The Effects of Adherence to Non-Steroidal Anti-Inflammatory Drugs and Factors Influencing Drug Adherence in Patients with Knee Osteoarthritis

Kwan Kyu Park,[1] Choong Hyeok Choi,[2] Chul-Won Ha,[3] and Myung Chul Lee[4]

[1]Department of Orthopedic Surgery, Yonsei University College of Medicine, Seoul, Korea; [2]Department of Orthopedic Surgery, Hanyang University College of Medicine, Seoul, Korea; [3]Department of Orthopedic Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea; [4]Department of Orthopedic Surgery, Seoul National University College of Medicine, Seoul, Korea

Address for Correspondence:
Myung Chul Lee, MD
Department of Orthopedic Surgery, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
E-mail: leemc@snu.ac.kr

We aimed to compare the clinical outcomes of knee osteoarthritis patients according to drug adherence; and to find out the factors the affecting those outcomes. We analyzed the drug adherence and clinical outcomes in 1,334 primary knee osteoarthritis patients who took non-steroidal anti-inflammatory drugs (NSAIDs) for 3 weeks. Clinical outcomes of Pain Numeric Rating Scale (NRS), Knee injury and Osteoarthritis Outcome Score (KOOS) and EQ-5D were compared at baseline and 3 weeks' follow-up between the two groups of adherent group and non-adherent group (1,167 vs. 167 patients). Logistic regression analysis was performed to examine the factors affecting the adherence, and the reasons for the non-adherence were asked. The follow-up clinical outcomes of NRS and KOOS symptom, pain and activity of daily life were significantly higher in the adherence group ($P = 0.003$, $P = 0.048$, $P = 0.005$, and $P = 0.003$, respectively). The adherence was better in the elderly and in the male group ($P = 0.042$ and $P = 0.034$, respectively) and the top reason for no strict adherence was "symptom improved" (21.5%) followed by side effects. In this study, the patients with better adherence to NSAIDs showed better outcomes compared to those with poor adherence. This study can contribute to the patient education for the pharmacological treatment in knee OA patients.

Keywords: Osteoarthritis, Knee; Anti-Inflammatory Agents, Non-Steroidal; Patient Adherence

INTRODUCTION

Knee osteoarthritis (OA) is one of the major sources of morbidity, disability, and loss of function, especially in elderly people; it can also result in severely impaired quality of life with persisting disease (1). OA is predicted to become the fourth leading cause of disability globally by 2020 (2). Of particular concern is the worldwide economic burden of knee OA, which will likely increase in the future, as longer life expectancy would lead to a growing elderly population (3). Medication management seems to be symptomatic, mostly with simple analgesics such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs) (4,5). However, there is neither known cure for OA nor effective interventions to slow disease progression (6). Although NSAIDs may not prevent the disease progression, it is well known as a proper medication that can relieve pain and help patients return to a normal life (7) with the pain thought blocking of the nociceptors (8).

Similar to most other chronic conditions, adherence to arthritis medications is known to be low (6,9-12). Factors implicated in adherence to OA with other rheumatoid disease include dosing frequency (12), pain and self-efficacy levels (9), and phy-

sician trust (6,13,14). Recently, another study reported that side effect, out-of pocket costs, mode of action, and treatment schedule also had a significant effect on the choice to continue medication (15). However, there is still little information about OA patient's treatment adherence and differences resulting from it.

Thus, in our prospective observational multicenter study, we targeted knee OA patients over 65 years old who were prescribed NSAIDs (including cyclooxygenase-2 [COX-2] inhibitors) for 3 weeks, and we tried to investigate the drug adherence and patient reported outcomes. The purposes of this study were the following: 1) to assess the differences in patient reported outcomes according to the drug adherence; and 2) to evaluate the factors affecting them. We hypothesized that the follow up clinical outcomes would be better in the subjects of the adherent group. We also hypothesized that gender, age, educational status, and frequency of daily NSAIDs administration could be associated with the adherence to NSAIDs in treatment of knee OA.

MATERIALS AND METHODS

Study design

This was a nationwide, multicenter, prospective, observational

study conducted in Korea involving 29 institutes. Considering 95% confidence level and 2.3% limits of prevalence error, we calculated the required sample size to be approximately 1,324 people. Considering 15% of dropout rate, we calculated the target sample size to be 1,500 people. The final total patients followed up in this study were 1,334 people.

