Demographics, clinical characteristics and predictive factors for total knee or hip replacement in patients with rheumatoid arthritis in Greece

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Abstract

Objectives

This paper aims to study the prevalence of total knee and hip replacements in Greek patients with rheumatoid arthritis (RA) and to identify possible predictive factors for future total hip or knee replacement.

Methods

A retrospective medical record review was performed in 750 RA patients who were recruited during 1994 to 2008 in a single Greek medical centre. Of the reviewed patients, 489 with a minimum follow-up duration of 1 year were enrolled in the study. The occurrence of total hip or knee replacement was used as the primary outcome variable in the predictive analysis.

Results

Total hip or knee replacement associated with RA was performed in 21 patients (4.3%). Total disease duration was the most significant factor associated with increased likelihood of total joint replacement. Erythrocyte sedimentation rate (ESR) at baseline examination was positively associated with subsequent knee or hip joint replacement (OR=1.023, 95%CI 1.005–1.04). Inadequate response to treatment was associated with a 3.12-times higher likelihood of joint replacement (95%CI, 1.28–7.58). The patients who underwent total hip or knee replacement had significantly higher ESRs and DAS 28 levels ($p<0.046$ and $p<0.002$, respectively) after the first year of follow-up.

Conclusion

The identification of factors associated with total joint hip or knee replacement can improve pharmacological treatment to maintain function and prevent destruction of the affected joints. Longer disease duration and inadequate response to treatment after the first year of follow-up increases the likelihood ratio for total joint replacement during the course of disease in Greek RA patients.

Key words

rheumatoid arthritis, knee replacement, hip replacement, biologic therapies

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Introduction

Current medical opinions widely agree that early and aggressive treatment, improves rheumatoid arthritis (RA) patient outcomes (1). Population-based studies have reported a decline in orthopaedic joint surgery in RA patients diagnosed after 1985 (2, 3). Despite the success of current treatment regimens, progressive joint destruction continues in a subgroup of RA patients. These patients eventually require joint surgery, which is an important component in the management of RA. The use of orthopaedic interventions in RA, particularly large joint replacement, is considered a marker of disease severity and damage as well as an indicator of medical management failure. From another point of view, total joint replacement can improve functional disability, relieve pain and correct the deformity and instability of a destroyed joint.

Previous studies have shown diverging rates of total joint replacements in RA patients. In a 23-year prospective study, Wolfe and Zwillich reported that 25% of patients underwent total joint replacement (4). Loza *et al*., in a retrospective study in Spain, found that 14% of 1379 patients had at least one total joint replacement (5). In a Finnish 25-year follow-up study, 27% of patients required a prosthetic device in at least one large joint (6). Several studies have shown that variables indicative of disease activity and severity, including low haemoglobin rates, high erythrocyte sedimentation rate (ESR), radiographic damage and disease duration, are predictors of a patient's need for future surgical interventions (4, 7, 8).

Rheumatoid arthritis patients in Greece differ from those in northern Europe with regard to clinical, serological and genetic characteristics (9, 10). To the best of our knowledge, the association between RA and total hip or knee replacement in Greek patients has not been previously evaluated.

The primary aim of the current study was to investigate the rate of total hip and knee replacement associated with rheumatoid arthritis in Greek patients. A second objective was to identify possible predictive factors for future total hip or knee replacement in RA patients.

Materials and methods

The study group comprised unselected rheumatoid arthritis patients who underwent follow-up examinations in the outpatient Rheumatology Unit of the Medical School's department of Pathophysiology of the University of Athens, Greece. All patients fulfilled the revised 1987 American College of Rheumatology criteria for rheumatoid arthritis (11). The data were obtained from patients' medical records containing information from January 1994 to December 2008. Of the 750 patients who were recruited during 1994-2008, 489 patients had a minimum clinic follow-up period of 1 year, and medical records of these patients were retrieved and evaluated in this study. All patient data were extracted from medical records by one investigator (senior author) using a pretested data collection form.

