

## Natural History of Knee Osteoarthritis and Risk for Arthroplasty: A 5-Year Follow-up Cohort Study

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### Abstract

**Objective:** To identify associating risk factors to total knee arthroplasty and to follow-up pain and function for up to 5 years after completing initial comprehensive rehabilitation.

**Design:** Naturalistic, observational cohort study with exploratory analyses of the impact of knee arthroplasty. Rehabilitation lasting 3 to 6 weeks was provided for 205 patients in a rehabilitation clinic setting. The main outcome measures were the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) and the Short Form 36 Health Survey.

**Results:** At group level, knee pain and function in patients without arthroplasty remained overall stable from mean=50.6, resp. 51.8 points at baseline to 53.3, resp. 52.7 points at the 5-year follow-up on the WOMAC (scale 0-100). In the course of knee osteoarthritis, 23.4% (n=48) of the patients significantly deteriorated in pain and function and was referred for knee arthroplasty. Total knee arthroplasty was associated with female sex (odds ratio=3.04), educated at university level (odds ratio=3.25), minus 1 comorbidity (odds ratio=1.41), and a decrease of 10 (of 100 possible) points on the WOMAC factor ascending/descending stairs (odds ratio=1.51).

**Conclusions:** Highly educated women with a lower number of comorbidities and higher disability to manage stairs were more likely to receive total knee arthroplasty.

**Keywords:** Knee osteoarthritis; Rehabilitation; Arthroplasty; Knee replacement

### What is Known

Studies that assessed mid- to long-term outcome of conservatively managed knee osteoarthritis showed that pain and function seem to be more or less stable in a high percentage of patients. Investigating trajectories of pain and function in a subgroup of patients before arthroplasty of the knee showed that worse pain and function levels were associated with timing of total knee arthroplasty.

### What is New

Worsening on the Western Ontario and McMaster Universities Osteoarthritis Index factor ascending / descending, low number

of comorbidities, female gender and high educational level were identified as significant risk factors for knee arthroplasty.

Osteoarthritis was ranked 11<sup>th</sup> of 289 diseases and injuries in the global burden of disease statistic of the World Health Organization in 2010 [1]. The knee is the most prevalently joint affected by osteoarthritis [1]. Knee osteoarthritis affects mobility, the most important physical function leading to substantial loss of quality of life.

Various treatment options are available to patients with knee osteoarthritis. Conservative non-surgical treatment options include oral medications, local applications, intra-articular joint injections, as well as non-pharmacological therapies including exercise therapy, stretching and physiotherapy [2-4]. A previous study showed that comprehensive rehabilitation, focusing on

active therapy, led to alleviation of knee pain in persons with knee osteoarthritis and a high burden of comorbidities [5]. The short-term effects of a 2-3 week inpatient rehabilitation program (n=164) revealed intra-individually corrected effect sizes from 0.21 to 0.62 for pain and function in knee osteoarthritis. Our former report of preliminary mid-term outcome results (2 years of follow-up) (n=128) recorded uncorrected (i.e. observed) effect sizes from 0.00 to 0.21, but did not stratify into hip and knee osteoarthritis [6]. Studies that assessed mid- to long-term outcome of conservatively managed knee osteoarthritis showed that pain and function seem to be more or less stable in a high percentage of patients for up to 9 years at follow-up (i.e., some studies showed improvement, some worsening) [7-11]. However, when the process of knee osteoarthritis is deteriorating, it would be assumable that this subgroup of patients suffers from increased pain and reduced function, mainly in the phase before arthroplasty. Two studies investigated trajectories of pain and function before arthroplasty of the knee and showed that worse pain and function levels were associated with timing of total knee arthroplasty [8,12]. When conservative treatment fails to relieve pain and reduce activity limitations, total knee arthroplasty is usually considered as an effective option [13]. Quantitative effects of waiting time until knee arthroplasty (for a few subjects >1 year) reflected a deterioration of Effect Sizes (ES) up to -0.15 for pain and -0.32 for function on the Short Form 36 (SF-36) Health Survey and the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), the two main outcome instruments of the present study [14].