Patient recruitment (inclusion and exclusion criteria)
Data were collected between November 2011 and October 2012. Among the knee OA patients who visited each institute, the patients who met all of the following conditions were selected under the doctor's judgment based on the radiographic findings and symptoms : first, patients diagnosed with knee OA under American College of Radiology (ACR) clinical criteria (16); second, patients older than 65 years; third, patients identified with having pain Numeric Rating Scale (NRS) 4 point or higher; fourth, patients diagnosed as the symptomatic knee OA by clinician; fifth, patients who need to take NSAIDs continuously for 3 weeks, where clinicians notated the reasons for required treatment period on the assessment form (Appendix 1). The following cases were excluded from participation in this study: first, patients with different types of acute or chronic pain other than OA pain who may influence differentially OA pain assessment or self-assessment; second, patients having known side effects against NSAIDs or cyclooxygenase inhibitor; third, patients who are determined by clinicians as not being capable of taking medications for 3 weeks due to severe renal dysfunction, hepatic dysfunction, or gastrointestinal disease; fourth, patients with a history of surgery or significant knee injury within the previous year; fifth, patients planning a surgical procedure during the study; sixth, patients currently participating in another clinical study; seventh, patients excluded by clinicians to participate in this research and data collection due to severe or unstable medical conditions.

Data collection
Patients filled out the questionnaires on the first visit (baseline) and the second visit (follow-up) after taking medication (non-selective cyclooxygenase inhibitor or selective cyclooygenage-2 inhibitor) for 3 weeks (Appendix 2). The demographics were collected on the first visit (baseline), and pain was measured using pain Numeric Rating Scale (NRS) (0 low, 10 high). Joint function was measured by the Korean version of Knee injury and Osteoarthritis Outcome Score (KOOS-K) (17), which was developed and modified from KOOS for Korean patients as an instrument to assess the patients' opinion about their knee and associated problems. KOOS-K consists of 5 subscales: Pain, other Symptoms, Activities of Daily Living (ADL), Function in sport and recreation (Sport/Rec), and knee related Quality of life (QOL). Standardized answer choices are given (5 Likert boxes) and each question gets a score from 0 to 4. A normalized

score (100 indicating no symptoms and 0 indicating extreme symptoms) is calculated for each subscale. QOL was measured by EQ-5D (Euro Quality of Life-Five Dimensions) and EQ-VAS (Euro Quality of Life-Visual Analogue Scale).

On the second visit (follow-up after 3 weeks), pain NRS, KOOS-K, EQ-5D, and EQ-VAS were measured like the first visit, and we investigated treatment adherence (Appendix 2). Patients responded to "Would you answer that you adhered to Doctor's treatment plan?" as one of the followings: ① Adhered strictly, ② Considered adhered well, ③ Moderately adhered, ④ Did not adhere, or ⑤ Did not adhere at all. And we asked the patients who did not select ① Adhered strictly to choose the reason (multiple selection). In the question about treatment adherence, we designated the patients who chose ① Adhered strictly, ② Considered adhered well as 'Adherent group', and the patients who chose the others as 'Non-adherent group'. Among the total of 1,334 patients, 1167 patients (87.5%; 95% CI, 85.6-89.2) selected ① Adhered strictly (870/1,334, 65.6%; 95% CI, 62.6-67.7) or ② considered adhered well(297/1,334, 20.1%; 95% CI, 20.1-24.6) and were classified as 'adherent group', while 167 (12.5%; 95% CI, 10.9-14.4) patients selected ③ moderately adhered (99/1,334, 6.13%; 95% CI, 6.1-9.0), ④ did not adhere (56/1,334, 4.2%; 95% CI, 3.3-5.4) or ⑤ did not adhere at all (12/1,334, 0.9%; 95% CI, 0.5-1.5), and were classified as 'Non-adherent group'.

Statistical analysis
To determine the differences between the adherent group and non-adherent group in the demography, we applied Student t-test and χ^2 test. To evaluate the changes between clinical outcome at the baseline and the follow up, paired t-test was performed. Student t-test was conducted to compare the clinical outcomes between the adherent group and non-adherent group. To identify the factors affecting adherence, we calculated the degree of impact by univariate analysis of predictors, and then model was designed using logistic regression analysis. The collected data was/were (either singular or plural is ok; just make sure to be consistent) analyzed using SAS (version 9.2. The statistical significance level was on the basis of 0.05.

Ethics statement
Institutional review board approval was obtained at Seoul National University Hospital (H-1110-031-381) and all the participants provided their written informed consent to participate in this study.

RESULTS

Demographics of the total patients and of the adherent and non-adherent groups are shown in Table 1. Female patients were 79.8% (95% Confidence interval [CI], 77.6%-81.9%) of the total patients and the average age was 74.3 ± 5.4 years (Table 1). More

than 1/3 of the patients were 70-74 years old and more than a half were elementary school graduates (52.4%; 95% CI, 49.7%-55.1%), which made up the majority (Table 1). For the frequency of daily NSAIDs administration, 778 patients were prescribed as taking medication once a day (58.3%; 95% CI, 55.7%-60.9%), 509 twice a day (38.2%; 95% CI, 35.6%-40.8%), and 47 three times a day (3.5%; 95% CI, 2.7%-4.7%). In comparisons between the 'adherent group' and 'non-adherent group', there was a differ-

ence in the distribution of the age group ($P = 0.027$) whereas the other factors did not show significant differences in their distribution (Table 1).

