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IP International Journal of Orthopaedic Rheumatology

Journal homepage: www.ijor.org

Review Article

Disease activity and flares after total knee arthroplasty in rheumatoid arthritis - Systematic review

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ARTICLE INFO

Article history:
Received 07-12-2022
Accepted 23-12-2022
Available online 23-01-2023

Keywords:
Rheumatoid arthritis
Total knee arthroplasty
Knee

ABSTRACT

Introduction: Despite the continuous therapeutic development of biological DMARDs which has delayed disease progression in Rheumatoid arthritis, joint destruction is inevitable and end-stage arthritis remains the ultimate outcome, following which surgical intervention becomes a necessity. Controversy still exists about the systemic effects following Total Knee Arthroplasty (TKA) on patients in terms of disease activity and flares during the peri-operative period since most patients present with varying levels of disease activity at the time of surgery. The objective of this review is to determine the influence of TKA on longitudinal disease activity and flares in patients with rheumatoid arthritis and to determine its influence on quality of life, laboratory parameters, and medication requirement during the peri-operative period and subsequent long-term follow-ups.

Materials and Methods: A complete search was conducted according to the PRISMA guidelines in Pubmed/MEDLINE, Scopus, Google Scholar, Web of Science electronic databases and trial registries on disease activity or flares in patients suffering from rheumatoid arthritis after total knee replacement in September 2022. A total of 16 studies were identified for final review. Flares (RA-FQ), DAS-28, CDAI, mHAQ, ESR, CRP and medication requirement were evaluated in serial follow-ups before and after TKA.

Results: Majority of the studies show confirm that a combination of TKA and pharmacological therapy can achieve better therapeutic effects and maintain disease activity at low/ remission levels in patients with end stage rheumatoid arthritis. Patients with high disease activity during the perioperative period are less compliant to rehabilitation and physiotherapy, thereby affecting their overall function scores and satisfaction with the procedure and are found to be more prone to flares.

Conclusion: TKA is found to reduce overall disease activity in RA and reduce the need for medication requirement. However, patients with a high disease activity pre-operatively remain at risk for flares and are unable to reach remission levels of activity after TKA and require supplemental long term pharmacological therapy thereby highlighting the need for adequate pre-operative optimization.

1. Introduction

Rheumatoid arthritis is a chronic inflammatory disease known to affect multiple synovial joints in the body characterized by synovitis and bone resorption.[1,2] In the last few decades, despite the continuous therapeutic development of biological DMARDs which has delayed disease progression, joint destruction is inevitable and end-stage arthritis remains the ultimate outcome, following which surgical intervention becomes a necessity.[3,4] Knee remains the most commonly affected large joint in patients with RA, and synovectomy and Total knee arthroplasty

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https://doi.org/10.18231/j.ijor.2022.016

(TKA) both have been shown to be effective surgical options that offer relief which are mainly aimed at targeting sites of TNF production such as the synovium and the damaged articular cartilage However, since even degenerative articular cartilage can also produce TNF, Total Knee Arthroplasty (TKA) which address both sites remains the superior choice and remains the most effective solution in improving quality of life for these patients with symptomatic end-stage joint damage.[5,6] Controversy still exists about the systemic effects following TKA on patients in terms of disease activity and flares during the peri-operative period since most patients present with varying levels of disease activity at the time of surgery. Most patients are on multiple drugs with varying drug regimens and dosages during the peri-operative period and their effects on disease activity are largely unstudied and remain a grey area in rheumatology.[7–13] Hence, the objective of this review is to determine the influence of total knee arthroplasty on longitudinal disease activity and flares in patients with rheumatoid arthritis and to determine the influence of TKA on quality of life, laboratory parameters, and medication requirement during the peri-operative period and subsequent long-term follow-ups.

2. Materials and Methods

A complete search was conducted according to the PRISMA guidelines[14] in Pubmed/MEDLINE, Scopus, Google Scholar and Web of Science electronic databases on disease activity or flares in patients suffering from rheumatoid arthritis after total knee replacement in September 2022 as mentioned in Figure 1.

Trial registers that were searched include US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov/), the World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch/), and the EU Clinical Trials Register (www.clinicaltrialsregister.eu/), and Clinical Trials Registry - India (CTRI) in order to identify registered trials.

