The decline in joint replacement surgery in rheumatoid arthritis is associated with a concomitant increase in the intensity of anti-rheumatic therapy

A nationwide register-based study from 1995 through 2010

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Background and purpose **Drug-based treatment of rheumatoid arthritis (RA) has evolved markedly over the past 2 decades. Using nationwide register data, we studied how this has affected the rates of hip, knee, shoulder, and elbow replacement from 1995 to 2010.**

Methods **The number of primary joint replacements was obtained from the Finnish Arthroplasty Register. To test the hypothesis that improvements in medical treatment of RA reduce the need for joint replacements, we also collected data about purchases of different disease-modifying anti-rheumatic agents (DMARDs) and biological drugs from the nationwide drug registers.**

Results **The annual incidence of primary joint replacements for RA declined from 19 per 10^5 in 1995 to 11 per 10^5 in 2010. The decline was greater for upper-limb operations than for lower-limb operations. At the same time, the numbers of individuals using methotrexate, hydroxychloroquine, and sulfasalazine (the most commonly used DMARDs) increased 2- to 4-fold.**

Interpretation **Our results are in accordance with observations from other countries, and indicate that the use of joint replacements in RA has decreased dramatically. Our data suggest that effective medical therapy is the most likely explanation for this favorable development.**

Rheumatoid arthritis (RA) has been regarded as one of the most disabling diseases of the twentieth century. Due to the lack of effective disease-modifying anti-rheumatic drugs (DMARDs) for retardation or prevention of joint destruction, more than half of the patients with RA diagnosed in the 1970s were either dead or severely disabled 2 decades later (Scott et al. 1987) and up to a quarter of them had undergone total joint replacement surgery of large joints by 20 years from disease onset (Wolfe and Zwillich 1998, Jäntti et al. 2002, Palm et al. 2002).

Since its introduction in the 1960s and 1970s, joint replacement surgery has provided pain relief and prevented severe restriction of mobility (Liang et al. 1982, Hakala et al. 1994). Consequently, joint replacement surgery was cited as the most important advance in the management of rheumatic diseases in the late 1980s (Fries 1989).

More recently, the outcome of RA has improved, particularly in terms of functional ability (Fries et al. 1996) and mortality (Choi et al. 2002). There have also been reports from several countries indicating that the use of orthopedic surgery in patients with RA has declined (da Silva et al. 2003, Weiss et al. 2006, Fevang et al. 2007, Weiss et al. 2008, Louie and Ward 2010, Momohara et al. 2010, Hekmat et al. 2011, Skyttä et al. 2012). Improved outcomes have been regarded as a merit of advancements in the medical treatment of RA—namely the introduction of more effective DMARDs (especially methotrexate), increased use of DMARD combination therapies and, most recently, availability of biological anti-rheumatic drugs (Fries et al. 1996 Choi et al. 2002). These changes have been considered to be probable reasons for the decrease in rheumaorthopedics as well (Weiss et al. 2008, Kolling et al. 2009, Louie and Ward 2010, Momohara et al. 2010, Hekmat et al. 2011), but earlier studies have been unable to analyze medication data.

In this nationwide register-based analysis, we found changes in the frequency of primary joint replacements for RA and in the use of DMARDs and biological drugs (later referred to as "anti-rheumatic drugs") from 1995 to 2010.

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Material and methods

We collected summarized nationwide data from the Finnish Arthoplasty Register and the drug registers of the Social Insurance Institution of Finland (SII) (Drug Prescription Register and Drug Reimbursement Register) concerning hip, knee, shoulder, and elbow replacements performed in patients with RA and concerning use of anti-rheumatic drugs from 1995 through 2010.