The first total hip or knee replacement following the diagnosis of RA was used as an outcome measure. Surgeries performed before the first clinic visit (baseline) in the rheumatology outpatient unit were excluded. The patients with primary osteoarthritis or post traumatic arthritis were excluded from the study. Thus, 108 men (22%) and 381 women (78%) were included in the final study population. The median age of disease onset was 48 years (38–57), and the median follow-up period for the study group was 4 years (2–7). At baseline, 314 of 489 individuals (66%) were positive for rheumatoid factor. The pattern of arthritis in the first visit was poly-articular in 416 of 489 (85%) patients, whereas 147 (30%) had an extra-articular manifestation. One-hundred and thirty-six patients (28%) suffered from sicca symptoms. In Table I, the demographic and disease variables in 489 patients who completed at least 1 year of follow-up are presented. Patients who received only non-steroidal anti-inflammatory drugs or corticosteroids were considered to have received inadequate treatment. Any treatment that included a disease-modifying anti-rheumatic drug (DMARD) or a biological agent was considered as adequate. This study was approved by the Ethics Committee of the Medical School of the University of Athens. Requirement for informed consent was waived by the Ethics Committee.

Demographic, clinical and laboratory variables

Trained physicians performed standard clinical and laboratory assessments at the first clinic visit and at yearly intervals thereafter for each patient. At baseline, sex and age were recorded. Other disease-related variables monitored at baseline included the age at which rheumatoid arthritis was diagnosed, the duration from disease onset to the first clinic visit and the duration of the follow-up period. Pharmacological variables such as drugs prescribed in the last 2 years including disease-modifying anti-rheumatic drugs (DMARDs), corticosteroids, and non-steroidal anti-inflammatory drugs (NSAID), were also recorded. The recorded laboratory variables included haemoglobin (Hb), white blood cells, (WBCs), platelets (PLTs), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) concentration, and rheumatoid factor (RF) titre. Clinical variables included the number of tender and swollen joints, the pattern of arthritis, extra-articular manifestations and the disease activity score (DAS28). (12). The use of DAS 28 facilitates the quantification of disease activity and provides a more reliable overall estimation of disease activity compared to any individual measurement. In this study, the DAS28 index was used with three variables in which the level of disease activity can be interpreted as low (DAS 28<3.2), moderate (3.2<DAS 28<5.1) or high (DAS 28>5.1) (13).

Response to treatment was measured using the EULAR response criteria (14), which classify patients as good, moderate or non-responders using the individual amount of change in the DAS 28 and the DAS 28 value (low, moderate, high) reached. A patient must show a significant change in DAS 28 value (Δ DAS>1.2), but must also reach low disease activity (DAS 28 <3.2).

Statistical analysis

Descriptive characteristics are presented as mean values ± SD or frequencies. Patients were subdivided in two groups: those who received total joint replacement and those who did not. To examine the distribution of demographic and clinical variables among total hip or knee joint replacement, we used the Student's *t*-test for the normally distributed variables, the Mann-Whitney non-parametric test for the skewed and the Pearson's χ^2 test for the categorical variables. Normality was tested using P-P plots. Multiple logistic adjusted and unadjusted regression analysis was then applied to evaluate factors associated with total joint replacement, and the results are presented as odds ratios and their corresponding 95% confidence intervals. In addition, the Wald test was used as an indicator of the most significant variable. The Hosmer-Lemeshow statistic was applied to evaluate the models' goodness-of-fit. All analyses were performed using SPSS version 18 (SPSS Inc, Chicago, IL, USA).