We included all studies including retrospective and prospective studies, RCTs and previous systematic reviews or meta-analysis. As there were no randomized control trials or meta-analysis that were found on the subject, they were not included in the study. Our search was not limited by language or year of publication.

The search strategies employed were as follows:

1. (Rheumatoid Arthritis) And (Rheumatoid Arthritis) And (Total Knee) And (Flares Or Activity) which had 456 results.
2. (((Rheumatoid Arthritis) Or (Flares)) Or (Disease Activity)) And (Total Knee Arthroplasty) which had 2,298 results.
3. (((Rheumatoid Arthritis) Or (Flares)) And (Disease Activity)) And (Total Knee Arthroplasty) which had 89 results.

Inclusion criteria were established following the PICO (Population, Intervention, Comparison, and Outcomes) approach:

Population: Patients suffering from arthritis of the knee due to rheumatoid arthritis. Intervention = patients undergoing total knee arthroplasty. Outcomes = disease flares and disease activity. Overall odds ratios (ORs) and associated 95% confidence intervals (CIs) for pooled effects were calculated.

Types of participants: Patients of all age groups suffering from rheumatoid arthritis as per the EULAR/ ACR 1987 or 2010 criteria were considered.[15,16] All patients undergoing total knee arthroplasty irrespective of their medication regimen (DMARDs, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids) and irrespective of their pre-operative disease activity score were included in the study. Patients having undergone previous surgical procedures (Osteotomies, soft tissue procedures and joint replacements) were also included. We excluded patients with other rheumatic diseases such as systemic lupus erythematosus, ankylosing spondylitis, psoriatic arthritis and crystalline arthropathies.

Disease activity was measured using simplified disease activity index (SDAI), Disease Activity Score in 28 joints (DAS28), Disease Activity Score (DAS), Clinical Disease Activity Index (CDAI), Routine Assessment of Patient Index Data 3 (RAPID-3), RA Disease Activity Index (RADAI), Modified Health Assessment Questionnaire (mHAQ) or Simplified Disease Activity Index (SDAI). Flares were assessed using Rheumatoid arthritis flare questionnaire (RA-FQ).

Our primary outcome was to assess the disease activity using either disease indices or patient reported outcome of flares at different stages of follow-up post-TKA. Low disease activity state was defined by clinical judgement of rheumatologist or disease activity score in 28 joints (DAS28) < 3.2; DAS < 2.4; CDAI < 10 or SDAI <11. Disease remission was defined by DAS28 < 2.6; DAS < 1.6; CDAI < 2.8; SDAI < 3.3 as per ACR/European League Against Rheumatism (EULAR) remission criteria.

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3. Results

Summary statistics of studies are shown in tables 1 to 4.

Goodman et al[17] in their study showed that the median time after surgery for a flare-up was 2 weeks and the flare usually lasted 4-7 days and was rated severe (> 7/10) in 36% patients. They also observed that flarers had higher baseline disease activity, higher DAS28, higher CDAI, RAPID-3, number of tender joints and RADAI joint score