The Finnish Arthroplasty Register is a nationwide health register that has covered joint replacement operations performed in Finland (including both public and private hospitals) since 1980. Since 1989, reporting to the register has been mandatory for operating hospitals, thus ensuring good coverage (e.g. 96% for primary knee replacements (Jämsen et al. 2009)). In this study, we collected data on annual numbers of primary hip, knee, shoulder, and elbow replacements performed due to RA (according to the report by the operating unit) and for other reasons (osteoarthritis, other arthritides, developmental hip dysplasia, or other disease). The numbers reported represent the number of operated joints.

The Drug Prescription Register of the SII includes data on prescriptions delivered from pharmacies since 1994. Thanks to the general sickness insurance covering all Finnish citizens, the register has good coverage of outpatient purchases of medications that require prescription, including anti-rheumatic drugs.

The Drug Reimbursement Register includes patients who have been entitled reimbursement for drug costs for certain severe chronic diseases after the year 1964. In the case of RA, patients are allowed a special reimbursement (72% instead of the basic reimbursement of 42%) for anti-rheumatic drugs after they have undergone evaluation by the SII. This evaluation is based on a medical certificate written by a specialist in internal medicine or rheumatology (or in a specialized healthcare unit of these disciplines) and detailing accurate diagnosis (according to the International Classification Diseases), diagnostic procedures, and a plan for treatment. Reimbursement for the use of biological drugs (biologics) is allowed separately and requires documentation of insufficient efficacy of conventional DMARDs. RA belongs to the same reimbursement group as some other rheumatic diseases (e.g. ankylosing spondylitis and systemic connective tissue disorders) and, in this millenium, it has accounted for about half of the diagnoses of incident cases in this reimbursement group (Lauri Virta, personal communication). Reimbursement for biologics became available in 2001, and it can be issued for treatment of RA, juvenile idiopathic arthritis, psoriatic arthritis, or ankylosing spondylitis.

For this study, we collected the annual numbers of patients who had purchased different DMARDs (excluding systemic steroids) or biologics (excluding drugs administered intravenously in hospitals or at outpatient clinics) and who were entitled to reimbursement for these drugs. We also recorded the total number of patients who had purchased any DMARDs or biologics and had received corresponding reimbursement.

Statistics

We report the total annual numbers and annual incidence of different joint replacement procedures and the rate of use of different anti-rheumatic drugs, with accompanying 95% confidence intervals (CIs), per 10^5 inhabitants, using mid-year population as denominator for the period 1995–2010. Mid-year population is available at the Statistics Finland website http://pxweb2.stat.fi/database/StatFin/vrm/vaerak/vaerak_en.asp. In addition, the proportion of operations performed due to RA of all primary joint replacements is reported for each year. As a sensitivity analysis, we repeated calculations of incidences of joint replacements also using the number of patients who had had reimbursment for purchases of anti-rheumatic drugs as denominator.

To analyze the changes related to treatment practices in more detail, we also performed the analyses in 4 periods of 4 years, which represented different treatment practices as follows: (1) 1995–1998—treatment practices of the mid-1990s, with increasing use of methotrexate and combination therapies; (2) 1999–2002—introduction and implementation of the Finnish Current Care Guideline for the management of RA (a working group set up by the Finnish Medical Society Duodecim and the Finnish Society for Rheumatology, 2011), which advocates intensive use of DMARD combinations in aggressive RA; (3) 2003–2006—introduction of biological drugs; and (4) 2007–2010—current care practices.

For each period, we calculated the average annual incidences of joint replacements and rates of use of DMARDs and biologics, with corresponding CIs.

The Poisson regression model was used for calculation of incidence rate ratios (IRRs; relative change in the incidence rates, with values < 1.0 indicating a decline) and for statistical analysis of linear trends over time. We also tested the association between the incidence of joint replacements and the use of methotrexate using Pearson correlation analysis.

Results

245,854 primary hip, knee, shoulder, and elbow replacements were performed in Finland during the study period (1995–2010). Of these, 13,037 joint replacements (5.3%) were performed in patients with RA. The annual numbers of hip, knee, and shoulder replacements performed for indications other than RA increased rapidly, whereas the numbers of operations performed due to RA decreased (Figure 1).

