Osteoarthritis of the Knee as One of the Major Musculoskeletal Diseases Responsible for Locomotive Syndrome: The Role of Synovitis in Pain

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Osteoarthritis of the knee (knee OA) is an increasingly important public health concern, as the prevalence of the disease is increasing with the aging of society. It is considered to be one of the major diseases responsible for locomotive syndrome, defined as being restricted in one's ability to walk owing to a dysfunction in one or more parts of the locomotion system. However, as no disease-modifying treatments for knee OA exist, all of the currently available treatments are symptom-modifying. Pain is the most prominent and disabling symptom of OA, and is also one of the factors predicting the progression of OA. There is an urgent need to improve our understanding of both the pathophysiology and the symptoms of the disease. Recently, the role of synovitis in OA has attracted particular attention, as synovitis has been revealed to be one of the potential indicators of knee pain and a predictive factor for both structural and symptomatic progression of the disease. In this review, we introduce the associations among pain, symptoms, and synovitis in patients from early- to end-stage knee OA, and also address future perspectives regarding the involvement of synovitis in the management of knee OA.

Key words: knee osteoarthritis, locomotive syndrome, MRI, biomarkers, JKOM score

Introduction

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 determinants of adult mortality from non-com-

municable diseases in 2007 (Figure-1)¹⁾. Cardiovascular diseases (CVDs) were the most prominent diseases that induced physical inactivity. It has been suggested that osteoarthritis (OA) of the knee is associated with an increased risk of CVDs (Table-1)²⁾. In population-based administrative data from British Columbia, Canada, the medical history of a random sample of 600,000 individuals

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Figure-1 Deaths from non-communicable diseases and injuries in females and males, and the deaths attributable to various risk factors in Japan in 2007¹⁾.

Table-1 The RRs and 95% CIs of cardiovascular diseases for OA patients according to the OA diagnosis and TJR²⁾.

Exposure		RRs (95% CI)
CVD	OA diagnosis	1.11 (1.05-1.17) *
	TJR	1.26 (1.12-1.41) *
IHD	OA diagnosis	1.30 (1.18-1.43) *
	TJR	1.44 (1.16-1.79) *
CHR	OA diagnosis	1.09 (0.97-1.23)
	TJR	1.46 (1.16-1.83) *

*In all cases, non-OA was the reference category. RR: relative risk, 95% CI: 95% confidence interval, OA: osteoarthritis, TJR: total joint replacement, CVD: cardiovascular disease, IHD: ischemic heart disease other than myocardial infarction, CHF: congestive heart failure

from 1991-2009 was analyzed, and OA was an independent predictor of CVD. The adjusted relative risks (RRs) for CVDs were 1.15 (95% confidence interval [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, younger females, and older females, respectively. OA patients who underwent total joint arthroplasty (TKA) had a 26% increased risk of CVD in comparison to non-OA cases. Although TKA has been shown to provide excellent results for the patients with end-stage knee OA, new strategies to treat early-stage knee OA are needed globally, which should ultimately reduce

the demand for TKA³⁾.

Locomotive syndrome is defined as a condition associated with being restricted in one's ability to walk or lead a normal life owing to a dysfunction in one or more of the parts of the locomotion system, including the muscles, bones, joints, cartilage or the intervertebral discs (Figure-2)⁴⁾. This syndrome especially refers to those elderly who have come to need nursing care services because of problems with the locomotive organs, or who have conditions which may require them to have such services in the near future. Japan faces a future as the most elderly society humankind has ever known, and with that prospect in mind, the Japanese Orthopaedic Association proposed the concept of locomotive syndrome in 2007. Steps need to be taken today to prevent locomotive syndrome and to extend the healthy life expectancy of the people living today, so that individuals can continue to be mobile for life. OA is considered to be one of the major diseases responsible for locomotive syndrome.

OA is an age-related progressive joint disease, which is characterized primarily by cartilage degradation⁵⁾. As the prevalence of this disease is gradually increasing due to the increasing longevity of the population, OA is becoming an increasingly important public health concern⁶⁾. OA-associated joint damage may be associated with clinical problems, but the severity of joint disease is only

Figure-2 Locomotive syndrome: A conceptual diagram⁴⁾.

weakly related to the clinical findings, as the only current sensitive diagnostic technique is classic radiography. Pain is the most prominent and disabling symptom of knee OA⁵⁾⁷⁾. Pain is the major reason why individuals seek medical attention from early- through end-stage knee OA, and is also a major determinant for the loss of joint function. Furthermore, there are currently no disease-modifying drugs (DMORDs) available for OA, and symptom-modifying therapy is the only available treatment for knee OA⁸⁾. 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 need to be investigated in terms of the severity of joint damage³⁾. In this review, we focus on the association between the pathogenesis and symptoms, including pain, in patients with knee OA and on the role of synovitis in pain.