The first aim of the present study was to identify further quantifiable risk factors to predict the need for joint replacement surgery. The second aim was to describe the natural course of knee osteoarthritis up to 5 years after completion of initial comprehensive rehabilitation and to compare the outcome to population-based norms.

## Materials and Methods

### Study Design and Ethics

A prospective, naturalistic, observational cohort study with assessments at baseline (admission to the clinic and start of rehabilitation), 1, 2, 3, 4, and 5 years after baseline was conducted. The structure of the study was reported according to the checklist of the STROBE statement for cohort studies (<http://www.strobe-statement.org>). The study was approved by the ethics committee of Aarau, canton Aarau, Switzerland (EK AG 2008/026). All participants gave written informed consent according to the Declaration of Helsinki of 1975, as revised in 1983.

### Setting and Participants

The study was conducted at the rehabilitation clinic RehaClinic (location Bad Zurzach, Switzerland), which is attended by severely disabled patients suffering from several

persistent musculoskeletal pain disorders. The Swiss health insurance companies reimburse comprehensive in- or outpatient rehabilitation on the condition that, after four cycles (each of 9 sessions) of outpatient physiotherapy, patients were still suffering the symptoms of osteoarthritis and required further treatment. From October 2008 to June 2018 patients with unilateral knee osteoarthritis were consecutively admitted to the study. Inclusion criteria were: 1) agreement to participate in the study in the form of written, informed consent and 2) fulfillment of the American College of Rheumatology (ACR) criteria for osteoarthritis [15]: left or right knee pain for more than 25 of the last 30 days, morning stiffness of less than 30 minutes and crepitation in the knee, or pain for more than 25 of the last 30 days and osteophytes on x-rays of the knee indicating knee osteoarthritis. Exclusion criteria were fulfilled if patients 1) had a history of medication abuse (e.g. addiction to opioids or tranquilizers) or non-compliance with outpatient therapies, 2) suffered from a severe illness, 3) had insufficient German language skills [5].

### Intervention

The initial intervention was a 3 week in- or 6 week outpatient program consisting of patient education, individual physiotherapy (mainly strengthening), group therapies (mainly endurance training and swimming with flippers), and various passive therapies (massage, fango packs) and is described in detail elsewhere [5]. At the end of the rehabilitation program patients were motivated to continue conservative treatment interventions in their ambulatory setting at home (instructed, non-supervised home-based exercise). If necessary, further supervised, outpatient treatment series were prescribed by the treating physician in the subsequent course. However, data on subsequent conservative interventions were not collected in this study.

### Measures

Socio-demographic and disease-relevant data as well as comorbidities were assessed as previously described [5,16]. The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) measures pain (5 items), stiffness (2 items), and function (17 items) [17,18]. It is a specific measure for osteoarthritis of the lower limb. Alternative measurement dimensions are provided by the WOMAC factors as obtained by Rasch analysis: lying/sitting, standing/walking, bending, and ascending/descending stairs [19]. The WOMAC factor ascending/descending (4 items) is the most responsive specific functional dimension for knee osteoarthritis and was therefore included in this study [20]. The generic Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) comprehensively measures health-related quality of life on 4 physical health scales (physical functioning, role physical, bodily pain, and general health) and 4 psycho-social scales (vitality, social functioning, role emotional, and mental health) [21]. The Hospital Anxiety and Depression Scale was administered only at baseline

to describe mental health of the cohort and for risk factor analysis [22].