The annual incidence of primary joint replacements for RA decreased from 18.5 per 10^5 in 1995 to 11 per 10^5 in 2010 ($p < 0.001$). Both the annual numbers (Table 1) and the incidence (Figure 2A) of hip, knee, shoulder, and elbow replacements performed due to RA decreased markedly. The decline

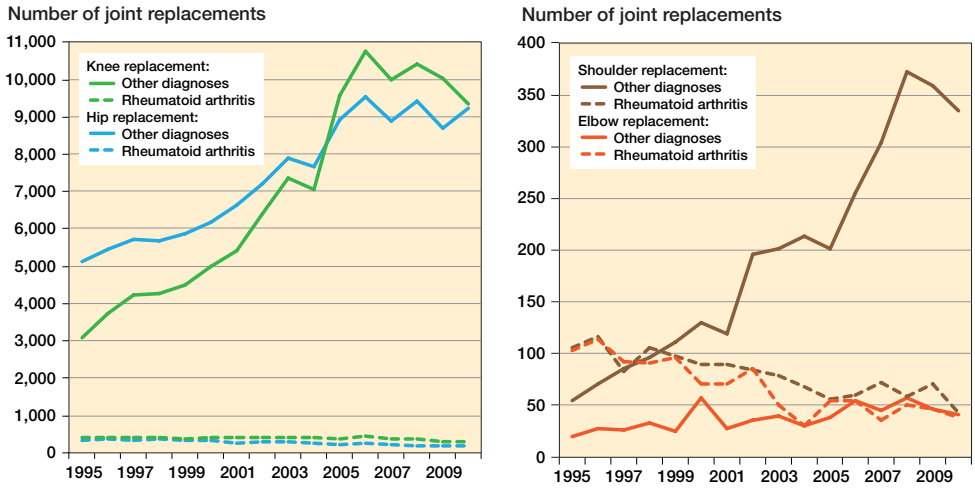

Figure 1. Annual absolute numbers of primary hip and knee replacements (left) and shoulder and elbow replacements (right) performed for RA and other diagnoses (including osteoarthritis, other arthritides, trauma, and developmental hip dysplasia) from 1995 through 2010.

Table 1. Operation numbers and annual incidence rates of hip, knee, shoulder, and elbow replacements for RA at the beginning and end of the observation period (1995 and 2010), and corresponding incidence rate ratios

	1995			2010			Incidence rate ratio (95% CI)	p-value
	n	Incidence per 100,000 n	(95% CI)	n	Incidence per 100,000 n	(95% CI)		
Hip replacement	331	6.5	(5.8–7.3)	187	3.5	(3.0–4.0)	0.54 (0.45–0.64)	< 0.001
Knee replacement	402	7.9	(7.1–8.7)	305	5.7	(5.1–6.4)	0.72 (0.62–0.84)	< 0.001
Shoulder replacement	106	2.1	(1.7–2.5)	43	0.8	(0.6–1.1)	0.39 (0.27–0.55)	< 0.001
Elbow replacement	103	2.0	(1.7–2.5)	39	0.7	(0.5–1.0)	0.36 (0.25–0.52)	< 0.001
All		18.5	(17.4–19.8)		10.8	(9.9–11.7)	0.58 (0.52–0.64)	< 0.001

was greater for upper-limb operations than for lower-limb operations (Table 1). Comparison of the different 4-year periods (1995–1998, 1999–2002, 2003–2006, and 2007–2010) indicated that the decline occurred later in knee replacements than in hip, shoulder, and elbow replacements (Table 2).

Whereas most shoulder and elbow replacements were performed because of RA in 1995 (66% (106/160) and 84% (103/123), respectively), the proportions dropped to 11% (43/377) and 49% (39/80) in 2010 ($p < 0.001$ for both comparisons). RA also became a less common reason for hip and knee replacements (Figure 2B) and accounted for only 2% (187/9,417) and 3% (305/9,654) of all joint replacements in 2010, as compared to 6% (331/5,450) and 12% (402/3,469) in 1995.