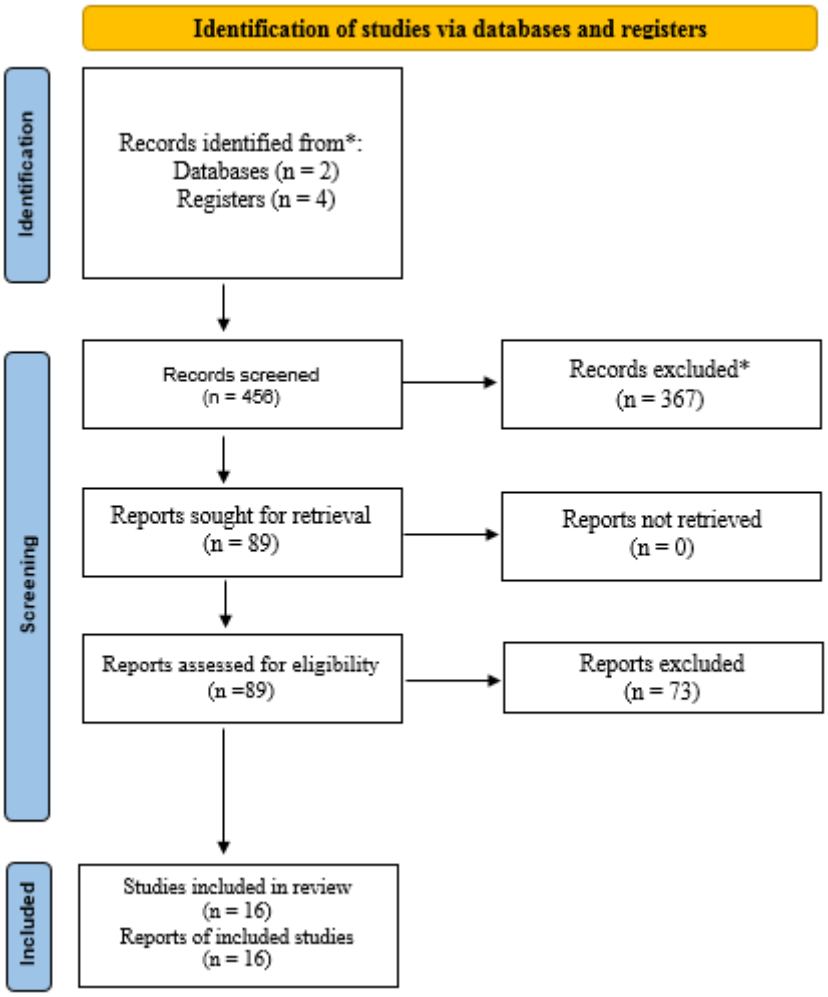

Fig. 1: PRISMA flowchart of included studies

pre-operatively. They also found that MD-HAQ was more at baseline and 6 weeks for flarers which was found to be significant. (mean 4.1; flarers vs 3.4; non-flarers, p = 0.009) and 6 weeks (median 3.7 vs 2.7, p = 0.002) respectively. Patients with higher baseline disease activity (>5.1) as measured by DAS28 had a 25 times higher chance of developing flare withing 6 weeks post-surgery when compared to patients with low baseline activity. (≤ 2.6) (p = 0.003). On multivariate analysis, DAS28 (OR 2.11, p = 0.015), increasing levels of CRP (OR 4.24, p = 0.035) and log-transformed RADAI joint score (OR 2.97, p = 0.023) were found to be independent predictors for risk of flare post-operatively. There was found to be no statistical association between disease duration, baseline medication use or intra-operative steroid use on determining post-operative disease flare and they also showed that stopping the use of bDMARDS for more than 2 dose intervals prior to surgery did not increase flare risk and use of MTX peri-operatively did not reduced flare risk.

Goodman et al[18] showed that baseline DAS28 was found to influence function at the end of 1 year post-TKA, and each 1 unit increase in DAS28 worsened 1 year pain by 2.41 (SE=1.05, p=.02) as measured using HOOS/KOOS. Flarers were found to have higher baseline disease activity (non-flare 3.07 ± 1.04 vs. flare 3.88 ± 1.29, p=0.0002) as measured using DAS28 and were also found to have worse HOOS/KOOS pre-operatively for pain (non-flare 46.56 ± 20.43 vs. flare 33.22 ± 16.50; p=0.004) and function (non-flare 51.98 ± 22.88 vs. flare 39.73 ± 16.87; p=0.02). at the 1-year follow-up they showed

Kumagai et al,[19] in their study showed that RA disease activity decreased significantly after TKA. They measured DAS28-CRP, CDAI and CRP both pre-operatively and on serial follow-ups and showed that disease activity reduced and maintained upto 2 years after TKA (p<0.05). Post operative knee function improved significantly post TKA which was assessed using KSS, JOA scores (p<0.05). they correlated both functional scores with disease activity and

found a significant correlation between disease control status and knee function but did not find any significant correlation between CRP levels and knee scores.

Oh et al,[10] in 48 lower limb surgeries showed that there was statistically significant improvement in DAS28-ESR and serum CRP after surgery at 12 months follow-up, but mHAQ did not show any improvement. Patients were further stratified into high-activity (poorly controlled) and low-activity (well controlled/ remission) group and they found that patients with high disease activity showed significant improvement in DAS28-ESR (Pre-op: 4.53; 12m: 3.71) but only 31.3% were able to reach remission/ low-activity levels; whereas 82.6% patients in the low-activity group were able to maintain remission levels 12 months after surgery and they also showed significant improvement with surgery (Pre-op: 2.5; 12m: 2.51)