For the reasons for no strict adherence, 464 patients answered the question (355 patients chose one answer, 93 chose 2 answers, 14 chose 3 answers, and 2 chose 4 answers) (Table 2). The top three reasons were: "My symptom has gone better" (21.5%); "Osteoarthritis medication is thought to be only a pain relief" (16.4%); and "It causes indigestion, discomfort, heart burn, and other GI events" (13.0%) (Table 2).

Table 3 shows the clinical outcomes of the baseline and the follow-up in the total patients group, adherent group, and non-adherent group. All clinical outcomes including pain NRS, KOOS-K, and EQ-5D were significantly improved at the follow-up compared to the baseline in the total patients group, adherent group,

Table 1. Demographics of the patients

Variables	Knee OA patients			
	Total (n = 1,334)	Adherent (n = 1,167)	Non-Adherent (n = 167)	P value*
Female, No. (%)	1,065 (79.8)	923 (79.1)	142 (85.0)	0.074
Age, mean (SD)	74.3 (5.4)	74.4 (5.4)	73.7 (5.5)	0.122
Age groups (yr), No. (%)				0.027
65-69	270 (20.2)	222 (19.0)	48 (27.7)	
70-74	500 (37.5)	440 (37.7)	60 (35.9)	
75-79	346 (25.9)	311 (26.6)	35 (21.0)	
80 ≤	218 (16.3)	194 (16.6)	24 (14.4)	
Education, No. (%)				0.555
Elementary school	676 (52.4)	594 (52.3)	82 (53.2)	
Middle school	279 (21.6)	252 (22.2)	27 (17.5)	
High school	265 (20.6)	231 (20.4)	34 (22.1)	
University	60 (4.7)	51 (4.5)	9 (5.8)	
Graduate school	9 (0.7)	7 (0.6)	2 (1.3)	
Height, mean (SD), cm	157.1 (6.9)	157.2 (6.9)	156.7 (6.8)	0.379
Weight, mean (SD), kg	30.3 (8.7)	60.2 (8.8)	60.6 (8.4)	0.594
BMI, mean (SD)	24.4 (3.1)	24.4 (3.1)	24.7 (3.0)	0.179
Duration (mon) of knee OA, mean (SD)	67.0 (78.5)	66.4 (78.9)	70.9 (75.1)	0.486
Number of NSAID treatment, No. (%)[†]				0.201
1	778 (58.3)	676 (57.9)	102 (61.1)	
2	509 (38.2)	453 (38.8)	56 (33.5)	
3	47 (3.5)	38 (3.3)	9 (5.4)	

OA, osteoarthritis; BMI, body mass index (kg/m^2); SD, standard deviation; NSAIDs, non-steroidal anti-inflammatory drugs.
Values are presented by number (%) or mean (SD).
*χ^2 test for categorical data and Student t-test for continuous data were performed; [†]Frequency of daily NSAIDs administration.

Table 2. Reasons for not adhering strictly*

Reasons	No. (%) of patients
Symptom improved.	127 (21.5)
Osteoarthritis medication is only for pain relief, not for treatment.	97 (16.4)
It causes indigestion, discomfort, heart burn and other GI events.	77 (13.0)
Medication is not working properly.	67 (11.3)
I am worried about the adverse effects.	49 (8.3)
I was advised to take medication when I only have pain.	44 (7.4)
I have too many pills to take.	39 (6.6)
I forgot.	32 (5.4)
It makes my body swell.	19 (3.2)
Lost medicine	14 (2.4)
The treatment plan is complicated.	10 (1.7)
I stopped because I needed to take other drugs.	7 (1.2)
I gained some weights.	3 (0.5)
The medicine is expensive.	0 (0.0)
Others	6 (1.0)
Total	591 (100.0)

Values are presented by number (%).
*Among 464 patients who did not answer "① Adhered strictly", 355 patients chose one answer for the reason that the patients did not adhere strictly, 93 patients chose 2 answers, 14 patients chose 3 answers, and 2 patients chose 4 answers.

Table 3. Clinical outcomes of the total patients and adherent and non-adherent groups (baseline and 3 weeks' follow-up)

