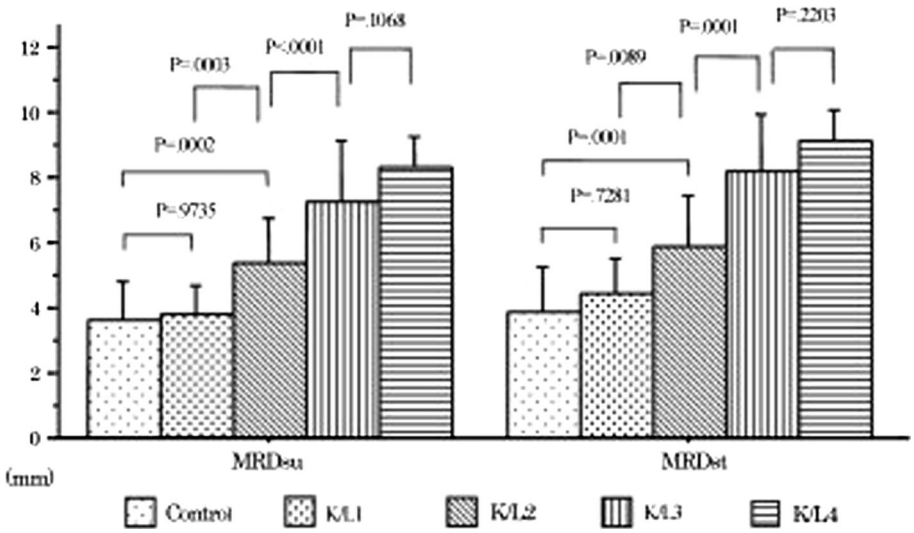


Fig. 29 Changes in medial radial displacement (MRD) of the medial meniscus in 20 control subjects and 78 patients with Kellgren–Lawrence (K/L) grades 1–4 knee OA by ultrasound with the subject in the supine (MRDsu) position and the standing (MRDst) position [73]. No significant difference between the control group and the K/L grade 1 group was noted, whereas there was a significant difference between the control group and K/L grade 2 (only the *p values for control knees vs. K/L grade* 2 OA knees are shown). Values are presented as the mean and SD

Future studies in the OA field must continue to focus on the degeneration of the articular cartilage. However, in addition to this concept, further studies must consider OA as both a "disease" and "illness" [12].

Future Perspective of Knee and Hip OA as One of Three Major Motor Diseases Responsible for "Locomotive Syndrome"

Knee and hip OA is anticipated to be more influential in our society in the future. Currently, patients who show radiographic end-stage knee OA, but do not have pain are not indicated to undergo surgical treatment, such as joint replacement surgery or HTO. Although all surgical treatments have a risk of side effects during and after operation, the symptoms, especially mobility impairment, in addition to pain, should also be considered for setting the indications of surgical operation in knee OA. We should also continue to focus on how to prevent the disease progression. In addition, as OA, at least in part, has been suggested to be a lifestyle-related disease, we should also take measures to manage preclinical middle-aged asymptomatic knee OA subjects. Moreover, knee and hip OA can also be considered to be a disease that may affect other organs, such as the heart. We must disseminate the current understanding of asymptomatic vary early-stage to end-stage OA, and make an effort to establish novel prevention and treatment methods according to the pathophysiology of these diseases under the concept of "locomotive syndrome."

Acknowledgments This study was funded by the Center of Innovation (COI) program from the Japan Science Technology Agency (JST) and the Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan, which is a large-scale and university–industry collaborated R&D platform in which universities concentrate all their powers on innovative research issues and corporations, leading to the commercialization of their achievements. The study was also supported by a High Technology Research Center Grant from the MEXT, Japan.

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Compliance with Ethical Standards

Conflict of interest Muneaki Ishijima, Haruka Kaneko, Shinnosuke Hada, Mayuko Kinoshita, Ryo Sadatsuki, Lizu Liu, Yukio Shimura, Hitoshi Arita, Jun Shiozawa, Anwarjan Yusup, Ippei Futami, Yuko Sakamoto, Masayoshi Ishibashi, Syuichi Machida, Hisashi Naito, Eri Arikawa-Hirasawa, Chieko Hamada, Yoshitomo Saita, Yuji Takazawa, Hiroshi Ikeda, Yasunori Okada, and Kazuo Kaneko declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

Informed Consent Informed consent was obtained from all individual participants included in the study.

Animal/Human Studies This article does not include any studies with human or animal subjects performed by the author.

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