### Data Analysis

Outcome after 5 years after completing initial comprehensive rehabilitation was described by the SF-36 and the WOMAC. On the SF-36, outcome was compared to normative data, which was stratified by sex, 5-year categories of age, and comorbidities (present/absent) from a German population survey (n=6948) [23]. All WOMAC scores were scaled from 0 (maximal pain, no function) to 100 (no pain, maximal function), as in the original SF-36 scoring system, to ease comparison. Further details to analyse the instruments' scales were published in our first study on osteoarthritis [5]. To reduce the amount of data and to improve comprehensiveness of the results, detailed analysis of long-term outcome including all follow-ups was limited on the scales SF-36 bodily pain, SF-36 vitality, WOMAC function, and WOMAC factor ascending/descending. This will give an overview of the most important construct entities. Pain measures demonstrated equal responsiveness on both instruments. Vitality is an important construct to reflect psycho-motoric health. WOMAC function measures global lower limb function more responsively than the SF-36 physical functioning [24]. Pre/post score changes were quantified using the standardized effect size, which is equal to the score at follow-up minus the score at baseline, divided by the group standard deviation of the score at baseline. A positive effect size reflects an improvement and a negative effect size a worsening in health. An effect size of 0.00-0.19 signifies a very small, 0.20-0.49 a small, 0.50-0.79 a moderate, and 0.80 or more a large effect [25].

To model the risk of requiring knee arthroplasty, step-wise, multivariate logistic regression analysis providing odds ratios were

used [26]. The odds ratio quantifies the cross-sectional, relative risk of the frequency of knee arthroplasty with the risk factor (e.g. sex=female) divided by the frequency of knee arthroplasty without the risk factor (e.g. sex=male). The dependent variable was the occurrence of knee arthroplasty (yes/no). The following independent co-variables were tested for significance: sex, age at baseline, living with partner (yes/no), education level, number of comorbidities, baseline depression and anxiety, all baseline scores and all follow-up scores from the last valid observation on the SF-36 and the WOMAC. The co-variables kept in the model were those that changed the fit of the model by a statistically significant increase [26].

Only patients with no missing values for baseline characteristics and with at least 3 measurements until 5 years of follow-up were included. To handle missing data, multiple imputation was performed using the missing data module of Statistical Package for the Social Sciences 23.0 [27]. All analyses were performed using the Statistical Package for the Social Sciences 23.0 for Windows (SPSS Inc., 233 S Wacker Dr, 11<sup>th</sup> Fl, Chicago, IL 60606, USA).

### Results

#### Patients, Baseline Characteristics and Flow through the Study

At baseline, 205 patients with knee osteoarthritis were included (Table 1). During the 5 years follow-up, 149 (72.7%) patients without surgical intervention were examined until the end of the observation period, 48 (23.4%) patients underwent knee arthroplasty, and 8 patients died in the course of the study. Of the 48 knee arthroplasties, 34 (70.8%) were implanted in the first 3 years.

Follow-up (years)	0	1	2	3	4	5
No knee arthroplasty	205	188	177	166	159	149
Knee arthroplasty		16	9	9	7	7
Death		1	2	2		3

**Table 1:** Flow of patients through the study (n = 205).

Sociodemographic and disease-relevant data are shown in Table 2. Baseline characteristics between groups with future knee arthroplasty and no knee arthroplasty were comparable except for sex and education level: future knee arthroplasty patients were more frequently female and higher educated.

	<b>No knee arthroplasty</b> (n=157)	<b>Future knee arthroplasty</b> (n=48)
Female (%)	73.9	87.5
Living with partner (%)	61.8	64.6
Education (%)		
Basic school (8-9 years)	42.0	18.8
Vocational training	46.5	54.2
College/high school/university	11.5	27.1
Comorbidities (%)		
none	0.6	0.0
1	04.5	10.4
2	19.7	14.6
3	26.1	35.4
≥4	49.1	39.6
Age (years; m±s)	65.4±10.8	66.4±08.7
HADS depression (m±s)	06.9±04.2	07.0±04.4
HADS anxiety (m±s)	06.0±03.5	05.9±04.2
m: mean; s: standard deviation; HADS: Hospital Anxiety and Depression Scale (range: 0=best; 21=worst).		