Yano et al,[9] evaluated 130 patients undergoing TKA with serial follow-ups up to 3 years. They found that DAS28 decreased in all patients post-TKA both at 6 months and 3 year follow-ups, but systemic reduction in disease activity was observed only in the moderate and high disease activity groups and was not statistically significant in the low disease activity group. In the high activity group, both SJC28 and TJC28 showed statistically significant improvement thereby confirming the systemic effect of TKA on systemic disease activity. Further, they analysed DAS levels 1 year prior to TKA and subsequent follow-ups and that there was no difference in DAS between 1 year prior to immediately before TKA, however post-TKA all subgroups (low, moderate, and high activity) showed significant reduction in DAS scores.

Nishikawa et al,[20] in their study on 10 year follow-up post-TKA, showed that among 30 patients who were operated, DAS28-CRP levels at final follow-up had 10 patients in remission and 11 and 9 patients with low and moderate disease activity respectively and none of the patients had high activity. tender joint counts were 0.1±0.4, 1.0±0.7, and 1.4±0.7; swollen joint counts were 0.2±0.6, 0.1±0.3, and 0.3±0.5; CRP levels were 0.21±0.19, 0.68±1.09, and 0.72±1.24 mg/dl; in remission, low and moderate activity groups respectively.

Yasui et al,[21] in their study on predictive factors for TKA in RA, showed that when compared to patients who did not undergo TKA during the course of 1 year, those who presented with knee involvement (64% vs. 23%), high Steinbrocker stage (III/IV), higher initial DAS28 scores (5.17 vs. 4.10), higher CDAI (22.6 vs. 14.0), and mHAQ (1.00 vs. 0.60) underwent TKA. Morse et al,[22] showed that the main determinants influencing length of hospital following joint arthroplasty (THA/TKA) using multivariate analysis were blood transfusion after surgery, female sex, TKA, pre-operative opioid usage; all of which were found to significantly increase duration of hospital stay.

Yamashita et al,[23] in their study with average follow-up of 10.6 years post-TKA showed that the cumulative survival rates were 98.9%, 98.4%, and 96.6% at 5 years, 10 years and at 15 years respectively. Hayashi et al,[8] in their study on 45 patients undergoing major joint replacement noted that mean DAS28-ESR 1 year before surgery to baseline values before surgery were same (4.08 ± 0.89 and 4.32 ± 0.99, P = 0.1496) and the 1 year post-operative value showed significant reduction (3.35 ± 0.93, P = 0.0007)

3.1. Medication requirement

Kumagai et al[19] in their study showed that the mean dose of methotrexate (Pre-op: 7.9 ± 3.1 vs. Post-op 2 years: 7.5 ± 3.1) and prednisone (Pre-op: 4.4 ± 2.3 vs. Post-op 2 years: 4.2 ± 2.9) did not change after surgery. Iwata et al,[24] patients divided into a low disease activity (well-controlled) group (n = 43) and a high disease activity (poorly controlled) group (n = 127) preoperatively, predisone usage in the well-controlled group showed a significant reduction in the average dose at 6 and 12 months postoperatively ($p < 0.01$ for both), while the poorly controlled group showed no significant difference. MTX showed no relation with disease activity and dose continued to remain same after surgery.

Momohara et al,[7] in 333 TKAs showed that although there was a trend towards decrease in prednisolone dose with disease activity, there was no statistical significant association. Nishikawa et al,[20] in their study on disease activity at 10 years follow-up post-TKA showed that among 30 patients, 13 patients discontinued the use of steroid, however the use of MTX increased from 4 to 20 patients and mean dose increased from 3.9 to 6.3 mg/week, both of which were found to be highly significant. Patients drug regimen changes include addition of mizoribine (1 to 4 patients), tacrolimus (0 to 14), combination DMARDs (4 to 17) and biologicals (0 to 4 patients)

Cunha et al,[25] in their study on patients undergoing hip and knee arthroplasty in the brazilian population showed using multiple regression analysis that among all other factors, "maximum dose of MTX' was the only one which had a positive correlation with CDAI. Hayashi et al[8] showed that using biological agents reduction in DAS28 score at 1 year follow-up after TKA reduced from 4.32 to 3.35 which was superior to the study by Yano et al[9] on 130 TKAs where reduction was from 4.85 to 3.97 with majority of the patients using cDMARDs. They concluded stating that biologicals (anti-TNF) agents not only restore joint damage but also attenuate systemic RA activity.

