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ABSTRACT. Objective. To compare clinical characteristics and treatment between simultaneously investigated Sudanese and Swedish outpatients with rheumatoid arthritis (RA).

Methods. Outpatients with RA from Sudan (n = 281) and Sweden (n = 542) diagnosed according to the 1987 American College of Rheumatology criteria were recruited between December 2008 and September 2010 and compared concerning clinical presentation, treatment, and laboratory findings, including immunoglobulin M with rheumatoid factor (IgM-RF).

Results. Sudanese patients had lower inclusion age (median 49 vs 68 yrs), disease duration (48 vs 107 mos), and disease onset age (43 vs 56 yrs) as compared with Swedish patients (p < 0.0001 for all). When stratified concerning the age of inclusion, Swedish patients between 41–50 years had, however, a significantly lower age of onset, with a similar trend for all age groups above 30 years. The female preponderance was higher among Sudanese patients (89.3% vs 72.5%, p < 0.0001), and smoking was nonexistent among Sudanese female patients (p < 0.0001). Erythrocyte sedimentation rate levels and number of tender joints were significantly higher among Sudanese patients. The proportion of IgM-RF positivity was lower among Sudanese patients with RA (52.4% vs 75.5%, p < 0.0001). Higher proportions of Sudanese patients with RA were treated with methotrexate (MTX) and disease-modifying antirheumatic drug combinations, but none of them used biologics. Sudanese patients used lower doses of MTX and sulfasalazine (p < 0.0001) and higher doses of prednisolone (p < 0.0001) than Swedish patients.

Conclusion. Sudanese patients with RA have significantly higher disease activity and are often IgM-RF-seronegative. Together with reports from Uganda and Cameroon, our data indicate a cluster of highly active and often seronegative RA in central Africa. (First Release August 1 2016; J Rheumatol 2016;43:1777–86; doi:10.3899/jrheum.160303)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
RHEUMATOID FACTOR

SUDAN
DISEASE SEVERITY
DISEASE-MODIFYING ANTIRHEUMATIC DRUGS

Studies on rheumatoid arthritis (RA) in Africa are encumbered with logistic challenges. Many countries on the continent are also currently undergoing economic transformations, urbanization, and acquisition of Western lifestyles, all factors that might change both the clinical presentation and prevalence of RA. Studies from different parts of Africa have reported varying RA disease severity^{1,2,3,4,5,6,7}. Two old reports from Zimbabwe and Nigeria described the disease being less severe in Africa when compared with white patients with RA^{8,9}. In central and western Africa, the disease severity has been

reported to be relatively low^{10,11,12}. Some reports from the eastern^{13,14} and southern¹ parts of Africa published during the last 40 years have claimed that disease severity is increasing. Two more reports have shown divergent results: In a population-based study, Malemba, *et al* argued that the clinical picture of RA in Congolese patients was less severe than in Western countries and that most patients had no extraarticular manifestation or bone erosions², whereas a study in Nigeria determined that the disease was severe and more than 29% of the patients had extraarticular manifestations¹⁵.

From the Department of Immunology, Genetics and Pathology, Uppsala University, Uppsala; Rheumatology Unit, Gävle Hospital, Gävle; Section of Rheumatology, Center for Research and Development, Uppsala University, Region of Gävleborg, Sweden; Khartoum Fertility Center; Rheumatology Unit, Alribat University Hospital, Khartoum; Rheumatology Unit, Military Hospital, Omdurman, Sudan.

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A.I. Elshafie, MD, PhD, Department of Immunology, Genetics and Pathology, Uppsala University; A.D. Elkhalfifa, MD, Rheumatology Unit, Gävle Hospital; S. Elbagir, MD, Department of Immunology, Genetics and

Pathology, Uppsala University, and Khartoum Fertility Center; M.I. Aledrissy, MD, Rheumatology Unit, Alribat University Hospital; E.M. Elagib, MD, FRCP, Rheumatology Unit, Military Hospital; M.A. Nur, MD, FRCP, Rheumatology Unit, Alribat University Hospital; T. Weitoft, MD, PhD, Rheumatology Unit, Gävle Hospital, and Section of Rheumatology, Center for Research and Development, Uppsala University; J. Rönnelid, MD, PhD, Department of Immunology, Genetics and Pathology, Uppsala University.

Address correspondence to Dr. A.I. Elshafie Hassan, Department of Immunology, Genetics and Pathology, Rudbeck Lab C5, Uppsala University Hospital, S-751 85 Uppsala, Sweden.
E-mail: amir.elshafie@igp.uu.se

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To date, the exact prevalence of RA in Africa is not well known¹. One reason might be that reports from different parts of Africa have used different RA criteria for diagnosis¹⁶ and that the age structure differs considerably¹¹. Some papers have reported the disease prevalence in Africa to be lower than that in Europe^{1,9,16}, others claim that the prevalence is increasing^{1,5,6,15,17}, and Kalla and Tikly postulated that this variation could be related to urbanization and the change in lifestyle in Africa⁴. A recent well-conducted epidemiological study from Kinshasa, the Democratic Republic of Congo, found the global prevalence of RA to be 0.6%, varying from 0.07% in the 18–28 age range to 6.25% among those aged 80–89 years¹.

To our knowledge, there are no scientific publications about the prevalence or the severity of RA in modern Sudan, only 1 paper describing the dental status of patients with unclassified RA in Khartoum from 2011¹⁸.

Although population-based studies are superior in comparing the clinical picture between 2 countries, Sudan imposes big problems because of economic and transportation issues, and the fact that rheumatology specialist care is only available in the capital Khartoum, among other things. Given the previous reports about the changing appearance of RA in Africa, we therefore decided to perform a comparative hospital-based study between all Sudanese and Swedish patients with RA attending outpatient clinics during the same time period.