Variables	Knee OA patients							
	Baseline				Follow up			
	Total (n = 1,334)	Adherent (n = 1,167)	Non-adherent (n = 167)	P value	Total (n = 1,334)	Adherent (n = 1,167)	Non-adherent (n = 167)	P value
Pain NRS, mean (SD)	6.2 (1.5)	6.1 (1.5)	6.4 (1.6)	0.027	4.4 (1.9)	4.3 (1.9)	4.9 (2.2)	0.003
KOOS-K, mean (SD)								
Symptom	67.1 (19.4)	67.0 (19.5)	67.9 (18.7)	0.579	74.0 (16.8)	74.3 (16.7)	71.6 (17.0)	0.048
Pain	59.8 (18.0)	59.6 (18.1)	61.2 (16.9)	0.234	67.2 (16.5)	68.6 (16.4)	64.9 (16.6)	0.005
ADLs	60.8 (18.4)	60.7 (18.6)	61.6 (17.5)	0.568	68.4 (16.5)	68.9 (16.4)	64.8 (17.3)	0.003
Sports/recreation	29.3 (21.7)	29.7 (21.3)	27.0 (21.7)	0.141	36.2 (23.7)	36.6 (23.3)	33.3 (26.2)	0.090
QOL	45.2 (16.9)	45.3 (16.9)	44.1 (17.3)	0.371	49.7 (17.1)	50.1 (16.9)	47.5 (18.5)	0.075
EQ-5D Index, mean (SD)	0.71 (0.2)	0.71 (0.1)	0.69 (0.2)	0.257	0.76 (0.1)	0.76 (0.1)	0.74 (0.2)	0.097
EQ-5D VAS, mean (SD)	59.7 (18.3)	59.4 (18.3)	61.9 (18.3)	0.109	66.2 (16.4)	66.2 (16.1)	66.3 (18.5)	0.917

Values are presented by mean (SD).
OA, osteoarthritis; NRS, Numeric Rating Scale; SD, standard deviation; KOOS-K, Knee injury and Osteoarthritis Outcome Score-Korean; ADL, Activities of Daily Living; QOL, Quality of life; EQ-5D Euro Quality of Life-Five Dimensions; EQ-VAS, Euro Quality of Life-Visual Analogue Scale.

Table 4. Risk factors associated with the adherence of knee OA patients using logistic regression analysis

Variables	Knee OA patients		
	Odds ratio	95% CI	
		Lower	Upper
Sex (ref. male)	0.535	0.315	0.910
Age, yr			
65-69	1.000	-	-
70-74	1.470	0.949	2.279
75-79	2.066	1.225	3.483
80 ≤	1.875	1.036	3.392
Education*	0.886	0.734	1.069
Number of NSAID treatment†	0.989	0.726	1.348
Duration of knee OA‡	0.999	0.997	1.001
BMI§	0.970	0.917	1.027

OA, osteoarthritis; CI, Confidence interval; NSAIDs, Non-steroidal anti-inflammatory drugs; BMI, Body mass index.
*Reference group, elementary school; †Frequency of daily NSAIDs administration/Reference group, frequency = 1; ‡Reference group, duration (months) of knee OA < 67.0 (mean); §Reference group, BMI < 24.4 (mean).

and non-adherent group (Table 3). Comparison of the clinical outcomes between the adherent group and non-adherent group showed no significant differences in any of the baseline variables except for pain NRS (6.1 ± 1.5 vs. 6.4 ± 1.6, *P* = 0.027), while, at follow-up, pain NRS (4.3 ± 1.9 vs. 4.9 ± 2.2, *P* = 0.003), KOOS-K symptom (74.3 ± 16.7 vs. 71.6 ± 17.0, *P* = 0.048), KOOS-K pain (68.6 ± 16.4 vs. 64.9 ± 16.6, *P* = 0.005), and KOOS-K ADLs score (68.9 ± 16.4 vs. 64.8 ± 17.3, *P* = 0.003) were significantly higher in the adherent group than non-adherent group (Table 3).

In the logistic regression analysis identifying the factors that affect adherence, elderly patients (70-74 years old and 75-79 years old) and male patients were found to be more adherent, while educational status, frequency of daily NSAIDs administration, duration of knee OA, and other factors did not affect adherence (Table 4).

DISCUSSION

We studied the patient's adherence by targeting knee OA patients who took NSAIDs (including COX-2 inhibitors) for 3 weeks, and identified the patient-reported outcomes as well as the factors affecting adherence. We hypothesized that the clinical outcomes would be better in the subjects of the adherent group, and gender, age, educational status, and frequency of daily NSAIDs administration could be associated with adherence to NSAIDs in treatment of knee OA. In this study, both the adherent group and non-adherent group showed significantly improved outcomes after 3 weeks of medication treatment, but most of the follow-up outcomes were significantly better in the adherent group as we hypothesized. Of those factors affecting the adherence to NSAIDs, older patients and male patients showed better adherence, while educational status, frequency of daily NSAIDs administration did not show difference in adherence.

Conservative treatment is very important for knee OA patients. Weight control and exercise are the top priority (7), but drug therapy is also considered to be highly important to avoid invasive treatment (7). While it is known that proper medication can relieve pain and help patients return to a normal life, patients tend to stop taking medicines or take them only when necessary (7,8). However, several studies reported low drug adherence for patients (6,9,11,12,15). In this study, we had a relatively high drug adherence with our patients group, which is inconsistent with the previous studies (approximately 10% of low adherence rate). We assumed the reasons for the relatively higher adherence in our study to be the following: 1) we targeted relatively older patients; and that 2) we studied a relatively short period compared to long-term treatment of OA; or 3) that it was a self-survey study which could show a relatively higher adherence than monitoring study depending on the patients' characteristics.