Table I. Demographic and clinical baseline characteristics of the study population.

n.	489
Male/female	108 (22%)/371(78%)
Age at disease onset (years)	48 (38–59)
Total duration of the disease (years)	9 (5–17)
Duration of follow-up (years)	4 (2–7)
Extra-articular manifestations (number of patients)	147 (30%)
RF positive	314 (66%)
Polyarthritis	416 (85%)
DMARD before baseline	53%
Inadequate treatment before baseline	192 (47%)

RF: rheumatoid factor; DMARD: disease-modifying anti-rheumatic drug.

Table II. Demographic and disease characteristics at baseline for the surgery group and the non-surgery group.

	Patients without replacement	Patients with replacement	*p*-value
n.	468	21	
Gender (female), %	363 (77.5%)	19 (90.4%)	0.18
Duration from first symptom (median years)	6.5 ± 5.4	10.5±4.7	0.08
Age of disease onset (years)	48 ± 7	43±5	0.23
Disease duration (median years)	11 ± 10	17±8	0.008
Haemoglobin (g/dL)	12.4 ± 1.4	12±1.7	0.12
White blood cells (count)	7997 ± 2299	7964±2685	0.14
ESR (mmHg/1sth)	44 ± 28	62±41	0.05
DAS 28 (per 1 unit)	5.5 ± 1.5	5.7±1.19	0.19
RF Pos, n (%)	285 (61%)	13 (62%)	0.23

ESR: erythrocyte sedimentation rate; DAS28: disease activity score, 28 variables; RF: rheumatoid factor.

Results

Frequency of orthopaedic surgery

Throughout the study period, primary total hip or knee replacement related to rheumatoid arthritis was performed in 21 of 489 patients (4.3%); 19 of these patients were women. Seventeen patients had 1 joint replacement, three patients had 2 and one patient had 3. The median time from disease onset to first joint replacement was 17.2 years. The knee joint was the most frequently replaced (twelve patients received knee joint replacements, eight patients received hip joint replacements and one patient received replacements in both joints). At baseline, 179 patients (36.6%) had tender or swollen knee joints and 205 (41.9%) had tender hip joints, as determined by clinical evaluation. Patients with affected knee joints at baseline had a significantly higher likelihood of requiring knee joint replacement during the course of their disease (p=0.02). In contrast, patients with affected hip joints at baseline had similar likelihood of requiring hip joint replacement (p=0.5).

Of the 408 patients who were treated for RA before baseline, 216 (53%) had received adequate treatment for their disease. In the joint replacement group, only six of the 21 patients had received adequate treatment before baseline (p=0.04). In Table II, the demographic and disease characteristics at baseline

for the surgery group and the non-surgery group are presented. There were no significant differences between the two groups considering age, Hb, WBCs, PLTs, DAS 28, or the number of tender and swollen joints. The patients who underwent total hip or knee replacement, had significantly higher levels of ESR and CRP at baseline, and a significantly longer duration of disease (p=0.008), compared with the patients who did not received surgery.

Multiple logistic regression analysis was then applied to evaluate factors associated with total joint replacement and the results are presented as odds ratios and their corresponding 95% confidence intervals (Table III). Total duration of the disease was the most significant factor (*i.e.* had the highest Wald test=10.2) related to total joint replacement. In particular, a 1-year longer disease duration was associated with a 1.07-times (95%CI 1.02–1.11,) higher likelihood of requiring joint replacement. Furthermore, higher ESR at baseline was positively associated with subsequent knee or hip joint replacement (p=0.014).

Table III. Results from multiple logistic regression analysis to evaluate factors at baseline associated with total joint replacement.

Predictive factors	Odds ratio	95%CI	*p*-value
Age (per 1 year)	0.97	0.94–1.01	0.21
Total duration (per 1 year)	1.07	1.02–1.11	0.001
CRP (per 1 mg/dL)	1.004	0.99–1.01	0.42
ESR (per 1 mm Hg)	1.02	1.005–1.04	0.01
DAS 28 (per 1 unit)	0.86	0.60–1.22	0.40

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: disease activity score, 28 variables.