The changes in the numbers and incidences of joint replacements occurred simultaneously with an increase in the numbers of users of different DMARDs (Figure 2C). The greatest increases were observed in the numbers of users of methotrexate and hydroxychloroquine (IRR = 2.60, CI: 2.54–2.66, and IRR = 2.30, CI: 2.24–2.36, respectively), whereas biological drugs were used on a wider scale only during the last 4 years of observation (Table 2). Pearson correlation analysis showed a strong correlation between the total annual numbers of joint replacements and of patients who had purchased methotrexate ($r = –0.93$; $p < 0.001$), the most commonly used DMARD (Figure 2D).

Sensitivity analysis

When the calculations of incidences of joint replacements were repeated using the number of patients whose purchases of anti-rheumatic drugs were reimbursed as the reference population (instead of the total population), the differences between 1995 and 2010 were even more obvious than in the initial analysis: the IRRs for hip, knee, shoulder, and elbow replacements were 0.35 (CI: 0.29–0.41), 0.46 (CI: 0.40–0.54), 0.25 (CI: 0.17–0.35), and 0.23 (CI: 0.16–0.33), respectively ($p < 0.001$ in all cases), indicating a 54–77% decline in incidence rates.

Discussion

From 1995 through 2010, the total numbers of primary hip, knee, shoulder, and elbow replacements performed due to RA

Table 2. Changes in the incidence of joint replacements for rheumatoid arthritis and use of anti-rheumatics in four-year periods from 1995 through 2010

	A	B		C		D		E	F
Incidence per 100,000 inhabitants									
Hip replacements	6.97	5.97	–14%	4.92	–29%	3.68	–47%	0.53 (0.44–0.63)	< 0.001
Knee replacements	8.12	7.73	–5%	7.77	–4%	6.31	–22%	0.78 (0.67–0.90)	< 0.001
Shoulder replacements	2.01	1.75	–13%	1.26	–37%	1.16	–43%	0.57 (0.42–0.79)	< 0.001
Elbow replacements	1.96	1.57	–20%	0.91	–53%	0.82	–58%	0.42 (0.29–0.60)	< 0.001
All	19	17	–11%	15	–22%	12	–37%	0.63 (0.57–0.69)	< 0.001
Users of anti-rheumatic drugs per 100,000 inhabitants									
Methotrexate	180	306	+70%	394	+119%	467	+160%	2.60 (2.54–2.66)	< 0.001
Sulfasalazine	246	305	+24%	337	+37%	363	+48%	1.48 (1.45–1.51)	< 0.001
Hydroxychloroquine	140	220	+58%	280	+101%	321	+130%	2.30 (2.24–2.36)	< 0.001
Gold	170	139	–18%	96	–43%	62	–63%	0.37 (0.35–0.38)	< 0.001
Leflunomide	0	27	–	64	–	81	–	–	< 0.001
Biologics	0	0	0	34	–	79	–	–	< 0.001
Others [a]	105	101	–3%	79	–27%	72	–32%	0.68 (065–0.71)	< 0.001

[a] Including azathioprine, penicillamine, chloroquine, and alkylating agents.
A Mean annual incidence 1995–1998
B Mean annual incidence 1999–2002 and percentage change compared to 1995–1998
C Mean annual incidence 2003–2006 and percentage change compared to 1995–1998
D Mean annual incidence 2007–2010 and percentage change compared to 1995–1998
E Incidence rate ratio (95% CI). Period 2007–2010 compared to 1995–1998
F p-value for trend over the 4 periods