MATERIALS AND METHODS

Patients. Our cross-sectional, hospital-based study was conducted in 3 different rheumatological outpatient clinics, Gävle Hospital in Sweden and Alribat University Hospital and Omdurman Military Hospital in Khartoum, Sudan. Every patient was included on the first occasion when they visited any of the outpatient clinics. The rheumatology clinic at Gävle Hospital serves as a referral center for primary healthcare and other hospital specialists in Gävleborg county, encompassing 170,000 inhabitants, and the clinical information used in our study had been stored in the nationwide online RA registry¹⁹, which is estimated to include 75%–80% of all patients with RA in the region. The Alribat University Hospital and the Military Hospital have the 2 biggest rheumatology outpatient units in Sudan. They serve patients related to the national police and military forces (employees and their relatives), and also provide help to unrelated civilian Sudanese patients without exception. Patients can approach the rheumatology units directly or indirectly through referral. Patients who cannot afford payment for the outpatient visit are also seen by the rheumatologist on equal terms. A maximum of 10% of all Sudanese patients with RA are estimated to be treated either in the private sector (evening services by the 4 rheumatologists in Sudan) or abroad; these patients generally have a better economic situation and are not included in our study. It is the impression of the Sudanese rheumatologists (MIEA, EME, and MAMN) that except for these external patients, there is no selection bias according to social background or financial circumstances. The coverage was good, with only 2% of the outpatients attending the Sudanese clinics for the first time during the inclusion period not wanting to participate. Our estimation was that these 2 units received 75%–85% of all Sudanese patients with RA attending rheumatologists in Sudan, and that the female:male ratio among the included patients represented the true ratio in Sudan. For the Sudanese patients, there are no centrally stored patient records, instead the individual record is kept by the patient and presented to the rheumatologist at admission. Clinical infor-

mation from all patients and blood samples from the Sudanese patients were obtained during outpatient visits between the first of December 2008 and the end of September 2010, and was recorded by 2 of the coauthors (AIE and SE) under the supervision of 3 rheumatology specialists (MIEA, EME, and MAMN). Data on disease onset and evaluation of radiological investigations were retrieved from the written patient records, which were brought by the patients themselves. None of the Sudanese patients had fever or any other general signs of infection at the time of inclusion.

These 3 rheumatologists represent 75% (3/4) of the known specialists working in Sudan during the time of patient inclusion. According to a 2008 census, the former Republic of Sudan had 39 million inhabitants at that time.

RA diagnosis was established by rheumatology specialists according to the 1987 American College of Rheumatology criteria²⁰. A total of 281 consecutive Sudanese patients with RA were included in our study. Serum was separated by centrifugation and frozen on dry ice within 2 h of sampling, stored at –70°C, and transported frozen on dry ice to Uppsala. Approval of the Sudanese studies was obtained from the Ethical Committees of Alribat University Hospital and Omdurman Military Hospital, and written informed consent was obtained from all patients before sampling.

The clinical data for the Swedish patients with RA had been entered by the patients themselves into the computerized national Swedish RA Quality-of-care registry and then completed by the responsible physician. At every visit, information was recorded about tender and swollen 28-joint counts, pain, and general health on visual analog scales, erythrocyte sedimentation rate (ESR), C-reactive protein, and 28-joint Disease Activity Score, in conjunction with the Health Assessment Questionnaire and the EQ-5D. Data on immunoglobulin M with rheumatoid factor (IgM-RF) and disease onset were recorded once. A total of 542 Swedish patients with RA were included during the same inclusion period as the Sudanese patients. Oral informed consent was obtained from each patient and approval to use the registry data was obtained from the regional ethical board in Uppsala.

The clinical data from the Sudanese and Swedish cohorts included age, sex, disease duration, age at symptom onset, age at time of diagnosis, number of tender joints counted from the European League Against Rheumatism 28-joint count²¹, smoking, IgM-RF status, ESR, smoking habits (ever smoker vs never smoker), and types and doses of treatments used. The blood hemoglobin (Hb) level was also recorded for 176 (62.6%) of the Sudanese patients, and evaluation of hand radiographs was available for 60 (21.4%) of the patients. Information about hand and wrist deformities (z-deformity, swan neck deformity, and boutonniere deformity) was recorded for 252 (89.7%) of the Sudanese patients with RA.

RF measurement. An enzyme immune assay (Elias, Phadia/ThermoFisher) was used to measure IgM-RF in the Sudanese patients; analyses were performed in Uppsala, Sweden. Positive results were defined as > 3.9 IU/ml, representing 97.6% specificity among 168 Sudanese healthy blood donors [specificity was aligned to the anticyclic citrullinated peptide 2 (CCP2) specificity in the same cohort]. For Swedish patients, IgM-RF was evaluated by latex agglutination and confirmed by nephelometry (Immage, Beckman Coulter). In a previous comparison between these 2 measures performed on 269 Swedish patients with RA, they showed a κ coefficient of 0.73 and very similar diagnostic sensitivity: 67.3% for the Immage nephelometry and 66.5% for IgM-RF with Phadia Elia (Johan Rönnelid, unpublished data). Anti-CCP2 data were not available in the Swedish RA registry.

Statistics. The Mann-Whitney U test was used to compare differences between groups. The chi-square test was used to test for differences between proportions, and using Fisher's exact test when appropriate. P values < 0.05 were considered significant.