Pain, cartilage metabolism and synovitis in early-stage knee OA

OA is characterized primarily 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 pain⁷⁾. Nevertheless, changes in articulation caused by structural changes and associated changes in extracellular matrix turnover in articular cartilage, reflected by cartilage biomarkers⁹⁾, 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. Synovitis and osteophyte formation are considered to be secondary phenomena in OA, as degenerated articular cartilage affects subchondral bone and the synovium¹⁰⁾⁻¹²⁾. In synovitis, the synovial membrane produces proteases and cytokines, which enhance the cartilage degradation. While synovitis occurs throughout the affected joint in cases with rheumatic arthritis, synovitis occurs locally and more mildly in OA¹³⁾. 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 a critical assessment of the pathophysiological processes that lead to joint failure and pain in OA patients¹⁴⁾⁻¹⁶⁾.

We tested the hypothesis that there are interrelationships between the presence or absence of knee pain and the changes in skeletal tissue and synovitis biomarkers in early-stage of radiographic knee OA (Figure-3)⁹⁾. 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 crosslinking telopeptide of type I collagen (uNTx), a biomarker of bone resorption and the serum hyaluronic acid (sHA), a marker of synovitis¹⁷⁾, all of which have been used to study the pathology of OA.

A total of 46 patients with a Kellgren-Lawrence (K/L) grade of 1 or 2 were enrolled in this study. Patients were divided into two groups according to the presence or absence of knee pain, and these two groups were evaluated by biomarker analyses (Figure-3). The levels of cartilage biomarkers,

Figure-3 The biomarker levels of the subjects with early-stage knee OA according to the presence or absence of knee pain⁹⁾.

All analyses were adjusted for age, gender, and body mass index. The urinary biomarkers were corrected for the creatinine level. There 30 subjects with knee pain and 16 without knee pain.

*Value of $p \leq 0.05$ 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, NTx: N-terminal crosslinking telopeptide of type I collagen, HA: hyaluronic acid

including sC2C, uCTX-II and sCPII, 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. In contrast, there was only a marginally ($p=0.05$) significant difference for the bone biomarker uNTx in patients with or without knee pain irrespective of the grade. 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, and that these are associated with knee pain in early-stage knee OA. These results also suggest that bone remodeling may contribute to joint pain even in the early stage of knee OA⁹⁾.

Disability and synovitis in end-stage knee OA

Pain and disability are also important for patients with end-stage knee OA, as the reason why most patients undergo TKA is to relieve pain³⁾. The use of clinical outcomes in clinical medicine is important. The Japanese Knee Osteoarthritis Measure (JKOM) was created as an outcome measure for Japanese patients with knee OA¹⁸⁾. This measure has been proven to have sufficient reliability and validity by means of statistical evaluations and comparisons with the Western Ontario and McMas-

ter Universities Arthritis Index (WOMAC) and the Medical Outcomes Study Short-Form 36-Item Health Survey (SF-36). Enhanced MRI using gadolinium diethylenetriaminepentaacetic acid (Gd-DTPA) has been proposed as a potentially valuable tool for evaluating synovitis either in RA or OA¹⁹⁾. We examined whether the synovitis in knee OA assessed by histological examinations and enhanced MRI correlated with the disability of the patients with end-stage knee OA who required TKA (Figure-4).

Thirty-four patients who fulfilled the American College of Rheumatology criteria for knee OA²⁰⁾ and required total knee arthroplasty (TKA) due to the end-stage OA knees of Kellgren and Lawrence grade 4²¹⁾ were enrolled in this study. The pain VAS score of patients was not correlated with either the mean total synovitis score evaluated by the histological analysis nor that evaluated by Gd-MRI (data not shown). On the other hand, the total JKOM score of the patients showed a significant positive correlation with both the mean total synovitis score evaluated by the histological analysis and that evaluated by Gd-MRI (Figure-4). The results of this study suggest that synovitis may play a crucial role not only in the progression of disease, but also in the current functional impairment and disability in patients with end-stage knee

Figure-4 A simple regression analysis comparing the histological- and enhanced-MRI evaluated synovitis score with the JKOM score in patients with end-stage knee OA ³⁷⁾.