**Table 2:** Baseline characteristics of the study populations.

### Health Status in the Natural Course

Table 3 shows the score changes in the SF-36 and WOMAC in the 157 patients with conservatively managed knee osteoarthritis scores at the 6 time points. In general, all SF-36 and WOMAC scales showed only minimal changes in scores between baseline and 5-year follow-up. Compared to the population norms, most SF-36 scores were significantly lower (most  $p < 0.001$ ; data not shown in detail) at baseline and at all 5 follow-up time points with only a few exceptions on SF-36 general health, mental health and the mental component summary.

<b>Years follow-up</b>	<b>Norm (m)</b>	<b>0</b>	<b>1</b>	<b>2</b>	<b>3</b>	<b>4</b>	<b>5</b>
SF-36							
Physical functioning	68.1	35.7±19.4	37.5±21.7	37.6±24.1	36.2±24.6	33.3±26.0	33.2±24.2
Role physical	63.8	16.7±27.9	31.4±40.5	29.6±38.6	24.4±36.1	20.0±39.7	20.3±37.5
Bodily pain	49.9	23.9±15.9	34.8±18.9	35.0±20.0	36.4±25.7	33.1±23.6	32.9±21.8
General health	53.6	52.2±18.4	49.9±18.1	51.3±18.0	48.1±20.6	49.4±20.1	47.1±18.3
Vitality	52.7	40.1±20.4	43.7±19.2	43.2±21.0	41.6±23.9	42.4±20.4	41.2±22.4
Social functioning	79.3	63.5±28.9	64.4±34.6	61.9±27.4	64.1±27.8	59.3±28.0	56.3±24.6
Role emotional	79.5	48.3±45.6	50.8±42.4	57.9±46.5	55.3±47.7	47.0±47.6	48.0±48.6
Mental health	66.9	61.5±21.1	63.6±17.9	62.3±21.3	63.0±21.8	60.8±18.9	61.7±19.3
Physical component summary	40.4	30.8±06.9	33.4±07.9	33.2±09.6	32.3±09.4	31.8±09.9	31.4±09.2

Mental component summary	49.7	46.0±13.2	46.3±11.4	46.6±12.9	46.8±13.4	45.1±12.0	45.0±12.1
WOMAC							
Pain	NA	50.6±20.6	58.2±24.1	55.9±27.0	57.7±25.6	56.6±24.9	53.3±24.7
Stiffness	NA	48.7±24.1	52.3±22.0	51.3±27.7	52.5±27.1	52.3±27.9	49.2±28.7
Function	NA	51.8±20.4	54.6±20.6	52.8±28.1	53.3±27.3	53.9±24.6	52.7±24.0
Global	NA	51.3±19.6	55.2±20.3	53.3±26.8	54.1±26.2	54.3±24.1	52.5±23.4
Factor ascending / descending stairs	NA	35.1±21.4	44.0±23.0	40.9±29.1	42.0±31.8	42.3±27.1	41.2±25.8
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index (range: 0=worst; 100=best); SF-36: medical outcomes study 36-item short form health survey (range: 0=worst; 100=best); NA: Not Applicable.							

**Table 3:** Natural history of conservatively managed knee osteoarthritis (mean score±standard deviation; n=157).

### Differences in Outcome Between Patients with and without Knee Arthroplasty

Table 4 shows the changes in scores of the 48 patients who received knee arthroplasty, and of the patients who were not referred for knee arthroplasty (n=157), at their individual last time point of follow-up before knee arthroplasty. Differences in scores at baseline of the WOMAC and SF-36 were not statistically significant (p=0.426 to 0.849; data not shown in detail). Mean WOMAC scores before arthroplasty were respectively 37.6 for function and 39.2 for pain: a difference of >10 points compared to the non-surgery group. As a result, in the knee surgery group, the effect sizes of the WOMAC scales pain and function significantly worsened (effect size=-0.42, resp. -0.54) at their last follow-up before surgery. In contrast to that, the other patients remained stable at their last follow-up (effect size=0.07 and -0.06). The score changes of the two groups were highly statistically significant on both scales. On SF-36 role physical, general health, and social functioning, the corresponding effects were close to zero reflecting stable outcomes and were not different between the two groups.