In comparisons of the clinical outcomes between the adherent group and non-adherent group, adherent group showed significantly improved outcomes in the follow-up among several important variables such as pain NRS, KOOS-K symptom, pain and activity of daily life, which were consistent with the non-adherent group. Although there were no differences in KOOS-K sports/recreation and quality of life, and EQ-5D, we could confirm that significant effect was shown in our three-week-study treatment period. Because this study was conducted for a short period of three weeks, there may be differences in results observed for quality of life depending on the study period.

Previous studies reported many factors affecting adherence to arthritis or anti-rheumatoid disease medication, such as dosing frequency (12), pain and self-efficacy levels (9), physician trust (6,13,14) and so on. When we directly asked patients for the top reasons for not adhering to drugs, the most frequent answer was that the symptom has gotten better (21.5%). Interestingly, the second most frequent answer from the patients was 'a drug for OA is just a painkiller (16.4%)' which was more frequent answer than stopping due to complications (13.0%) (Table 2). There are controversies about the effect of NSAIDs on knee OA. Even though NSAIDs may not change the disease entity, NSAIDs can help patients return to exercise which is essential for knee OA patients. We assumed that doctors need to explain more about the functions of the medication to these kinds of patient group. Logistic regression analysis, which was performed in our study to find out the factors associated with adherence, showed gender and age to be the factors affecting adherence. Educational status and frequency of daily NSAIDs administration did not affect adherence, which differs from the previous studies (9,12). In particular, while we hypothesized high medication adherence in female patients, it turned out that male patients had shown better adherence; this may be because the proportion of male patients in our study was smaller (20%) com-

pared to the studies from the western countries (18). It can be predicted that the proportion of female OA patients is especially high in Korea, but the exact reason is unknown (18).

We should also note several limitations of our study. First, because it is a self-survey study, it is possible for the accuracy to be lower than monitoring research (13). We admit that there could be inappropriate to assess the adherence. It is also possible that the patients we classified as adherent or non-adherent group may not present the patients' characteristics completely due to the absence of monitoring. However, we believe our study is meaningful because we conducted a study comparing the clinical outcomes of the adherent and non-adherent group with relatively large number of patients from multi-centers. Second, because we targeted 65-year-old patients, the result may differ with the inclusion of younger patients. Finally, the scope of study was limited to Korean patients, with predominantly female group representing unique gender distribution in the knee OA patients in Korea (18,19), and a cultural difference of the patient's attitude towards the doctor. Not to make the results of our study too complicated, the various demographic characteristics that have been reported from various counties (1,20-26) may not have been taken into account in this study. Therefore, we need to be cautious about generalizing our results to a population with different characteristics. Furthermore, we did not include the results of the data analyses using many variables such as all different types of NSAIDs, radiologic severity, symptom duration, pain intensity, or previous analgesic medication history, not to make the results of our study too complicated, but these kind of characteristics should be also considered when our results is applied to other group of patients. Further study comparing the treatment adherence among other variables including different types of NSAIDs may be useful to provide more information on the reasons for non-adherence or discontinuation of the specific NSAIDs.

In conclusion, the patients with better adherence to NSAIDs showed better outcomes compared to those with poor adherence, and we hope this study can contribute to the patient education for the pharmacological treatment in knee OA patients.

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DISCLOSURE

AUTHOR CONTRIBUTION

Study concept and design: Lee MC. Data collection: Choi CH, Ha CW. Data interpretation: Lee MC. Statistical analysis: Park KK. Writing: Park KK. Review & revision: Lee MC. Approval of final manuscript: all authors.

ORCID

Kwan Kyu Park http://orcid.org/0000-0003-0514-3257
Choong Hyeok Choi http://orcid.org/0000-0001-7401-9116
Chul-Won Ha http://orcid.org/0000-0001-5123-6513
Myung Chul Lee http://orcid.org/0000-0002-8150-1573

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< Appendix 1 >

FIRST ASSESSMENT - DOCTOR

Visit Date: | d | d |/| m | m | m |/| y | y | y | y |

Patient who meets all the criteria below can only be enrolled.