RESULTS

Age and sex aspects. Among the 281 Sudanese patients with RA, 251 were women and 30 men, with a mean age of 48.3 years (SD 13.0) and a median of 49 years (range 18–80). The 542 Swedish patients with RA consisted of 393 women and

149 men with a mean age of 66.6 years (SD 12.9) and a median of 68 years (range 24–92). The number of patients with early RA (disease duration ≤ 12 mos) from Sudan and Sweden were 81 and 71, respectively. The median age of the Sudanese patients was significantly lower than that of the Swedish patients ($p < 0.0001$; Figure 1A and Table 1); this

was also true for patients with early RA investigated separately (Table 1). The percentage of women among the Sudanese patients was significantly higher than that among the Swedish patients (89.3% vs 72.5%, $p < 0.0001$). This difference was also seen in patients with early RA (Table 1). Sudanese patients had significantly shorter disease duration

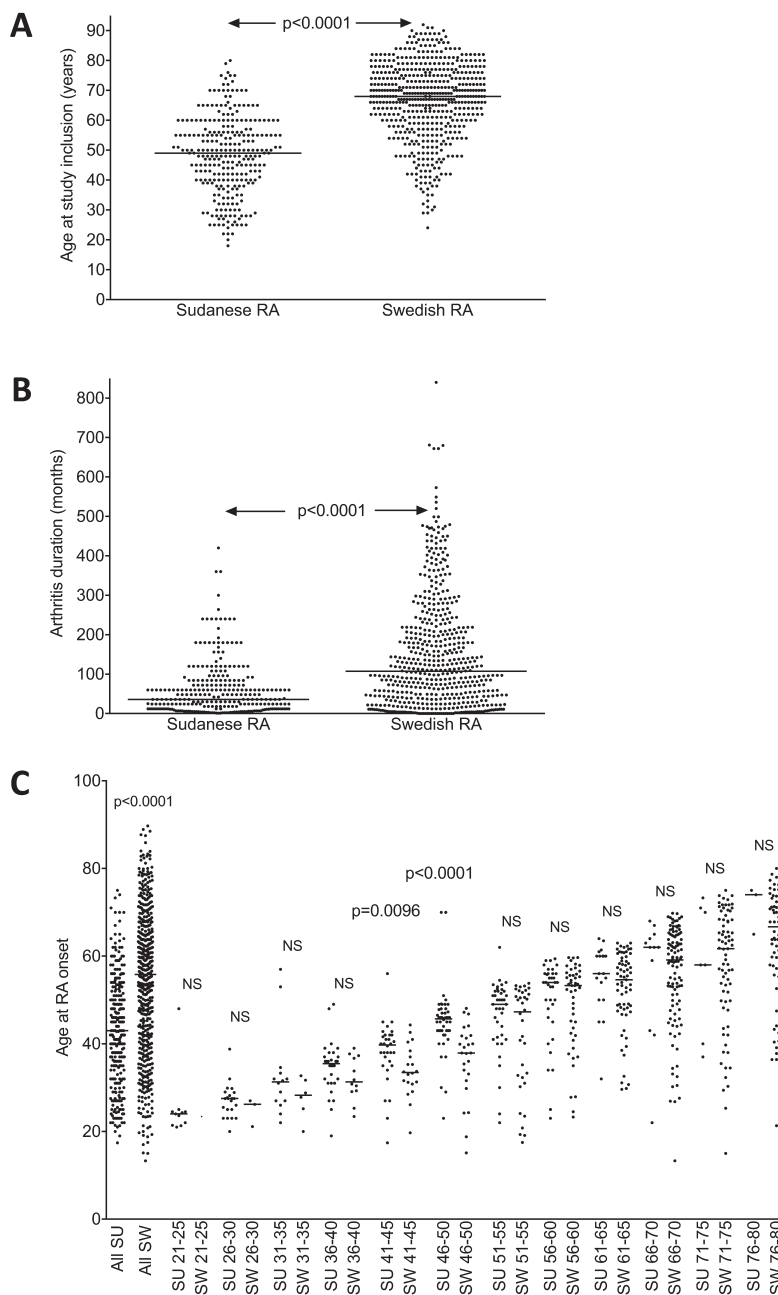


Figure 1. Temporal differences between Sudanese and Swedish patients with RA. A. Distribution of age at study inclusion. B. Distribution of disease duration at study inclusion. C. Age at RA onset, calculated by subtracting disease duration from age at study inclusion. In panel C, data for all patients are depicted to the left, and patients are thereafter stratified in 5-year groups according to age of inclusion in the study. P value depicts differences between median values obtained with the Mann-Whitney U test. Horizontal bars represent median levels. RA: rheumatoid arthritis; SU: Sudan; SW: Sweden; NS: not significant.

Table 1. Clinical characteristics of patients with RA from Khartoum (n = 281) and Gävle (n = 542) at the time of study inclusion. Quantitative differences between median levels were investigated with the Mann-Whitney U test, and differences between proportions with the chi-square test or Fisher's exact test when appropriate. Individual data are missing from some of the Sudanese patients, therefore the proportional data are given as proportions of the number of patients with existing information for each variable.