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. * and ** indicate that the p value was less than 0.05 and 0.01, respectively.

Table-2 The results of a semi-quantitative analysis of the expression levels of the mediators of inflammation in the lining and sublining layers of the synovial tissue in the knee OA patients ²³⁾.

	Early to middle stage (K/L 2/3)	End stage (K/L 4)	p
MMP-1	2.0 (0.8, 0.7-3.3)	1.0 (0.6, 0.7-1.3)	0.03*
COX-2	1.4 (0.7, 0.2-2.5)	0.5 (0.3, 0.3-0.7)	0.01*
IL-1 β	2.1 (0.7, 1.0-3.2)	1.1 (0.6, 0.9-1.4)	0.02*
NF- κ B1	1.5 (0.4, 0.9-2.2)	1.1 (0.5, 0.8-1.3)	0.08
TGF- β	0.1 (0.1, -0.1 to 0.2)	0.6 (0.3, 0.5-0.8)	<0.01*

OA who require TKA.

Pain and inflammatory cytokines in knee OA

Inflammatory mediators play a pivotal role in the initiation and perpetuation of the OA process ²²⁾. Such mediators would be produced locally. The local production of inflammatory mediators, which are released by the degenerated articular cartilage, is well known to contribute to further cartilage degradation and synovial cell activation. Synovial membrane inflammation may also have a role in the pathophysiology of OA. Synovitis in OA may be a secondary phenomenon related to the cartilage and bone alterations induced by the release of degenerative compounds from the extracellular matrix of hyaline cartilage. This could further stimulate cartilage damage ^{9) 22)}. Therefore, it has been proposed that the inflammation in the synovial tissue observed in knee OA is a focal phenomenon ¹³⁾. As

the synovial inflammation in OA occurs locally in areas of cartilage loss, the inflammation of the medial perimeniscal synovium is common in medial femoro-tibial OA. Of note, MRI and ultrasonography have demonstrated synovitis in early OA, even in joints where synovitis was not detected clinically. Immunohistochemical studies have confirmed that the synovial tissue from patients with early OA is characterized by mononuclear cell infiltration, as well as the production of proinflammatory cytokines and mediators of joint damage. We examined whether the expression levels of the inflammatory mediators and growth factors in the medial perimeniscal synovium correlated with the severity of OA evaluated by radiographic parameters and a patient-oriented outcome measure in patients with medial knee OA (Table-2) ²³⁾, as described below.

Twenty-three patients (21 female and two males) who had medial knee OA and underwent either joint replacement ($n=19$) or arthroscopic

Figure-5 The correlation between the expression levels of inflammatory mediators and growth factor in the medial perimeniscal synovial tissue with the radiographic parameters and patient-oriented outcome measures for knee OA in patients²³⁾.

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: femoro-tibial angle, JKOM: Japanese Knee Osteoarthritis Measure

surgery (n=4) in the hospital were recruited as the subjects based on the criteria for knee OA defined by the American College of Rheumatology criteria, as well as standard exclusion criteria²⁰⁾. An immunohistochemical analysis in both the lining and sublining layers of the synovial tissue revealed that the MMP-1 expression of the patients with K/L grade 4 was significantly reduced in comparison to that of those with either K/L grades 2 or 3. The COX-2 and IL-1 β expression in both the lining and sublining layers of the synovial tissues of the patients with K/L grade 4 were also significantly decreased in comparison with those of the patients with either K/L grade 2 or 3. In contrast, the TGF- β expression in the sublining layer of the synovial tissues of the patients with K/L grade 4 was significantly increased in comparison to that observed in the patients with either K/L grade 2 or

3 (Table-2).

As the K/L classification is a categorical and subjective radiographic parameter used to evaluate the severity of OA, we next used continuous and objective radiographic parameters, the JSW and femoro-tibial angle (FTA), and examined whether any correlations existed between the expression levels of the molecules and these parameters in all of the patients evaluated in that study (Figure-5). The expression levels of MMP-1 and IL-1 β in both the lining and sublining layers of the medial perimeniscal synovial tissue showed significant correlations with the radiographic severity. For example, the JSW of the medial tibio-femoral joint was positively correlated with the expression levels, while FTA was negatively associated with the levels, in the patients with medial knee OA. On the other hand, the COX-2 expression levels in both the

lining and sublining layers of the synovial tissue did not correlate with either the JSW of the medial tibio-femoral joint or the FTA. The expression levels of TGF- β in the sublining 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 K/L classification, 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-1 β 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 showed a significant positive correlation with the JKOM score (Figure-5).