Table IV. Laboratory and clinical variables at the first year of follow-up.

	Patients without arthroplasty (n=468)	Patients with arthroplasty (n=21)	*p*-value
Haemoglobin (g/dL)	12.8 ± 1.54	12.1 ± 1.68	0.06
White blood cells (count)	7420 ± 1900	7780 ± 2200	0.15
ESR (mmHg/1sth)	29 ± 19	43 ± 28	0.046
DAS28 (per 1 unit)	3.6 ± 1.1	4.8 ± 1.2	0.002

ESR: erythrocyte sedimentation rate; DAS28: disease activity score, 28 variables.

Table V. Results from multiple logistic regression analysis to evaluate variables 1 year from baseline associated with total joint replacement.

Predictive factors	Odds ratio	95%CI	*p*-value
Haemoglobin (g/dL)	0.81	0.59–1.11	0.19
CRP (per 1 mg/dL)	0.99	0.99–1.03	0.22
ESR (mmHg/1sth)	1.01	0.96–1.01	0.46
DAS 28 (per 1 unit)	1.51	1.04–2.20	0.02

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; DAS28: disease activity score, 28 variables.

First year follow-up period

Laboratory and clinical variables after the first year follow-up period are summarised in Table IV. The patients who underwent total hip or knee replacements had significantly higher levels of ESR and DAS28 (p=0.046 and p=0.002, respectively) at the first year follow-up. The number of tender joints and swollen joints at first year follow-up were found to be significantly higher in patients who underwent replacement (p=0.003 and p=0.008, respectively) as compared with those that did not. One year following baseline, 139 of 489 patients (28.4%) had an affected knee joint and 126 of 489 (25.7%) had a tender or swollen hip joint. Patients with an affected knee joint at first year follow-up had a significantly higher likelihood of undergoing knee replacement (p=0.002). Similarly, patients with a tender hip joint at first year follow-up had a higher likelihood of receiving hip joint replacement (p=0.006). Based on the multiple adjusted logistic regression analysis (Table V), DAS28 was the most significant factor associated with total joint replacement at 1 year after baseline (OR=1.51, 95%CI 1.04–2.2, p=0.02).

Response to treatment

By the first year of follow-up, 464 (95%) patients had received at least one DMARD. The most frequently prescribed DMARD was methotrexate, which was used in approximately 88% of cases. An early intervention with a biological agent as a monotherapy or in combination with conventional DMARDs was used in 112 (23%) patients. According to EULAR response criteria, at the first year of follow-up, 162 (33.1%) patients had good responses to treatment, 175 (35.8%) had moderate responses and 152 (31.1%) had inadequate responses. There was a significant relationship between inadequate response to treatment and joint replacement (p=0.008). Unadjusted logistic regression analysis revealed that inadequate response to treatment was associated with a 3.12-times higher likelihood (95%CI, 1.28–7.58) of requiring joint replacement. Furthermore, multiple adjusted analysis revealed that this association was moderated after controlling for total duration of the disease, age and haemoglobin levels at the first year of follow-up (Table VI).

Discussion

A central finding of the current study was that in Greek RA patients, simple clinical and laboratory measures such as ESR at baseline and at the first year of follow-up, as well as DAS28 at the first year of follow-up, were identified as strong predictive factors for future total hip or knee joint replacement. Furthermore, patients with an affected knee joint at the baseline and at the first year of follow-up, as well as patients with an affected hip joint at the first year of

Table VI. Results from multi adjusted logistic regression analysis. Association between response to treatment and total joint replacement after controlling for total duration of the disease, age and rate of haemoglobin at first year of follow-up.