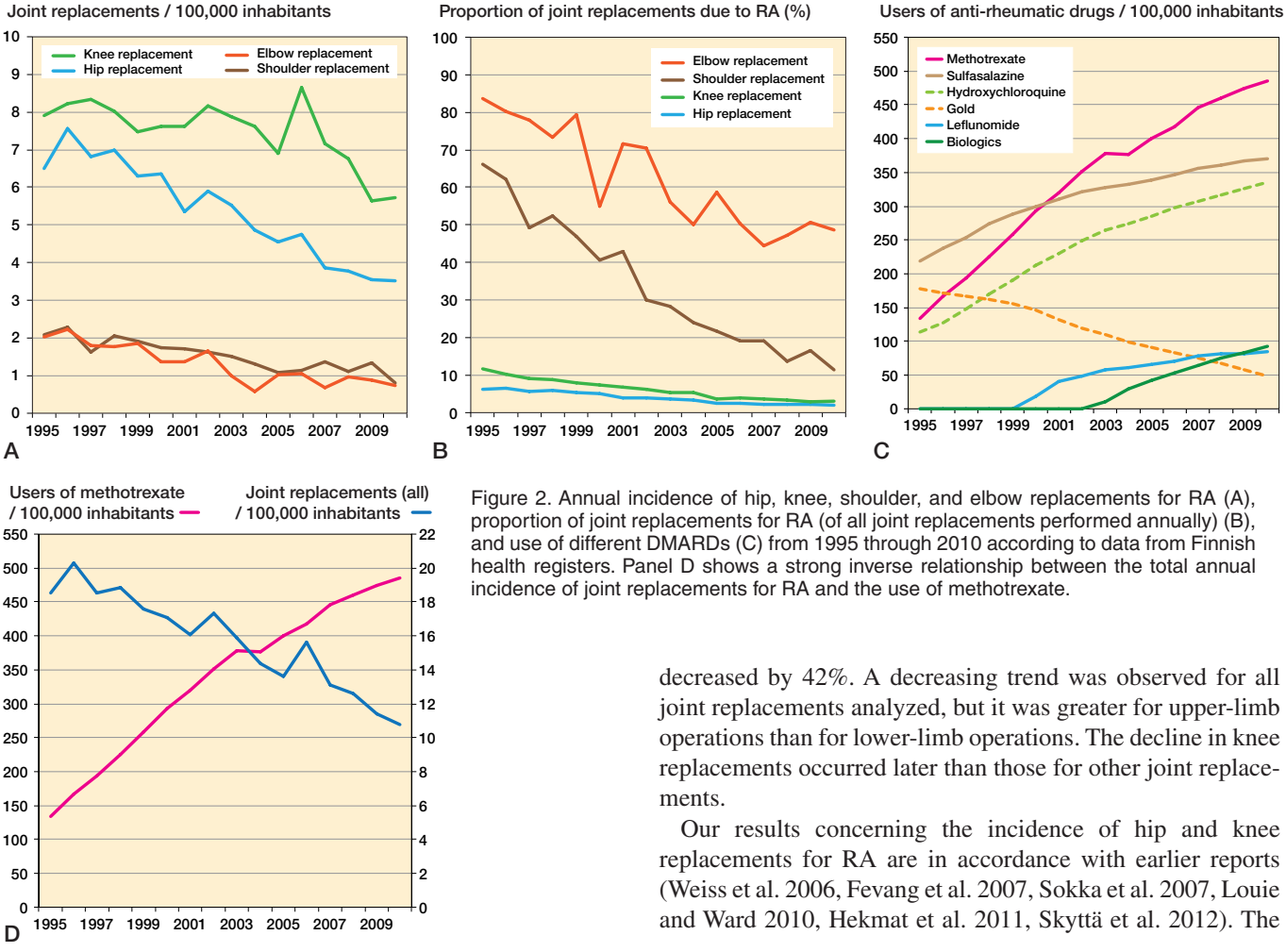

Figure 2. Annual incidence of hip, knee, shoulder, and elbow replacements for RA (A), proportion of joint replacements for RA (of all joint replacements performed annually) (B), and use of different DMARDs (C) from 1995 through 2010 according to data from Finnish health registers. Panel D shows a strong inverse relationship between the total annual incidence of joint replacements for RA and the use of methotrexate.

decreased by 42%. A decreasing trend was observed for all joint replacements analyzed, but it was greater for upper-limb operations than for lower-limb operations. The decline in knee replacements occurred later than those for other joint replacements.