4. Discussion

Rheumatoid arthritis is known to have a varied course, ranging from mild self-limiting disease to rapidly progressive joint destruction. The knee being the most commonly affected large joint due to rheumatoid arthritis

Table 1: Demographic and baseline characteristics

Variable	Level	Goodman et al. (risk factors)	Goodman et al (Flares)	Kumagai et al	Iwata et al	Momohara et al	Oh et al	Yano et al	Nishikawa et al	Yasui et al	Cunah et al	Morse et al	Yamashita et al	Hayashi et al
Number		67	Total- 122 THA- 56 (46%) TKA- 66 (54%)	76	Total- 79 TKA- 47; THA- 22; ankle- 10;	TKA- 333	Total- 48 TKA- 21; THA- 8; Others- 19	130	42	76	32 TKA- 19 THA- 17	252 TKA- 146 THA- 106	142 (201 knees)	Total- 45 TKA- 35; THA- 19; ankle-1
Age	Mean ± SD	62.5 ± 9.1	61.5 ± 11.35	67.1 ± 8.9	65.2	59.04 ± 11	61.2	58.49 ± 10.82	59.9	61.2 ± 9.7	59		66.0 ± 10.6	57.91 ± 12.74
Sex	Female N(%)	59 (88%)	104 (85%)	61 (80.2%)		295 (88.5%)	45 (93.75%)		26 (86.6%)	69 (90.7%)	28 (87.5%)		185 (92%)	37 (82.2%)
BMI	Mean ± SD					21.57 ± 3.33							21.5 ± 3.7 (15.3e38.5)	
Race	White	50 (77%)	98 (80%)									186 (73.8%)		
	Asian	0		76 (100%)	79 (100%)	333 (100%)	48 (100%)	130 (100%)		76 (100%)		6 (2.4%)		
	Others- (Black/Hispanic)	8 (12%)	24 (20%)								32 (100%)	60 (23.8%)		
Medications	None cDMARDs	51	Non-Flarers- 26 (53.06%) Flarers- 35 (52.24%)	65 (85.5%)		105 (31.53%)		119 (91.53%)	21 (70%)	36 (47.3%)	27 (84.3%)	117 (48.8%)	116 (82%)	34 (77.6%)

Table 1: Continue

	bDMARDs	36 (55%)	Non-Flarers-22 (44.9%) Flarers-36 (53.73%)	13 (17.1%)		48 (100%) Infliximab: 25, Etanercept: 12; Tocilizumab: 9, Adalimumab: 1	2 (1.53%)		18 (23.6%)	8 (25%)	128 (53.6%)	24 (22%)	45 (100%)
	Steroids	55 (87%)	Non-Flarers-17 (34.69%) Flarers-28 (41.79%)	45 (59.2%)	81 (24.32%)		105 (80.76%)	18 (60%)	60 (78.9%)		87 (36.1%)	109 (79%)	26 (58.6%)
Labs	RA factor positive	32 (48%)	Non-flarers-20 (41.67%) Flarers-26 (38.24%)		193.49 ± 451	141.05 ± 248.17	80 (61.53%)			51%			
	Anti-CCP positive	33 (49%)	Non-flarers-35 (71.43%) Flarers-46 (67.65%)							62%			
	CRP (mg/dl)	1.2 (0.0–2.5)	NA	≈3	2.18 ± 2.22	1.44 ± 2.03	2.21 ± 2.05	2.63			1.7 ± 2.5	3.70 ± 3.53	1.71
	ESR (mm/h)	15.0 (7.0–31.0)	NA		50.47 ± 27.46	37.57 ± 25.26	48.9 ± 24				20.4 ± 19.7	56.8 ± 33.7	40.3