Variables	All Patients	p	Patients with Early RA	p
Age at inclusion, yrs	49/68*	< 0.0001	42/66*	< 0.0001
Female	251:281 (89.3)/393:542 (72.5)**	< 0.0001	77:81 (95.1)/44:71 (62.0)**	< 0.0001
Disease duration at study inclusion, mos	48/107*	< 0.0001	6/4*	0.07
Age at onset of symptoms, yrs	43/56*	< 0.0001	45/65*	< 0.0001
IgM-RF–positive	131:250 (52.4)/389:515 (75.5)**	< 0.0001	31:66 (47.0)/40:64 (62.5)**	0.08
ESR, mm/h	55/20*	< 0.0001	50/23*	< 0.0001
No. tender joints, 28-joint count	6/1*	< 0.0001	5/2*	0.001
Occurrence of tender joints	210:254 (82.7)/264:539 (49.0)**	< 0.0001	63:70 (90.0)/50:71 (70.4)**	0.004
Patients receiving MTX only	139:267 (52.1)/238:542 (43.9)**	0.029	38:76 (50.0)/44:71 (62.0)**	0.14
Patients receiving DMARD combination	56:267 (22.0)/73:542 (13.5)**	0.006	11:76 (14.5)/3:71 (4.2)**	0.03
MTX dose, patients receiving MTX only, mg/week	12.5/15*	< 0.0001	10/15*	< 0.0001
Patients receiving PSL only	10:267 (3.7)/28:542 (5.2)**	0.37	3:76 (3.9)/1:71 (1.4)**	0.34
PSL dose, mg/day	5/5*	< 0.0001	5/5*	0.095
Patients receiving NSAID only	37:267 (13.9)/31:542 (5.7)**	< 0.0001	14:76 (18.4)/3:71 (4.2)**	0.007
Patients receiving SSZ only	10:267 (3.7)/30:542 (5.5)**	0.27	6:76 (7.9)/1:71 (1.4)**	0.07
SSZ dose, mg/day	1000/2000*	< 0.0001	2000/2000*	0.10
Patients receiving AZA only	7:267 (2.6)/7:542 (1.3)**	0.17	2:76 (2.6)/1:71 (1.4)**	0.60
AZA dose, mg/day	50/100*	0.02	75/100*	0.47
Patients receiving LEF only	2:267 (0.7)/12:542 (2.2)**	0.13	0:76(0%)/0:71(0%)**	—
LEF dose, mg/day	10/10*	0.17	—	—
Patients receiving biologics	0:267 (0)/72:542 (13.3)**	< 0.0001	0:76(0)/10:71 (14.1)**	0.0007

* Median value for Khartoum patients/median value for Gävle patients. ** Proportion of patients with the characteristic: all investigated patients (%) in Khartoum/proportion of patients with the characteristic: all investigated patients (%) in Gävle. RA: rheumatoid arthritis; IgM: immunoglobulin M; RF: rheumatoid factor; ESR: erythrocyte sedimentation rate; MTX: methotrexate; DMARD: disease-modifying antirheumatic drugs; PSL: prednisolone; NSAID: nonsteroidal antiinflammatory drugs; SSZ: sulfasalazine; AZA: azathioprine; LEF: leflunomide.

than Swedish patients with RA (median 48 vs 107 mos, $p < 0.0001$; Figure 1B and Table 1).

The median age at disease onset was significantly lower in the full Sudanese patient cohort when compared with all Swedish patients (43 vs 55.8 yrs, $p < 0.0001$; Table 1 and Figure 1C). When we divided our patients into 5-year age intervals and compared age at study inclusion, an inverse picture appeared. Sudanese patients included at ages 41–45 years and 46–50 years were significantly older than Swedish patients ($p = 0.0096$ and $p < 0.0001$, respectively). A similar trend was found for all patients above 30 years (Figure 1C).

The median age of RA onset was 45 years for IgM-RF–positive patients, and 42 years for IgM-RF–negative patients from Sudan ($p = 0.03$). The corresponding figures for Swedish patients were 58 years and 55 years ($p = 0.047$). Thus, IgM-RF seropositivity was associated with a lower age of RA onset in both Sudan and Sweden (data not shown).

Disease severity. The disease severity was more pronounced among Sudanese patients when compared with Swedish patients. ESR was higher among Sudanese than among Swedish patients (median 55 mm/h vs 20 mm/h, $p < 0.0001$; Table 1 and Figure 2A); the same difference was also evident in patients with early RA (Table 1). Sudanese patients had more tender joints than Swedish patients (6 vs 1 joints, $p < 0.0001$; Table 1 and Figure 2B). Significantly fewer Sudanese

patients were IgM-RF–positive [131/250 (52.4%) vs 389/515 (75.5%), $p < 0.0001$; Table 1]. In the Sudanese cohort, the median Hb level was 12 g/dl among both men and women, and no difference was found between women in childbearing age (< 50 yrs) and elderly women (age > 50 yrs; Figure 2C). Hand examination showed that 81/252 (32.1%) had ulnar deviation, 68/252 (27.0%) had z-deformity, 38/252 (15.1%) had swan neck deformity, and 25/252 (9.9%) had boutonniere deformity. Erosions on hand radiographs were found in 56.7% (34/60) of the Sudanese patients with data available. No data on erosions or hand deformities were available in the RA registry for the Swedish patients.

Treatment. Comparing the full cohorts, the proportion of the Sudanese patients receiving methotrexate (MTX) and disease-modifying antirheumatic drug (DMARD) combinations was statistically higher than the proportion of Swedish patients, significantly more patients in Sudan were treated with nonsteroidal antiinflammatory drugs (NSAID) alone, and none of the biologics used in Sweden (etanercept, adalimumab, infliximab, rituximab, abatacept, and tocilizumab) were used in the Sudanese RA population (Figure 3A). The proportion of Swedes receiving antimalarial drugs was statistically higher than Sudanese (Figure 3A). The most commonly prescribed DMARD in Sudan was MTX (52.1%), followed by sulfasalazine (SSZ; 3.7%), azathioprine (AZA;