Our results concerning the incidence of hip and knee replacements for RA are in accordance with earlier reports (Weiss et al. 2006, Fevang et al. 2007, Sokka et al. 2007, Louie and Ward 2010, Hekmat et al. 2011, Skyttä et al. 2012). The

decline in shoulder and elbow replacements instead contrast with the Swedish report (Weiss et al. 2008), where the annual numbers of these operations remained unchanged from 1998 through 2004 and where the total number of upper-limb joint replacements in fact increased slightly. In that study, RA did not need to be the primary diagnosis for a procedure, so it is possible that a proportion of the operations were performed due to primary or secondary osteoarthritis or trauma, which are all coded separately in the Finnish Arthroplasty Register used in the present study. A decline in non-joint-replacement upper-limb operations, which are probably more specific to RA, has been documented by several authors (Fevang et al. 2007, Weiss et al. 2008, Kolling et al. 2009, Louie and Ward 2010, Momonara et al. 2010).

Interestingly, the decline in knee replacements was less than in other joint replacements. As the knee is one of the joints that are often affected in early RA (Palm et al. 2002, Kapetanovic et al. 2008), a greater decline could have been expected but, on the other hand, our result is in line with earlier studies from Norway (Fevang et al. 2007) and California (Louie and Ward 2010). Insufficient operating capacity is an unlikely explanation, as the numbers of knee replacements performed due to osteoarthritis rocketed over the observation period (Figure 1) (Leskinen et al. 2012, Skyttä et al. 2012).

One explanation may be that RA-initiated cartilage destruction in knees could progress under stress related to body weight and loading (Bennell et al. 2011), even though rheumatic inflammation was controlled (i.e. promoting the course of secondary OA). However, we included only joint replacements that were performed due to RA, and therefore operations performed, for example, due to OA or trauma in patients with RA were not taken into account. In fact, we believe that the lower decline in knee replacements is not related to the course of RA or to the effects of DMARDs and biological drugs. In 2005, statutory care guarantee legislation was introduced in Finland, which forced hospitals to cut their queuing times. These had been particularly long for knee replacements. This therefore led to a peak in the annual numbers of hip and knee replacements in 2006. Moreover, the improvements in the durability (Himanen et al. 2005) and clinical results of knee replacements, compared to experiences of the 1980s, have resulted in a rapid increase in the overall use of knee replacements (Leskinen et al. 2012). This enthusiasm may also have lowered the threshold for operating knees in RA.

At the same time as the decrease in the use of joint replacement surgery in RA, the numbers of users of anti-rheumatic drugs increased markedly (Figure 1C), indicating wider use of these drugs and their combinations. In particular, the use of methotrexate and hydroxychloroquine became more common. These drugs (together with sulfasalazine and prednisolone) belong to a combination which has been shown to be effective not only in controlling inflammation (Möttönen et al. 1999) but also in reducing joint damage in long-term follow-up, compared to initial treatment with a single DMARD (Korpela et al. 2004, Rantalaiho et al. 2010). Damage in large joints could be diagnosed in 13% of patients in the combination DMARD group and 26% of patients in the single DMARD group after 11 years of follow-up (Rantalaiho et al. 2010). The value of DMARD combinations over the use of single DMARDs has also been shown in other series (Graudal and Jürgens 2010), but patient numbers and follow-up periods in clinical trials have not been sufficient to allow analysis of the rates of joint replacements.