Table 2: Pre-operative status

Variable		Goodman et al. (risk factors)	Goodman et al (Flares)	Kumagai et al	Iwata et al	Momohara et al	Oh et al	Yano et al	Nishikawa et al	Yasui et al	Cunah et al	Morse et al	Yamashita et al	Hayashi et al
Duration of disease	median (IQR)	16.1 (8.9–25.3)				12.97 ± 8.34	12.1	13.87 ± 9.05	12.6	15.3 ± 10.4	20	14.1 ± 12.0	15.3 ± 9.9	13.4
No. swollen joints	median (IQR)	3.0 (1.0–8.0)	Non-flarers- 3.57 ± 3.61 Flarers- 5.43 ± 6.02		3.0 ± 3.4	3.7 ± 4.82		4.25 ± 4.6 Low: 0.69 ± 0.99 High: 7.27 ± 5.3		5.3 ± 6.6			9.7 ± 7.4	
No. tender joints	median (IQR)	1.0 (0.0–5.0)	Non-flarers- 2.77 ± 4.44 Flarers- 3.78 ± 5.23		2.9 ± 3.5			5.18 ± 5.77 Low: 1.08± 1.38 High: 9.6 ± 6.85		3.5 ± 4.7			5.8 ± 6.4	
Flare status at baseline	yes	39 (58%)	37 (54.41%)											
DAS28-ESR	Mean ± SD	3.8 ± 1.5	Non-flarers- 3.07 ± 1.04. Flarers- 3.88 ± 1.29	≈5 (DAS28-CRP)	4.3 ± 1.2	4.66 ± 1.1	3.71 ± 1.19 Low: 2.5 High: 4.53	4.85 Low: 2.86 High: 5.79		5.17 ± 1.17		3.7 ± 1.3		4.32 ± 0.99
CRP				≈3	1.2 ± 1.9	2.18 ± 2.22	1.27 ± 1.96	2.21 ± 2.05	2.63	2 ± 1.8		1.7 ± 2.5		1.71

Table 2: Continue

CDAI	median (IQR)	17.0 (10.0–27.0)		≈22					22.6 ± 14.2	14.7 (0.5–56.4)	18.4 ± 10.9	
MDHAQ	Mean ± SD		Non-flarers- 3.31 ± 1.62 Flarers- 4.11 ± 1.35		1.0 ± 0.7 (mHAQ)	1.48 (J-HAQ)	0.65 ± 0.56 (mHAQ	1.55 ± 0.66 (J-HAQ)	1 ± 0.68	1.8 (0.25–2.875)	3.8 ± 1.7	1.03 ± 0.62
RAPID3	Mean ± SD	16.0 ± 5.0	Non-flarers- 12.77 ± 6.06 Flarers- 17.07 ± 4.09									
RADAI	Mean ± SD	9.0 (4.0–16.0)	Non-flarers- 6.96 ± 5.85 Flarers- 12.26 ± 8.53									
		Median (IQR)										
HOOS/KOOS pain at baseline			Non-flarers- 46.56 ± 20.43 Flarers- 33.22 ± 16.50									
HOOS/KOOS function at baseline		Non-flarers- 51.5 Flarers- 38.3	Non-flarers- 51.98 ± 22.88 Flarers- 39.73 ± 16.87 0.02									
KSS at baseline				≈40								

Table 3: Post-operative disease activity and flare status

		Goodman et al. (risk factors)	Goodman et al (Flares	Kumagai et al (2 years follow-up)	Iwata et al	Momohara et al	Oh et al	Yano et al	Nishikawa et al	Yasui et al	Yamashita et al	Hayashi et al
Flares	Yes No (%)		68 (58.1%) within 6 weeks									
DAS28-ESR				≈2 (DAS28-CRP)	6m: 3.5 ± 1.1 12m: 3.5 ± 1.2	3 yrs: 4.02 5 yrs: 3.94	6m: 3.37 ± 1.22 12m: 3.24 ± 1.05 Low: 12m: 2.51 High: 12m: 3.71	6m: 4.14 3yrs: 3.97 Low: (NS) 6m: 2.75 3yrs: 2.62 High: 6m:4.86 3yrs: 4.37	10yrs: 2.5±0.6 (DAS28-CRP)	12m: 4.48		12m: 3.35 ± 0.93*
TJC28					6m: 1.4 ± 2.1 12m: 1.7 ± 2.8			6m: 4.42 ± 6.1 3yrs: 3.34 ± 4.39	10yrs: 0.9±0.8		1.4 ± 2.6*	
SJC28					6m:1.5 ± 2.0 12m: 1.7 ± 2.4			6m: 3.22 ± 4.26 3yrs: 2.66 ± 3.32	10yrs: 0.2±0.4		3.2 ± 4.2*	
CRP				1			6m: 0.92 ± 1.83 12m: 0.49 ± 1.12	6m: 1.65 ±2.07 3yrs: 1.39 ± 1.7	Final: 0.61		Final (10 yrs): 1.31 ± 2.70*	1m: 1.72 3m: 1.28 12m: 0.9*
CDAI				≈10								
HOOS/KOOS pain at 1 year			Non-flarers-97.20±13.9 Flarers-87.5±20.00		‘							
HOOS/KOOS function at 1 year			Non-flarers-93.35±20.60 Flarers-86.80±20.60									
KSS				≈80					10yrs: 91.0±10.0 KSS function score: 57.0±27.1			
mHAQ					6m: 0.83 12m: 0.79	3 yrs: 1.45 5 yrs: 1.47 (J-HAQ)	6m: 0.65 ± 0.56 12m: 0.54 ± 0.54		10yrs: 0.78±0.67	12m: 0.89	0.85 ± 0.79*	