1. **Patients included in Knee OA as ACR standard** ☐

   - **ACR criteria: Patient who meets following three criteria of idiopathic Knee osteoarthritis categorized by clinical and radiological standard.**

   ① Knee joint pain

   ② Exist one of following three symptoms:

      - Age > 50 y

      - Morning stiffness < 30 minutes

      - Friction sound

   ③ Evidence of osteophyte in the X-ray

2. **Age over 65 years old** ☐

3. **Pain NRS≥4 (If pain exist in both side of knee joints, mark the worse side as pain index.** ☐

   (0: Free from pain, 10: the worst pain ever)

0	1	2	3	4	5	6	7	8	9	10
☐	☐	☐	☐	☐	☐	☐	☐	☐	☐	☐

4. **Patient diagnosed as symptomatic knee OA by a clinician** ☐

5. **Recommended NSAIDs (including COX-2 inhibitors) for 3 weeks from a clinician.** ☐

   - **What is the reason for prescribing NSAIDs (including COX-2 inhibitors)? (Answer can be multiple)**

   ① Due to severe pain

   ② NSAIDs have a relatively better effectiveness compared to other medicine.

   ③ Low effectiveness when used for 1~2 weeks

   ④ Signs of Inflammation present.

   ⑤ etc:

   ⑥ Unable to answer

   - **What is the usage for prescribed NSAIDs(including COX-2 inhibitors)?**
     1 day (　　　) times

Respondent's signature: **Date:**   year   mm

< Appendix 2 >

FIRST ASSESSMENT – *PATIENT*

Visit Date: |_d_|_d_|/|_m_|_m_|_m_|/|_y_|_y_|_y_|_y_|

1. General and clinical characteristics

Gender	① M ② F	Date of Birth	_____year _____mm _____dd
Height	cm	**Weight**	Kg
Education	① Below elementary school graduate ② Middle school graduate ③ High school graduate ④ University graduate ⑤ above Masters degree		
Disease duration	Duration of Knee osteoarthritis : _____year _____month		

2. KOOS-K

● | **KOOS KNEE SURVEY** |

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.

Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms

These questions should be answered thinking of your knee symptoms during the last week.

S1. Do you have swelling in your knee?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

S3. Does your knee catch or hang up when moving?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

S4. Can you straighten your knee fully?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

S5. Can you bend your knee fully?

☐ Never ☐ Rarely ☐ Sometimes ☐ Often ☐ Always

Stiffness

The following questions concern the amount of joint stiffness you have experienced during the last week in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day?**

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

Pain

P1. How often do you experience knee pain?

☐ Never ☐ Monthly ☐ Weekly ☐ Daily ☐ Always

What amount of knee pain have you experienced the last week during the following activities?

P2. Twisting/pivoting on your knee

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

P3. Straightening knee fully

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

P4. Bending knee fully

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

P5. Walking on flat surface

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

P6. Going up or down stairs

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

P7. At night while in bed

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

P8. Sitting or lying

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

P9. Standing upright

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A1. Descending stairs

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A2. Ascending stairs

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A3. Rising from sitting

 A3-K. Rising from floor

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

  A3-W. Rising from chair/sofa

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A4. Standing

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A5. Bending to floor/pick up an object

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A6. Walking on flat surface

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A7. Getting in/out of car

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A8. Going shopping

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A9. Putting on socks/stockings

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A10.   Rising   from   bed
(In either occidental or oriental manner, tick the box that you are currently utilizing in your daily life. If the both method are applicable, please tick the both section)

A10-K. Rising from floor bedding

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A10-W. Rising from bed

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A11. Taking off socks/stockings

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A12. Lying in bed (turning over, maintaining knee position)

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A13. Getting in/out of bath

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A14.   Sitting
(In either occidental or oriental manner, tick the box that you are currently utilizing in your daily life. If the both method are applicable, please tick the both section)
A14-K Sitting on floor

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A14-W Sitting on chair/sofa

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A15.   Getting   on/off   toilet
(In either occidental or oriental manner, tick the box that you are currently utilizing in your daily life. If the both method are applicable, please tick the both section)
A15-K Getting on/off from Conventional toilet

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A15-W Getting on/off from toilet bowl

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A17. Light domestic duties (cooking, dusting, etc)

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

Function, sports and recreational activities
The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

SP2. Running

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

SP3. Jumping

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

SP4. Twisting/pivoting on your injured knee

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

SP5. Kneeling

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

Quality of Life

Q1. How often are you aware of your knee problem?

☐ Never   ☐ Monthly   ☐ Weekly   ☐ Daily   ☐ Consistently

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

☐ Not at all   ☐ Mildly   ☐ Moderately   ☐ Severely   ☐ Totally

Q3. How much are you troubled with lack of confidence in your knee?

☐ Not at all   ☐ Mildly   ☐ Moderately   ☐ Severely   ☐ Extremely

Q4. In general, how much difficulty do you have with your knee?