Supporting earlier observations (da Silva et al. 2003, Weiss et al. 2006, Fevang et al. 2007, Weiss et al. 2008, Louie and Ward 2010, Skyttä et al. 2012), the decline in the use of joint replacement surgery in RA had already started before DMARD combinations and biological drugs were used on a wider scale. Thus, it appears that the early, serial, and continuous use of single DMARDs, particularly that of methotrexate, which gained ground in the late 1980s and early 1990s (Fries 1990, Sokka et al. 2000), has contributed to the present results.

There have been some preliminary results on the effect of biological drugs on the need for joint replacement, but with conflicting results. Using nationwide register-based data similar to ours, Harty et al. (2012) reported that in Ireland, the numbers of elective hip and knee replacements for RA became reduced along with increasing use of tumor necrosis factor-α antagonists. In a Finnish study based on detailed patient-level data, patients on biological drugs instead had higher incidence of primary joint replacements than patients in the matched-comparison group who were treated with conventional DMARDs (Aaltonen et al. 2013). Because biological drugs have mostly been used in cases of aggressive, DMARD-resistant RA, the result is probably explained by permanent joint damage existing at the time that biological drugs were initiated. To determine the true potential of biological drugs, we must wait for follow-up studies of patients whose disease started in the 2000s, i.e. for whom these drugs were initiated at the stage of minimal joint damage. Nevertheless, one would expect that on a nationwide scale, the decline will continue when previously treatment-resistant cases can also be managed more effectively.

The present study had certain limitations. Firstly, as we relied on summary statistics from health registers rather than on accurate patient-level data, we could not take into account the effects of patient-level factors (including use of different DMARDs and biologics, clinical indicators of disease severity such as inflammatory parameters, and radiological degree of joint destruction). Nor were we able to take the duration of disease into account. It therefore remains unclear whether changes in the natural course of RA and later disease onset have an effect on joint replacement rates. It is, however, unlikely that such changes—which would take years or decades to occur—could explain the observed rapid change in joint replacement rates.

Secondly, the incidences of joint replacement should ideally be calculated using the number of patients with RA as denom-

inator. Because the same drug reimbursement group included some other diagnoses in addition to RA, accurate numbers of prevalent cases of RA were not available in the drug registers used in this study (or in any other nationwide Finnish register). If there had been changes in the epidemiology of rheumatic disorders, and in particular in the relationship between RA and other rheumatic diseases, this could have biased our observations. However, occurrence of such dramatic changes over a 16-year period appears unlikely. Moreover, the incidence trends were similar in the analyses using the whole population and the patients who were reimbursed for purchases of DMARDs; it is therefore unlikely that this issue would affect our key results. Finally, we were unable to perform analyses with adjustment for age and sex (both of which may affect suitability for and willingness to undergo joint replacement). However, Weiss et al. (2006) found that age and sex did not affect the analysis of time trends and they ignored these factors in their later study (Weiss et al. 2008).

In conclusion, the present study supports earlier studies indicating that there is a decline in the use of joint replacements in patients with RA in countries with resources and tradition of active anti-rheumatic drug therapy. This dramatic decline has implications for how rheumaorthopedic surgery should be arranged so that sufficient operation volume and quality can be maintained and, on the other hand, it creates a challenge for maintaining highly specialized rheumatology centers (Kauppi et al. 2012). More active medical treatment appears to be the strongest explanation for the decline, which in particular seems to have been attributable to the increased use of different DMARDs already before wider introduction of combination treatments and biologicals. To confirm the influence of the use of DMARD combinations and biologics on the need for joint replacement, large observational studies—where the actual treatment of each patient can be analyzed—will be required.

MUKL and MH initiated this collaborative project. MUKL and LJV provided the data and EJ and LJV analyzed it. EJ wrote the first draft of the manuscript and took care of revisions. All authors contributed to interpretation of the results and to preparation of the manuscript.

No competing interests declared.

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