Table 4: Medication requirement

Medications	Kumagai et al	Iwata et al	Momohara et al	Oh et al	Yano et al	Nishikawa et al	Hayashi et al
DMARDs (MTX)-mg/week	Pre: 7.9 ± 3.1 6m: 7.8 ± 2.9 12m: 7.8 ± 3.3 18m: 7.7 ± 2.9 24m: 7.5 ± 3.1	Pre: 6.6 ± 3.1 6m: 6.9 ± 3.2 12m: 6.8 ± 3.4	Pre: 6.7 ± 3.19		Pre: 4.46 ± 3.66 6m: 4.72 ± 3.58 3yrs: 5.57 ± 3.95*	Pre: 3.9 Post: 6.3 *	Pre: 7
Steroids (PSL)-mg/day	Pre: 4.4 ± 2.3 6m: 3.9 ± 1.8 12m: 4.3 ± 2.5 18m: 3.9 ± 2.9 24m: 4.2 ± 2.9	Pre: 5.2 ± 3.3 6m: 4.8 ± 3.1 12m: 4.6 ± 3.6*	Pre: 5.4 ± 2.69	Pre: 4.4 ± 3.8 12m: 4.1 ± 2.6 (NS)	Pre: 4.01 ± 2.73 6m: 4.12 ± 2.91 3yrs: 3.51 ± 3.05 (NS)	Pre: 5.4 Post: 3.4	Pre: 5.04

commonly needs surgical intervention in the form TKA in end-stage arthritis.

Predictive factors for undergoing TKA in rheumatoid arthritis patients have been analyzed by many authors. Crilly et al[26] claimed higher ESR and positive HLA-DRB1 to be risk factors to determine major joint surgery. James et al,[27] in their study among England hospitals reported lower Hb, higher ESR, higher Larsen stage, higher DAS, and positive HLA-DRB1 to be significant risk factors for undergoing major joint replacement among early RA patients within 5 years.[28] Momohara et al reported higher HAQ score, VAS pain score, and positive RA factor as major risk factors that determine need of joint replacement surgery within next 5 years.[29] Rheumatoid factor (RF) shows no correlation with patient functionality and disease activity as shown in most studies.[25]

Hirsch et al,[29] in their study on racial disparities in 164 patients undergoing arthroplasty, showed using univariate analysis that education level and sex (female) were significant predictors for disease activity ($p<0.05$). Both MDHAQ score (White- 11.6 ± 5.3, Others- 12.3 ± 5.1) and DAS28-ESR score (White- 3.8 ± 1.2, Others- 4.1 ± 1.3) showed no significance difference between races. They concluded that race (white/black/Hispanic) of the patient had no influence on pain, function or disease activity at the time of arthroplasty.

Systemic/ local inflammation is also known to play a vital role in the process of aseptic loosening. Debris generated between bearing surfaces due to friction leads to activation of immune cells which release pro-inflammatory markers (TNF-alpha and IL-6) which are then known to cause osteoclast activation and osteolysis. Bohler et al,[30] in their study on 49 patients who underwent THA/TKA to assess risk of aseptic loosening in RA, showed that disease activity post arthroplasty was a significant determinant of aseptic loosening. Patients in remission were found to have no evidence of radiological loosening and none of them underwent revision surgery for aseptic loosening. They also showed that patients receiving bDMARDs (mainly anti-TNF agents) were at a significantly lower risk of loosening compared to patients on conventional DMARDs. This confirms the role of TNF-alpha in the disease process.