Variable	Knee arthroplasty (n = 48)			No knee arthroplasty (n = 157)			P
	m±s at baseline	m±s at last follow-up before surgery	ES	m±s at baseline	m±s at last follow-up after 5 year	ES	
WOMAC pain	49.2±23.5	39.2±24.2	-0.42	50.6±20.6	52.5±22.9	0.07	0.001
WOMAC function	48.7±20.6	37.6±22.7	-0.54	51.8±20.4	49.9±23.6	-0.06	0.002
SF-36 role physical	15.1±27.2	17.2±31.0	0.08	16.7±27.9	20.2±33.6	0.15	0.539
SF-36 general health	53.8±22.5	49.6±20.9	-0.19	52.2±18.4	49.1±18.5	-0.20	0.797
SF-36 social functioning	62.2±28.3	60.4±31.7	-0.07	63.5±28.9	58.8±27.1	-0.15	0.666
m: mean score; s: standard deviation; ES: effect size; P: significance level; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index (range: 0=worst; 100=best); SF-36: medical outcomes study 36-item short form health survey (range: 0=worst; 100=best).							

**Table 4:** Comparison of change of outcome over time between patients with and without knee arthroplasty.

### Risk Factors for Knee Arthroplasty

The step-wise, multivariate logistic regression model ultimately showed 4 statistically significant risk factors for knee arthroplasty, explaining 24.8% of the variance (Table 5). Female gender and a high educational level (i.e. at a college, high school or university level) both increased the risk of becoming referred for knee arthroplasty by 3.04 to 3.25 fold. Requiring total knee arthroplasty was also statistically significantly associated with minus 1 comorbidity (odds ratio=1.41). Finally, a deterioration of 10 points at the last follow-up on the WOMAC scale ascending / descending stairs increased the risk of being referred for knee surgery by 51%.



Risk factor	Odds ratio (95% CI)	<i>p</i>	<i>R</i> <sup>2</sup>
Sex female	3.04 (1.09 to 8.54)	0.034	0.248
High educational level	3.25 (1.25 to 8.47)	0.017	
Minus one comorbidity	1.41 (1.08 to 1.84)	0.013	
WOMAC asc/desc at last FU: 10 score points lower	1.51 (1.26 to 1.80)	<0.001	

95% CI: 95% Confidence Interval; *p*: significance level; *R*<sup>2</sup>: explained variance of logistic regression attributed to Nagelkerke; WOMAC asc/desc at last FU: Western Ontario and McMaster Universities Osteoarthritis Index factor ascending / descending stairs score at last follow-up.

**Table 5:** Risk of being referred for knee arthroplasty.

## Discussion

This study showed that the natural course in patients with unilateral knee osteoarthritis after initial comprehensive in- or outpatient rehabilitation at group level remains overall stable in pain and function that lasts up to the 5-year follow-up. However, in the course of this degenerative disease about one quarter of the patients (23.4%) significantly deteriorated and was referred for knee arthroplasty. The WOMAC scales pain and function successfully screened for worsening at the last follow-up time point before surgery. Finally, female gender, high educational level, low number of comorbidities and a worsening of the WOMAC factor ascending / descending at the last follow-up were identified as significant risk factors for knee arthroplasty.