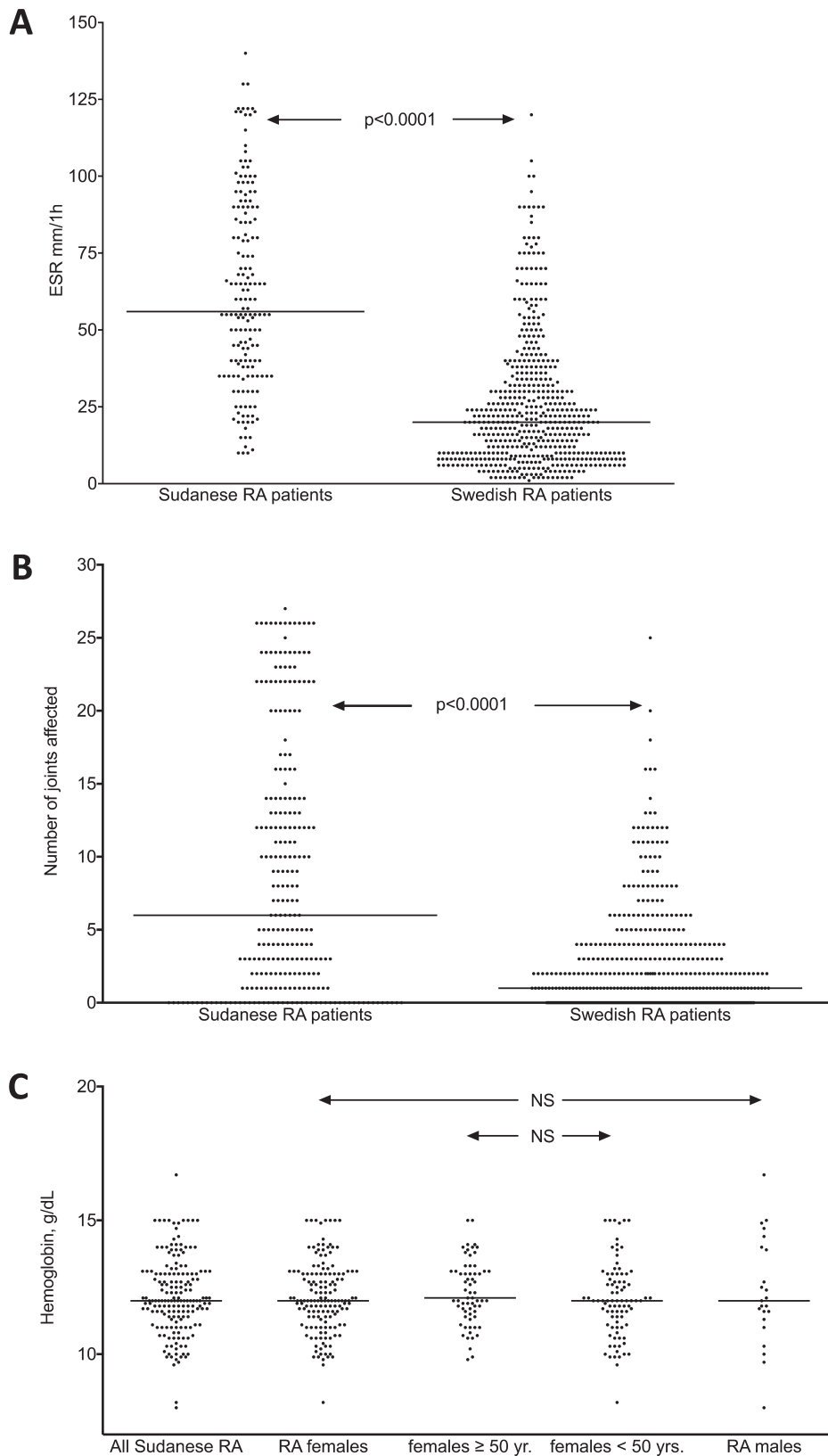


Figure 2. Measures of disease activity in Sudan and Sweden. A. ESR levels. B. No. affected joints. C. Hemoglobin levels in Sudanese patients. Lower reference ranges are represented with dotted lines (men 12.3 g/dl and women 12.1 g/dl). P value depicts differences between median values obtained with the Mann-Whitney U test. Horizontal bars represent median levels. RA: rheumatoid arthritis; ESR: erythrocyte sedimentation rate; NS: not significant.