This study revealed that the expression levels of MMP-1, COX-2 and IL-1 β in the medial perimeniscal synovium were decreased, and the levels of TGF- β were increased, according to the severity of the disease in patients with medial knee OA. The progression of the disease was assessed not only by the classical K/L radiographic classification but also by other radiographic parameters, such as the FTA and JSW, and a patient-oriented outcome measure for OA, the JKOM score, thereby confirming the results of this study.

As the expression of MMP-1, COX2 and IL-1 β 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 the patients with either K/L grade 2 or 3 of knee OA in comparison to those with K/L grade 4 knee OA.

Pain and subchondral bone changes in knee OA

Precisely how the disease progresses in patients with knee OA remains unclear. MRI is more sensitive than radiography for detecting bone and soft tissue changes, which are features of OA²⁴⁾. The morphological changes, such as cartilage lesions, bone attrition, cysts, bone marrow abnormalities (BMAs), osteophytes, meniscal pathology,

synovitis and ligament changes, can be visualized and semi-quantified by MRI. In addition, it is also possible to evaluate the OA-induced structural joint changes semi-quantitatively by, for instance, using the Whole Organ Magnetic Resonance Imaging Score (WORMS) (Figure-6). These techniques may improve the understanding of the very early stage of knee OA²⁵⁾.

BMAs are findings with a high signal intensity in T2-weighted fat-suppressed images. Although the pathogenesis of BMA is still poorly understood^{26) 27)}, BMAs have been linked to pain, in addition to cartilage defects and the progression of cartilage loss^{24) 28) 29)}. We collected one hundred twenty-two patients with knee OA (71.1 years on average), and the frequency of the presence of BMAs in these patients was investigated³⁰⁾. MRI for the affected knee joint, in addition to radiography, were

Figure-6 The Whole Organ Magnetic Resonance Imaging Score (WORMS)²⁵⁾.

The morphological changes due to OA detected by MRI consisted of eight components. Each component was scored semi-quantitatively.

Figure-7 The frequency of BMAs in patients with painful knee OA³⁰⁾.

Table-3 The BMA scores at baseline in the progression and non-progression groups³⁰⁾.

Δ s-score (n=122)	Non-progression (63)	Progression (59)	p
K/L1 (16)	-5.1 (5.2, -17.8 to 7.5) (9)	5.0 (2.6, -6.4 to 16.4) (7)	0.07
K/L2 (54)	-2.7 (1.8, -6.4 to 1.0) (31)	11.9 (6.3, -5.3 to 27.3) (23)	<0.05*
K/L3 (52)	0.6 (1.2, -1.8 to 3.0) (23)	-1.2 (2.6, -7.0 to 4.5) (29)	0.57

Data (SD, 95%CI)

The data show the means (SD, 95%CI) (n).

conducted two times in all patients at the baseline and six months or later at the time of follow-up. Approximately ninety percent of the advanced (K/L grade 3) and end-stage (K/L grade 4) painful knee OA patients showed BMAs, and half of the primary stage (K/L grades 1 and 2) painful knee OA patients showed BMAs (Figure-7). The proportion of enlarging BMAs in patients with K/L grades 1, 2 and 3 were 18.8%, 18.5% and 30.8%, respectively. Although the patients with K/L grade 3 showed a higher rate of disease progression during the follow-up, no significant differences in the OA progression rates were observed between the patients with K/L grades 1, 2 and 3.

When we examined whether the enlarging BMAs were increased in the progression group compared to the non-progression group, the BMA score was significantly higher in the progression group than in the non-progression group in patients with K/L grade 2 (Table-3). Conversely, patients with K/L grades -1 and -3 had no significant differences in their BMA scores between those with and without progression (Table-3). These results suggest that the relationships between the size and enlargement of BMAs and the progression of OAs are altered depending on the severity of OA. However, the results clearly indicated that the BMAs, subchondral abnormalities, play a critical role in the pain and progression of knee OA, especially in the primary to middle stages of knee OA.