After the first year, health state improved in all dimensions of the SF-36 (except general health) and the WOMAC. Those improvements partly declined in the further course, therefore, at the 5-year follow-up most of the SF-36 and WOMAC scales were comparable to their original baseline scores. While short-term improvements might be attributed to the initial rehabilitation interventions, it is unlikely that the outcome after 5 years still can be explained by the initial comprehensive rehabilitation in a substantial amount. However, it is interesting how stable the patients in the conservatively treated group stayed in pain and function over the 5-year course of the degenerative condition of knee osteoarthritis. This finding is in accordance with the results of other studies [9,28].

The results of this study on risk factors for being referred to knee arthroplasty are overall in line with the results of the systematic review and meta-analysis by de Rooij and colleagues [29]. They found strong evidence for a number of prognostic factors predicting deterioration in pain, e.g. higher knee pain at baseline and depressive symptoms, and for prognostic factors predicting deterioration in physical functioning, e.g. worsening of knee pain and higher comorbidity count. However, sex and demographics did not predict pain and function in their review as it did in our data. In the cohort study of Gademán, et al. the 84 patients receiving arthroplasty were somewhat older at baseline

and had worse WOMAC pain and function scores compared to the patients without arthroplasty [8]. These baseline differences could not be replicated in our study. However, mean WOMAC scores of the Gademán study and our study before arthroplasty were comparable: respectively 43.5 and 37.6 for function and 45.2 and 39.2 for pain. In the Gademán study, irrespective of receiving arthroplasty or not, about two-thirds of patients showed at least one period of deterioration of pain/function ( $\geq 10$  points WOMAC subscale) at the annual follow-up [8]. In contrast to these results, the non-surgery patients in the present study did not report a period of deterioration in the course of the 5-year follow-up. Only the arthroplasty patients experienced significantly increased pain and decline in function in the immediate year before arthroplasty. A possible explanation might be that at baseline the cohort of Dutch patients in the Gademán study had early osteoarthritis symptoms at a rather early disease stage. In contrast, in the present Swiss cohort, the study participants suffered at baseline from disabling osteoarthritis symptoms and had been referred for interprofessional rehabilitation. This may be further illustrated by the fact that during the 9-year follow-up about 10% of patients in the Gademán study received arthroplasty in contrast to almost 25% within 5-year follow up in our setting [8].

We found that highly educated women with less comorbidities have a higher risk of undergoing knee arthroplasty. Highly educated patients may follow the postoperative regimen better, which may be a possible reason for positive selection for surgery by the orthopaedic surgeons. Patients with a higher level of education may also be more demanding with regard to eliminating impairment by joint surgery. Less comorbidities preoperatively might reduce the risks to patients who can be expected to achieve favourable long-term postoperative outcomes. On the other hand, patients with more severe pain, more comorbidities, and higher functional restrictions, have a worse prognosis 1 to 2 year after knee arthroplasty [30].

Not only for research purposes, but also in clinical care, the WOMAC is a reliable and valid instrument for the assessment of symptoms and physical functional disability in patients with knee

osteoarthritis [17]. Since it only takes 5-10 minutes to fill out the questionnaire, it is a practical tool in daily clinical practice. In our study, the WOMAC scales pain and function were able to identify predictively those patients who would or would not undergo arthroplasty. For these reasons, the WOMAC, applied for monitoring on a regular base, may serve in clinical care as a tool to early detect patients at risk for surgery.

Strengths of the study were the large number of patients, length of follow-up and the use of well-validated assessment tools.

### Study Limitations

As we did not have data on subsequent conservative interventions like for example knee injections, medication, hydrotherapy, changing habits or lifestyle and continued ambulatory exercise therapy, change of outcome over time cannot be attributed to the initial comprehensive rehabilitation.

### Conclusions

Over a period of 5 years after an initial rehabilitation intervention, patients with knee osteoarthritis were followed up over the course under conservative management or until the time point of knee arthroplasty. The WOMAC was able to specify condition-specific health between these two groups at the last possible follow-up. Risk factors were identified that were highly relevant to referral to knee arthroplasty. Finally, knee pain, function and psychosocial health remained overall stable in the conservative treated patients up to 5 years.

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