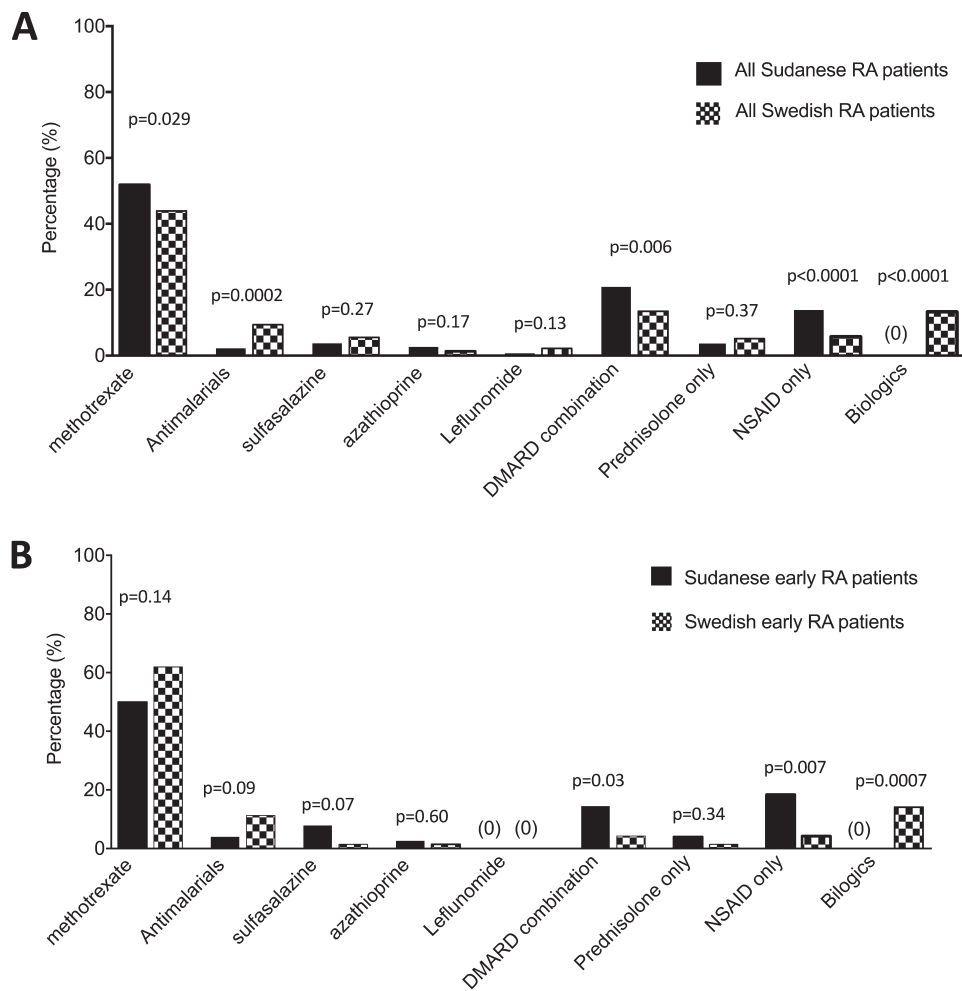


Figure 3. Comparison between Sudan and Sweden in the types and dosage of drugs used. A. Antirheumatic therapies used in all patients. B. Treatments used in patients with early RA (< 12 mos of disease duration). RA: rheumatoid arthritis; DMARD: disease-modifying antirheumatic drugs; NSAID: nonsteroidal antiinflammatory drugs.

2.6%), antimalarials (2.3%), and leflunomide (LEF; 0.8%). There was no difference in the proportion of patients using only prednisolone (PSL), SSZ, or LEF (Figure 3A). Sudanese patients used lower doses of MTX ($p < 0.0001$), SSZ ($p < 0.0001$), and AZA ($p = 0.02$) when compared with Swedish patients; doses of PSL were the same for both groups ($p < 0.0001$; Table 1, Figures 4A and 4F). Doses of antimalarial drugs could not be compared. Swedish patients used either hydroxychloroquine or chloroquine phosphate, while in Sudan, the patients used chloroquine phosphate only. For patients with early RA, the proportions of the Sudanese patients using DMARD combinations and NSAID only were statistically higher compared with the Swedish patients ($p = 0.03$ and $p = 0.007$, respectively; Figure 3B).

Environmental factors. Among the Sudanese patients with RA with data available on smoking history, 3/255 (1.2%) were ever smokers, which differed significantly ($p < 0.0001$) from 63.2% (252/399) ever smokers in the Swedish RA

population. All female Sudanese patients with RA were nonsmokers and 3/27 (11.1%) of the men had a history of smoking (difference between sexes $p < 0.0001$), while there was no sex difference for Swedish patients. Similar comparisons also applied to patients with early RA investigated separately (Table 2).

DISCUSSION

The general age at RA symptom onset was significantly lower among the Sudanese than the Swedish patients. This finding agrees with another north-south comparative study between a developing and an industrialized country, showing that Canadian patients with RA also had a higher age of onset compared with patients with RA from Mexico²². We hypothesized that our finding might be secondary to the fact that Swedes have a 20-year longer life expectancy than Sudanese²³. Therefore, we divided our patients into 5-year percentiles concerning age of inclusion. Contrary to our