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

3. Health Questionnaire

EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today..
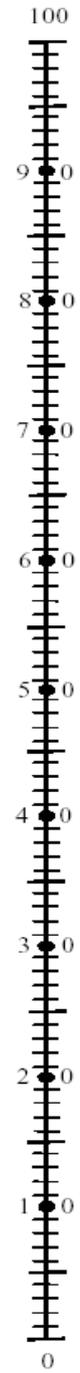
Mobility	
I have no problems in walking about.	☐
I have some problems in walking about.	☐
I am confined to bed.	☐
Self-Care	
I have no problems with self-care.	☐
I have some problems washing or dressing myself.	☐
I am unable to wash or dress myself.	☐
Usual Activities (e.g. work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities.	☐
I have some problems with performing my usual activities.	☐
I am unable to perform my usual activities.	☐
Pain/Discomfort	
I have no pain or discomfort.	☐
I have moderate pain or discomfort.	☐
I have extreme pain or discomfort.	☐
Anxiety/Depression	
I am not anxious or depressed.	☐
I am moderately anxious or depressed.	☐
I am extremely anxious or depressed.	☐

EQ-5D Visual Analogue Scale

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0. We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own
health state
today

100 : the best state you can imagine

0 : the worst state you can imagine

3. Pain NRS (Numeric rating scale)

SECOND ASSESSMENT-PATIENT (*AFTER TREATMENT 3WEEKS±3DAYS)*

Visit Date: | d | d |/| m | m | m |/| y | y | y | y |

1. Treatment Adherence

The following questions are regarding how you took the prescribed knee osteoarthritis medication recently.

1) Have you taken the medication in accordance with Dr's treatment plan?
(Not at all: 0%, Adhered every day: 100%)


```
0    10   20   30   40   50   60   70   80   90   100
```
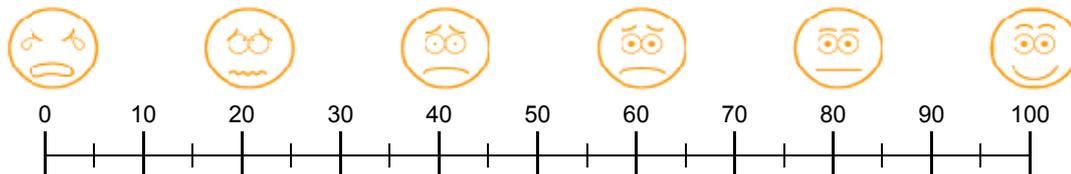
2) Would you answer that you adhered to Dr's treatment plan? Please choose the best answer below.
① Adhered strictly
② Considered adhered well
③ Moderately adhered
④ Did not adhere
⑤ Did not adhere at all (including no consumption of medication)

2. Patient's Awareness on treatment adherence of Knee osteoarthritis

If you did not answer ① above, what was the reason? (Answer can be multiple)

① Osteoarthritis medication is thought to be only a pain relief.
② I was advised to take medication when I only have pain: (Who was the advisor?_____)
③ My symptom has gone better.
④ Medication is not working properly.
⑤ I am worried about the adverse effects.
⑥ It causes indigestion, discomfort, heart burn and other GI events.
⑦ It makes my body swell.
⑧ I gained some weights.
⑨ I have too many pills to take.
⑩ The medicine is expensive.
⑪ The treatment plan is complicated.
⑫ Lost medicine
⑬ etc:

Please refer to the pictures below and answer your pain level.
0 states pain free and 10 states maximum pain, how would you score your pain level over the last week? [   ]

2. KOOS-K

● KOOS KNEE SURVEY

INSTRUCTIONS: This survey asks for your view about your knee. This information will help us keep track of how you feel about your knee and how well you are able to perform your usual activities.
Answer every question by ticking the appropriate box, only one box for each question. If you are unsure about how to answer a question, please give the best answer you can.

Symptoms
These questions should be answered thinking of your knee symptoms during the last week.

S1. Do you have swelling in your knee?
☐ Never   ☐ Rarely   ☐ Sometimes   ☐ Often   ☐ Always

S2. Do you feel grinding, hear clicking or any other type of noise when your knee moves?
☐ Never   ☐ Rarely   ☐ Sometimes   ☐ Often   ☐ Always

S3. Does your knee catch or hang up when moving?
☐ Never   ☐ Rarely   ☐ Sometimes   ☐ Often   ☐ Always

S4. Can you straighten your knee fully?
☐ Never   ☐ Rarely   ☐ Sometimes   ☐ Often   ☐ Always

S5. Can you bend your knee fully?
☐ Never   ☐ Rarely   ☐ Sometimes   ☐ Often   ☐ Always

Stiffness

The following questions concern the amount of joint stiffness you have experienced during the last week in your knee. Stiffness is a sensation of restriction or slowness in the ease with which you move your knee joint.

S6. How severe is your knee joint stiffness after first wakening in the morning?

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

S7. How severe is your knee stiffness after sitting, lying or resting **later in the day?**

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

Pain

P1. How often do you experience knee pain?

☐ Never   ☐ Monthly   ☐ Weekly   ☐ Daily   ☐ Always

What amount of knee pain have you experienced the last week during the following activities?