Predictive factors	Odds ratio	95%CI	*p*-value
Haemoglobin (g/dL)	0.79	0.58–1.08	0.14
Age (per 1 year)	0.99	0.96–1.03	0.95
Response to treatment (yes *vs*. no)	2.27	0.89–5.80	0.08
Total duration (per 1 year)	1.05	1.01–1.11	0.01

follow-up, had a significantly higher likelihood of having knee and hip joint replacement, respectively. In several studies, high ESR, functional disability, radiographic damage and long disease duration have been reported as risk factors for surgical intervention in RA patients. In a study of 183 patients with rheumatoid arthritis, Kapetanovic *et al*. highlighted that patients with history of total joint replacement had significantly higher levels of CRP and ESR at inclusion (15). Verstappen *et al*. identified high ESR and joint score as two clinical parameters that could serve as prognostic factors (1). Similarly, James *et al*. observed that factors associated with total joint replacement surgery for RA at presentation included a low haemoglobin concentration, ESR, disease activity and low radiological erosion scores (7).

Another key finding of the present study is that individuals who underwent total hip or knee replacement had significantly longer disease duration. In particular, an additional year of disease duration was associated with a 1.07-times higher likelihood of joint replacement. In a large study in Japan of 2.695 patients, the authors reported that the prevalence of total joint replacement increased in relation to the disease duration (16). Likewise, Da Silva *et al*. determined that the likelihood of surgery was higher in patients who were diagnosed at younger ages (2).

The prevalence of total joint replacement in Greek RA patients in this study was 4.3%, and this was lower than had been previously reported for other ethnic groups. Our RA patients were treated with an aggressive protocol and probably were among the best controlled European RA groups. Moreover, it is well-established that rheumatoid arthritis in Greek patients is a milder joint disorder than RA in patients of northern European origin. Rheumatoid arthritis in Greece differs with regard to clinical, serological and genetic characteristics when compared to RA in northern Europe. A comparative clinical study between British and Greek RA patients revealed that British patients had more severe articular involvement than Greeks, as confirmed by the duration of morning stiffness, grip strength, and the number of tender and swollen joints (9).

Early and aggressive treatment with DMARDS has been shown to improve long-term outcomes in RA patients and, as a result, has a positive impact on the subsequent need for joint replacement. In the current study, only six out of twenty-one patients received adequate treatment prior to baseline. The patients who received inadequate treatment prior to baseline had a significantly higher likelihood of receiving knee or hip joint replacement. A study of the Utrecht RA cohort, reported that good response to treatment decreased the risk for joint surgery. Early treatment with DMARDS and response to treatment were found to reduce the need for orthopaedic intervention in patients with recent onset of RA (1). Our study revealed that 31.1% of the patients had inadequate response to treatment and these patients were 3.12-times (95%CI, 1.28–7.58) more likely to undergo total joint replacement compared to those who responded to treatment. This relationship was moderated when other factors such as total duration of disease or age at baseline were considered in the analysis. A comparison between different DMARDs or biological agents was not performed due to the limited number of treatments. Several other authors reported that treatment with biological agents in combination with conventional DMARDS, mostly methotrexate, reduced the development of joint damage. Recently, a long- term population-based study has reported a drop in the use of orthopaedic surgery, including joint replacement surgery, in patients with RA diagnosed after 1985 (2). This may signify advancements in disease management and could be an indication that modern therapies for RA are having a positive impact on important outcomes. Additionally, the total number of RA-related procedures of the lower limbs in Swedish patients declined between 1987 and 2001. Explanations for this include early and aggressive approaches to treatment and the accessibility of newer, more efficient treatments (17).

The limitation of the present study is that it was a retrospective analysis based on medical record review and, therefore, there were no data concerning crucial RA variables such as human leucocyte antigen status or early radiographic changes, which have been found to be predictors of joint surgery in previous studies.

Conclusion

The identification of factors associated with total joint hip or knee replacement can lead to better pharmacological treatment strategies to maintain function and prevent destruction of the affected joints. Clinicians and healthcare professionals should focus their attention on patients' treatment responses and on suppression of disease activity in order to reduce the eventual need for total hip or knee joint replacement.

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