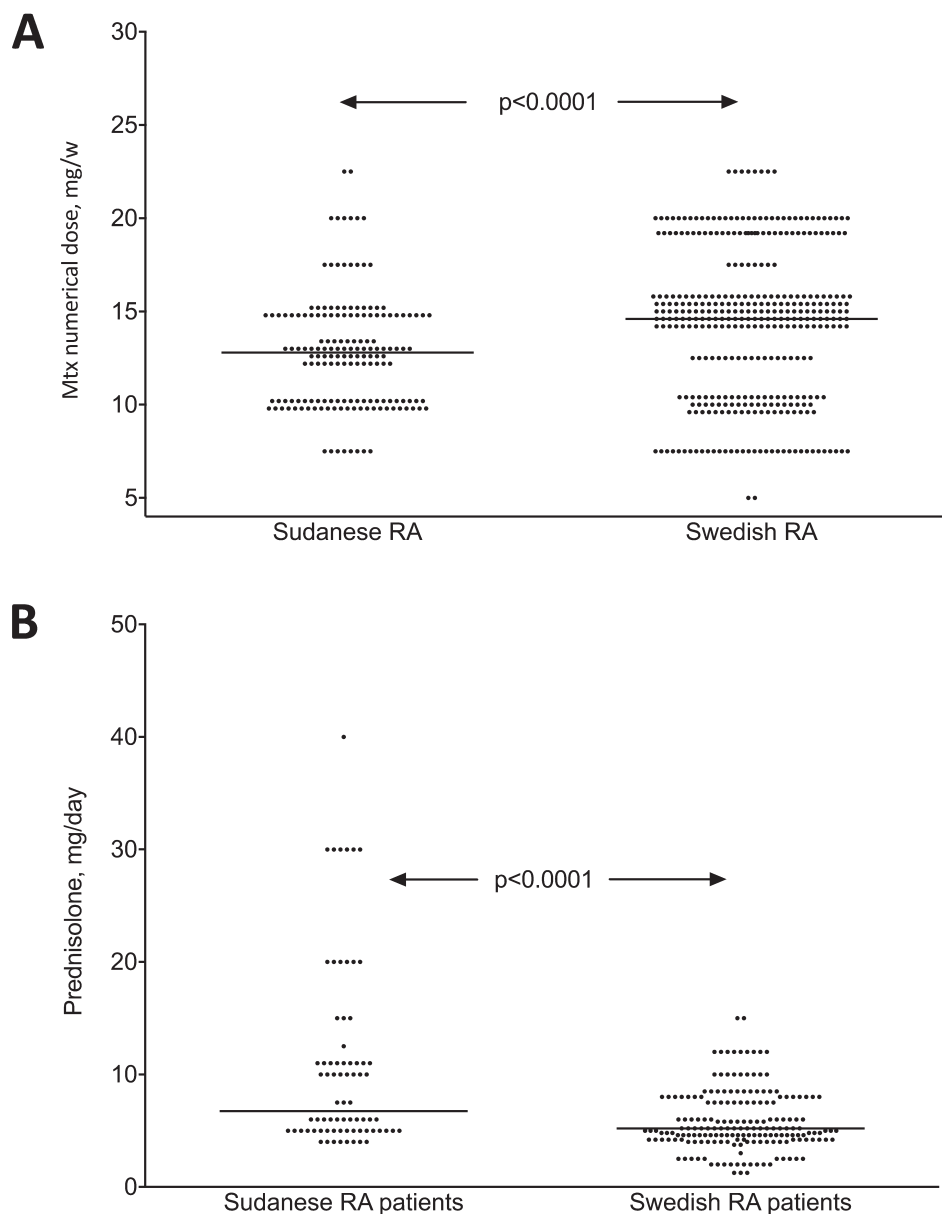


Figure 4. Doses of (A) MTX and (B) prednisolone used in the treatment of Sudanese and Swedish patients with RA. All patients receiving MTX and prednisolone are included, irrespective of any other concomitant antirheumatic therapies. P value depicts differences in median values obtained with the Mann-Whitney U test. MTX: methotrexate; RA: rheumatoid arthritis.

expectations, there was a general trend for higher age at symptom onset in Sudan for all age groups above 30 years, being significant in the 41–45-year and 46–50-year groups. One possible explanation for the higher age of RA onset among the Sudanese patients could be the higher parity among Sudanese than Swedish women²⁴, because high parity may delay RA onset^{25,26,27}. Another reason might be the lower percentage of IgM-RF seropositivity in Sudan, in conjunction with the significantly younger age of IgM-RF-positive patients with RA compared with

RF-negative patients in both Sudan and Sweden; this latter finding is in agreement with a previous Danish study²⁸.

The proportion of women in the Sudanese cohort was higher than among the Swedish patients. Our Swedish RA cohort with 72.5% women is representative for the full Swedish RA population with 73% women²⁹, and also in agreement with other countries in the northeast of Europe: Finland (72%), Denmark (77%), and the Netherlands (66%)³⁰. Conversely, the higher female preponderance in Sudan is in agreement with a high female preponderance in

Table 2. Comparison between smoking habits among female and male patients with RA in Sudan and Sweden. Differences between proportions were calculated with the chi-square test or Fisher's exact test when appropriate.

Variables	All Patients		p	Patients with Early RA		p
	No. Females Smoking: Total Women with Smoking Data (%)	No. Males Smoking: Total Men with Smoking Data (%)		No. Females Smoking: Total Females with Smoking Data (%)	No. Males Smoking: Total Males with Smoking Data (%)	
Ever smoker by sex, Khartoum	0:228 (0)	3:27 (11.1)	<0.0001	0:66 (0)	2:4 (50.0)	<0.0001
Ever smoker by sex, Gävle	193:300 (64.3)	59:99 (59.6)	0.39	20:35 (57.1)	10:12 (83.3)	0.10

RA: rheumatoid arthritis.

Burkina Faso (81%), Egypt (85%), Cameroon (95%), and Senegal (91%)^{3,31,32,33}. Thus, there seems to be a rather uniform finding of a higher female preponderance of RA in Africa as compared with in Europe.

Significantly fewer Sudanese patients with RA were IgM-RF–positive, agreeing with previous studies from other countries in west and central Africa: Nigeria (48% and 13% seropositive)^{9,12}, Congo (33%)¹, Uganda (28%)³⁴, and Zimbabwe (37%)³⁵, but differing from western Africa: Senegal (84% in rural areas and 88% in urban areas)³² and Morocco (78%)³⁶, or from eastern Africa: Kenya (77%)³⁷. This discrepancy may hint that different RA subsets dominate in different parts of Africa, and that the genetic and/or environmental triggering mechanisms might differ³⁸. The Swedish RA registry does not contain information regarding anti-CCP or anticitrullinated protein antibodies (ACPA) in general, and no comparison could be made. We believe the difference in the distribution of RF reactivity in Africa would be accompanied with the same pattern for anti-CCP, because of the close association between the occurrence of RF and anti-CCP in both our earlier Swedish³⁹ and our present Sudanese cohort (data not included).