P2. Twisting/pivoting on your knee

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

P3. Straightening knee fully

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

P4. Bending knee fully

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

P5. Walking on flat surface

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

P6. Going up or down stairs

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

P7. At night while in bed

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

P8. Sitting or lying

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

P9. Standing upright

☐ None　　　　☐ Mild　　　　☐ Moderate　　　　☐ Severe　　　　☐ Extreme

Function, daily living

The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A1. Descending stairs

☐ None　　　　☐ Mild　　　　☐ Moderate　　　　☐ Severe　　　　☐ Extreme

A2. Ascending stairs

☐ None　　　　☐ Mild　　　　☐ Moderate　　　　☐ Severe　　　　☐ Extreme

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A3. Rising from sitting

　A3-K. Rising from floor

☐ None　　　　☐ Mild　　　　☐ Moderate　　　　☐ Severe　　　　☐ Extreme

　　A3-W. Rising from chair/sofa

☐ None　　　　☐ Mild　　　　☐ Moderate　　　　☐ Severe　　　　☐ Extreme

A4. Standing

☐ None　　　　☐ Mild　　　　☐ Moderate　　　　☐ Severe　　　　☐ Extreme

A5. Bending to floor/pick up an object

☐ None　　　　☐ Mild　　　　☐ Moderate　　　　☐ Severe　　　　☐ Extreme

A6. Walking on flat surface

☐ None　　　　☐ Mild　　　　☐ Moderate　　　　☐ Severe　　　　☐ Extreme

A7. Getting in/out of car

☐ None　　　　☐ Mild　　　　☐ Moderate　　　　☐ Severe　　　　☐ Extreme

A8. Going shopping

☐ None　　　　☐ Mild　　　　☐ Moderate　　　　☐ Severe　　　　☐ Extreme

A9. Putting on socks/stockings

☐ None　　　　☐ Mild　　　　☐ Moderate　　　　☐ Severe　　　　☐ Extreme

A10.   Rising   from   bed

(In either occidental or oriental manner, tick the box that you are currently utilizing in your daily life. If the both method are applicable, please tick the both section)

A10-K. Rising from floor bedding

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A10-W. Rising from bed

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A11. Taking off socks/stockings

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A12. Lying in bed (turning over, maintaining knee position)

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A13. Getting in/out of bath

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A14.   Sitting

(In either occidental or oriental manner, tick the box that you are currently utilizing in your daily life. If the both method are applicable, please tick the both section)

A14-K Sitting on floor

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A14-W Sitting on chair/sofa

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A15.   Getting   on/off   toilet

(In either occidental or oriental manner, tick the box that you are currently utilizing in your daily life. If the both method are applicable, please tick the both section)

A15-K Getting on/off from Conventional toilet

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A15-W Getting on/off from toilet bowl

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

For each of the following activities please indicate the degree of difficulty you have experienced in the last week due to your knee.

A16. Heavy domestic duties (moving heavy boxes, scrubbing floors, etc)

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

A17. Light domestic duties (cooking, dusting, etc)

☐ None   ☐ Mild   ☐ Moderate   ☐ Severe   ☐ Extreme

Function, sports and recreational activities

The following questions concern your physical function when being active on a higher level. The questions should be answered thinking of what degree of difficulty you have experienced during the **last week** due to your knee.

SP1. Squatting

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

SP2. Running

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

SP3. Jumping

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

SP4. Twisting/pivoting on your injured knee

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

SP5. Kneeling

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

Quality of Life

Q1. How often are you aware of your knee problem?

☐ Never ☐ Monthly ☐ Weekly ☐ Daily ☐ Consistently

Q2. Have you modified your life style to avoid potentially damaging activities to your knee?

☐ Not at all ☐ Mildly ☐ Moderately ☐ Severely ☐ Totally

Q3. How much are you troubled with lack of confidence in your knee?

☐ Not at all ☐ Mildly ☐ Moderately ☐ Severely ☐ Extremely

Q4. In general, how much difficulty do you have with your knee?

☐ None ☐ Mild ☐ Moderate ☐ Severe ☐ Extreme

3. Health Questionnaire

EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today..

Mobility	
I have no problems in walking about.	☐
I have some problems in walking about.	☐
I am confined to bed.	☐
Self-Care	
I have no problems with self-care.	☐
I have some problems washing or dressing myself.	☐
I am unable to wash or dress myself.	☐
Usual Activities (e.g. work, study, housework, family or leisure activities)	
I have no problems with performing my usual activities.	☐
I have some problems with performing my usual activities.	☐
I am unable to perform my usual activities.	☐
Pain/Discomfort	
I have no pain or discomfort.	☐
I have moderate pain or discomfort.	☐
I have extreme pain or discomfort.	☐
Anxiety/Depression	
I am not anxious or depressed.	☐
I am moderately anxious or depressed.	☐
I am extremely anxious or depressed.	☐

EQ-5D Visual Analogue Scale

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0. We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own
health state
today

100 : the best state you can imagine

0 : the worst state you can imagine