Pain components vary depending on the disease progression

The pain associated with knee OA is a type of

nociceptive pain⁷⁾. It has been speculated that detrimental mechanical loading across the joint, which, for instance, was estimated by the knee adduction moment (KAM)³¹⁾, and inflammation, especially synovitis, may be the main factors associated with the severity of pain⁶⁾. Detrimental mechanical loading across the knee joint is speculated to be one of the main factors underlying the pathophysiology of knee OA. The malalignment of the lower limb and excess body mass have both been considered to be risk factors for the progression of knee OA, due to the association between these factors and the joint load³¹⁾⁻³³⁾. While the 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 based on the progression of the disease. We hypothesized that the factors associated with pain in knee OA varied according to the disease progression. To verify this hypothesis, we divided the patients into two groups according to the radiographic severity of knee OA and investigated the pain severity, the serum IL-6 levels and the alignment of the lower limb in patients with knee OA, and examined whether the factors associated with pain in knee OA varied according to the radiographic disease severity³⁴⁾.

One hundred and sixty patients with primary- 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] were included in this study. A multiple linear regression analysis indicated that the serum IL-6 levels and the anatomical alignment angle (AAA) were both associated with the pain severity, as evaluated by the pain VAS score in the patients when the whole

Table-4 The factors associated with the pain VAS score in patients with knee OA ³⁴⁾.

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 BMI. [#]A 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).

Abbreviations: IL-6, Interleukin 6; AAA, anatomical axis angle; 95%CI, 95% confidence interval.

cohort of patients was included in the analysis (Table-4). On the other hand, the serum levels of IL-6 were solely associated with the pain VAS score in the 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. Although, it is still unclear precisely how joint loading induces pain in patients with knee OA, and since such joint loading was not measured in the present study, the results of the present study suggest that the pain in the advanced-stage of knee OA is associated with the mechanical loading across the knee joint, which is associated with a deterioration of the lower limb alignment ³⁵⁾. The presence of a higher level of sIL-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.

Synovitis in knee OA: Future perspective

The role of synovitis, even though it is a secondary phenomenon caused by the joint damage induced by OA, has attracted particular attention, as it has been revealed to be one of the potential indicators for knee pain and a predictive factor for both structural and symptomatic progression of the disease ³⁶⁾. As shown in this manuscript, synovitis is associated with the pain and/or disability of the patients from the early to end-stages of knee

Figure-8 A hypothetical model of the associations among pain, the avoidance of activities, reduced muscle strength and limitation in activity ³⁸⁾.

OA ^{9) 37)}. On the other hand, the expression levels of inflammatory cytokines, such as COX-2 and IL-1 β , in end-stage knee OA are reduced in comparison to those in primary stage knee OA ²³⁾. In addition, the pain in the advanced stage of knee OA is associated with the mechanical loading across the knee joint ³⁴⁾. Based on these findings, it has currently been focused on a major factor(s) underlying the pathophysiology associated of end-stage knee OA. As there are no current interventions proven to restore cartilage or curtail the disease processes, and since OA ultimately results in joint destruction, chronic pain, disability and other associated conditions, such as depression and social isolation, this

Table-5 The mediating effects of muscle strength on the relationship between the avoidance of activity and performance-based limitations in activities³⁸⁾.

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*

*The potential confounders were age, gender, the duration of complaints, BMI, education level and comorbidities.

Figure-9 The principles of the management of osteoarthritis⁶⁾.
The suggested sequential, pyramidal approach to disease management.

matter needs further investigation¹⁶⁾.

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, to greater limitations in activities (Figure-8)³⁸⁾. As pain is a major cause of avoidance of activity in patients with knee OA (Table-5), it is necessary to better understand the pain in OA and to develop ways to prevent or at least provide better relief of this pain.

The ideal management of knee OA is illustrated as a sequential, pyramidal approach (Figure-9)⁶⁾. While it has been estimated that there are 25 million people with knee OA diagnosed as radiographic K/L grade 2 or more advanced in Japan, and it has

been speculated that eight million have knee pain³⁹⁾, seventy thousand cases of TKA are currently being performed each year. The concept of "locomotive syndrome" should therefore be promoted so that the patients with knee OA who either need or don't need TKA can be identified more clearly from the perspective of the locomotive syndrome, and to allow for the earlier identification of patients with symptomatic knee OA to prevent the development of locomotive syndrome by providing adequate pain relief.

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