Except for smoking, which has consistently been related to an increased risk of RA^{38,40}, relatively little is known about environmental factors contributing to RA development. Smoking among women is very uncommon in Sudanese society. Earlier data on cigarette smoking in Sudan⁴¹ revealed the prevalence of cigarette smoking among women to be much lower (0.7%) than among men (12.1%); data matching our RA cohort (0% and 11.1%, respectively). So what could be the triggering mechanism behind RA development among Sudanese women? We hypothesize that dukhan (smoke baths)⁴² practiced by Sudanese women might be a triggering factor for the development of RA in Sudan. Dukhan is a universal custom among married women in Sudan. The women sit covered by a blanket on a low footstool over a hollowing in the ground where tall wood is burned. The women will then be exposed to the smoke of the burning wood, and the inhaled smoke may reach the lungs, leading to systemic inflammation⁴³. Dukhan is not common among Sudanese men. We have no epidemiological data about dukhan habits in our cohort or in Sudan in general, but it is practiced by almost all married Sudanese women. Thus, we

hypothesize that dukhan might be another environmental RA risk factor acting through the lungs in a similar manner to cigarette smoking³⁸, silica exposure^{44,45}, traffic pollution⁴⁶, or most recently, occupational exposure to textile dust⁴⁷. The low prevalence of autoantibody-positive RA in our Sudanese cohort is, however, an argument against this hypothesis, because the strong association between smoking and RA has been reported to be confined to the ACPA-positive RA subset, at least among whites³⁸.

The Sudanese patients with RA had higher disease activity, as reflected by higher ESR and numbers of tender joints. In comparison with what had been claimed about the disease severity of patients with RA from Africa^{1,15}, our Sudanese patients have very active disease and high frequency of radiological erosions and hand deformities. Reports from Uganda described RA as severe, many with erosions (70%), and < 30% of the patients with IgM-RF³⁴. Considering our results and the Ugandan data, there seems to be a clustering of highly active and often seronegative disease in central Africa. Median Hb levels were similar among Sudanese men and women with RA. At Alribat University Hospital, the reference range for women was 11–14 g/dl, and for men 12–16 g/dl (Professor Anwar Kurdo-fani and Professor Abderhman Tambal, personal communication). Using these Sudanese reference ranges that are lower than in Sweden, 16% of our female patients with RA with Hb information were anemic.

The varieties of treatment used were similar in the 2 populations except for biologics, which were used only in Sweden. Most probably this is a cost issue. Sudanese patients have less money and must pay for their own drugs, whereas Swedish patients are part of a social welfare system that pays for all prescribed drugs over a certain limit (currently about US\$ 260/yr). There has also been an argument that tumor necrosis factor blockers might impose safety issues in developing countries in which the proportion of inhabitants with manifest or latent tuberculosis is high⁴⁸. A higher proportion of Sudanese patients with RA used MTX alone or DMARD combinations when compared with the Swedish patients with RA. This difference, especially the increased use of DMARD combinations in Sudan, should probably be viewed in the context of the absence of biologics among the Sudanese patients because combined therapy has

been found to be superior than the use of MTX monotherapy alone^{49,50}.

Treatment with NSAID only was significantly more common among Sudanese patients, and this was also seen for patients with early RA, investigated separately. Among the Sudanese patients, 13.9% (37/267) used only NSAID, and among the patients with early RA, the corresponding figure was 18.4%. We hypothesize that the reasons might be a fear of using what might be regarded as cytotoxic drugs, inadequate access to drugs, a cost issue, or a combination of these factors. This finding is important and merits further investigation. Focused information on the importance of early and efficient treatment to patients with newly diagnosed RA might represent a very cost-effective way of decreasing disease activity and disability among Sudanese patients with RA.

Sudanese patients generally used lower doses of MTX and higher doses of PSL than Swedish patients. Increased PSL usage might be due to an intent to obtain a fast clinical response in patients with flares in a healthcare context in which regular followup is difficult.

The clinical comparison between Sudan and Sweden has obvious weaknesses. The most obvious is the patient selection—all rheumatology specialists active in Sudan at the time of inclusion were situated in Khartoum, i.e., far from many areas of the country. We are also aware that the social situation differs substantially between Sudan and Sweden, and that this probably has an effect on which patients with RA will have the possibility to approach a rheumatology outpatient clinic in the 2 countries. The included patients correctly describe patients with RA attending rheumatology specialist care during the inclusion period, because almost all patients with RA attending 3 of the 4 Sudanese rheumatologists active during the inclusion period have been participating in our study. Although there probably is a selection bias concerning which patients with RA eventually attended the outpatient clinics, the social responsibility that is associated with the Sudanese family structure together with the Sudanese charity system will help patients in need to see a rheumatologist. Thereafter, the compliance to prescribed treatment is probably a bigger problem, both economically (because MTX is less affordable than, for example, anti-parasite drugs) as well as logistically, because many patients live far from pharmacies, which have irregular supplies of drugs.

Data on Hb and radiographs were available only from a fraction of the patients, and there is an obvious risk that patients for whom these investigations had been ordered represented a subgroup with highly active disease and/or patients who could afford these investigations. Also, no followup data are available for the patients in our cross-sectional study.

The time given to inform a newly diagnosed patient about RA differs considerably between the 2 countries. Whereas a

Gävle patient commonly attends a 1-h visit with the rheumatologist to receive an introduction to her/his disease and its treatment during an individual encounter at the doctor's office, the corresponding time in Khartoum is about half as long, and the consultation most often takes place in a common outpatient room with many other consultations going on in parallel.

We have determined that Sudanese patients with RA have more widespread joint involvement and stronger laboratory signs of inflammation compared with Swedish patients with RA. Sudanese patients also have radiological erosions and RA-associated hand deformities to a large extent, although only half of the patients are IgM-RF seropositive. This finding of highly active and often seronegative RA in east-central Africa differs from the rather widespread belief that RA in Africa has a mild clinical course. The Sudanese use of lower MTX doses and higher PSL doses, more patients receiving DMARD combinations, and many patients treated with NSAID only might be owing to structural dissimilarities between healthcare systems, economic prerequisites, and possibilities for extensive patient education and clinical followup of patients with RA in Sudan and Sweden.

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