In the recent meta analysis evaluating over 7000 patients from eleven studies by duren et al on the safety and efficacy of bDMARDs, they suggested that bDMARDs may not associated with increased risk of PJI/SSI or wound complications during the perioperative period and recommended their continuation during the course of surgery. They also stated that only 3 (7.3%) of the 41 patients who continued use of bDMARDs experienced disease flares during the post-op period.[31]

The benefits of TKA are associated with the fact that removal of the synovium during the surgery reduces the production of cytokines and enzymes which propagate joint and cartilage destruction.[5] and also replacement of the worn out and degenerated articular cartilage with femoral and tibial components during TKA further reduce disease activity allowing drug efficacy to be restored.[7,9]

Momohara et al,[7] in their study on 333 TKAs which was a continuation of the 3 year follow-up study by Yano et al[9] showed that although J-HAQ scores did not change at 3 years and 5 years post-surgery, DAS28 showed significant improvement after TKA, especially in patients with moderate to high disease activity before surgery. DAS-28 levels never dropped less than 3.2 even post-TKA, even at the 5 year follow-up, indicating that remission/ low disease activity levels were not reached even with surgery. They also showed that sub section analysis of HAQ scores showed lower extremity function improved after TKA, but there was consequent worsening of the upper limb function scores (eating, gripping) suggestive that this procedure only impacts walking, rising and step climbing.

Yamashita et al,[23] the rate of outdoor ambulation was 87.8% at 5 years, 72.8% at 10 years and 48.8% at

15 years and they showed that age of TKA (younger), body weight (higher), steroid use (higher) and usage of biologicals (lower) were significant factors that determine walking ability post-TKA. They concluded stating that decreasing steroid use and controlling RA activity using pharmacological therapy (cDMARDs/ bDMARDs) are important factors for preserving outdoor ambulation.

Not only pharmacological therapy but a combination of TKA and pharmacological therapy can achieve better therapeutic effects and maintain disease activity at low/ remission levels in patients with end stage arthritis of the knee due to rheumatoid arthritis. [8]

Suboptimal dosage of DMARDs was seen in some studies and this might explain the moderate- high disease activity levels in most patients. Patients having high disease activity during the perioperative period are less compliant to rehabilitation and physiotherapy, thereby affecting their overall functioning and satisfaction with the procedure, indicating the need for optimizing dosage for individual patients either by the rheumatologist or treating surgeon.

The importance of early diagnosis of RA and maintaining disease activity at low/ remission levels is highlighted in most studies. Although patients with high disease activity levels benefit the most from TKA, most studies confirm that post-operative disease activity rarely reach remission levels and pharmacological therapy becomes essential in achieving and maintaining disease activity at low levels.

5. Conclusion

Total Knee Arthroplasty remains a great option for rheumatoid patients with end stage arthritis of the knee, which is not only found to reduce the overall (systemic) disease activity but also the need for subsequent pharmacological therapy. However, patients with a high disease activity pre-operatively remain at risk for flares and are unable to reach remission levels of activity after TKA and require supplemental long term pharmacological therapy thereby highlighting the need for adequate pre-operative optimization.

6. Abbreviations

RA rheumatoid arthritis; BMI body mass index; TKA total knee arthroplasty; THA total hip arthroplasty; cDMARDs: conventional disease modifying anti- rheumatic drugs; bDMARDs: biological disease modifying anti- rheumatic drugs; MDHAQ Multi-dimensional Health Assessment Questionnaire; DAS Disease Activity Score; ESR erythrocyte sedimentation rate; CRP C-reactive protein; HOOS Hip Disability and Osteoarthritis Outcomes Score; KOOS Knee Injury and Osteoarthritis Outcomes Score; RF: rheumatoid factor; anti-CCP: anticyclic citrullinated peptide; DAS28: 28-joint Disease Activity Score; RAPID-3: Routine Assessment of Patient Index Data 3; RADAI: RA Disease Activity Index; CDAI: Clinical Disease Activity Index

7. Conflict of Interest

None.

8. Source of Funding

None.

Acknowledgements

None.

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Cite this article: Jayakumar T, Nayak PS. Disease activity and flares after total knee arthroplasty in rheumatoid arthritis - Systematic review. *IP Int J Orthop Rheumatol* 2022;8(2):72-83.