

Rheumatoid arthritis in Saudi Arabia

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ABSTRACT

تمت دراسة وضع التهاب المفاصل الروماتويدي (RA) في المملكة العربية السعودية من مناح عدة بناءً على مراجعة علمية منهجية موثقة لكل ما تم نشره وبناءً أيضاً على خبرة المؤلفين. لقد تم عمل مسح علمي للشبكة المعلوماتية الطبية باستخدام قاعدة بيانات البيميد (Pubmed) وموقع الأفيدي (OVID) وموقع الإيبسكو (EBSCO) وبعض المجلات الطبية المحلية لاستخراج جميع الدراسات والأبحاث التي عملت عن مرض التهاب المفاصل الروماتيزمي في السعودية ما نتج عن 43 دراسة. لقد تم استنتاج أن هذه الدراسات والأبحاث لا تبين الوضع العام لرعاية هذا المرض بشكل دقيق وذلك على الرغم من الجهد الكبير المبذول في هذه الأبحاث إذ أن أغلبها يمثل مراكز طبية محدودة. وتمت ملاحظة أنه وعلى الرغم من شيوع استخدام العلاجات الحيوية على المستويين الحكومي والخاص في السعودية إلا أنه لا توجد إلى الآن لوائح وطنية تنظم طرق وصف وعلاج هذا المرض في السعودية بناءً على الاحتياجات والنظم المحلية. كما تمت ملاحظة أنه لا توجد إلى الآن أية قاعدة معلومات وطنية لهذا المرض على الرغم من الجهد المبذول. وبالمحصلة النهائية، فإن هذا التحليل قد يساهم في التخطيط المستقبلي لإعداد لوائح وتوجهات لرعاية مرض التهاب المفاصل الروماتيزمي في السعودية.

The status of rheumatoid arthritis (RA) in Saudi Arabia (SA) was examined from various perspectives based on a systematic literature review and the authors' personal experiences. In this regard, database and journal search were conducted to identify studies on RA in SA, yielding a total of 43 articles. Although efforts have been made to promote RA research in SA, current studies mostly represent only a few centers and may not accurately portray the national status of RA care. Notably, biological therapies were introduced early for almost all practicing rheumatologists in SA (government and private). However, no national guidelines regarding the management of RA have been developed based on local needs and regulations. Also, while efforts were made to establish RA data registries, they have not been successful. Taken together, this analysis can contribute to the planning of future guidelines and directives for RA care in SA.

Saudi Med J 2014; Vol. 35 (12): 1442-1454

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Rheumatoid arthritis (RA) is a chronic inflammatory disorder that usually occurs in middle-aged individuals and leads to tissue destruction in the synovial joints (for example, hands, wrists, knees). Although RA manifestation includes pain, stiffness, swelling, and functional impairment, it can be difficult to diagnose in the early stages, as its symptoms can closely mimic other diseases.¹ Moreover, clinical management of RA can be complicated by the fact that it represents a variable disease that exhibits differential therapeutic responses.² For this reason, ongoing investigation into the origin of patient variability and ways to enhance RA management/treatment are essential for improving the current level of clinical care provided by rheumatologists. There are several methods presently employed for RA diagnosis and monitoring of therapeutic outcomes,³ such as direct examinations, and more sophisticated imaging technologies (for example, ultrasound).⁴ Following diagnosis, therapy for RA focuses on controlling symptoms to prevent further joint damage. In this regard, RA is commonly treated using disease-modifying anti-rheumatic drugs (DMARDs) and/or biological therapies (for example, anti-tumor necrosis factor alpha [TNF- α]).³ Notably, the study of the differential utilization of these management options in various centers or regions, as well as the way in which distinct clinical practices can influence the efficacy of diagnosis, monitoring, and treatment strategies, can yield insight into effective treatment options for RA patients. To improve patient care, there has recently been a growing initiative to conduct RA-related studies in various regions of Saudi Arabia (SA). Nevertheless, data

from these investigations have not yet been compiled to highlight the current status of RA management in SA. Therefore, the purpose of this review was to systematically analyze the literature regarding RA in SA to thoroughly examine this topic from various perspectives, including our own personal experiences. Here, we discuss the results of our analysis, which can contribute to the planning of future national guidelines and directives on the care of RA patients in SA. In addition, our findings can promote further research aimed at solving current obstacles in RA management at both the national and international levels.

Systematic search strategy and study selection. Here, we have conducted an electronic literature search via MEDLINE using PubMed (US National Library of Medicine, 1984 to February 2014), Ovid, and EBSCO databases. In addition, we performed an electronic search in 3 local journals (for example, Saudi Medical Journal, Annals of Saudi Medicine, and Journal of King Abdulaziz University Medical Science), identifying 2 more articles.^{5,6} The following search terms were used: “rheumatoid arthritis in Saudi Arabia”, “rheumatoid factor in Saudi Arabia”, “diagnosis of rheumatoid arthritis in Saudi Arabia”, “Saudi rheumatoid arthritis patients”, and “anti-TNF- α in Saudi Arabia”. Studies on RA in SA were reviewed, and relevant articles were selected (Table 1). Included articles fulfilled the

following criteria: 1) prospective study, retrospective study, or review article; and 2) written in English. However, articles on juvenile RA, systemic lupus erythematosus (SLE), Sjögren syndrome, or other rheumatic diseases were excluded. Moreover, studies regarding RA in non-Saudi populations and case reports were excluded. Data were classified according to different categories: epidemiological, clinical features, laboratory, radiological, management, and reviews (Table 2). Eight studies were excluded: 2 represented double publications,^{7,8} 5 were case reports,⁹⁻¹³ and one was conducted on non-Saudi RA patients.¹⁴ Ultimately, a total of 43 studies were identified through our literature searches.

Study types and characteristics. We first analyzed the features of the articles identified in our systematic literature search regarding RA in SA (Table 1). We found that most studies involved only a single center.^{7,15-18} Also, there were a few early articles published by single authors, reporting their own experiences, including retrospective case series following patients over one or 5-year periods at a single center (King Khalid University Hospital).^{15,16} Subsequently, this pattern of publication continued, with one^{17,19-21} or multiple authors^{18,22,23} using a retrospective case methodology to report findings. These publications included both clinical, and laboratory results, which were obtained from cohorts

Table 1 - Results from a systematic literature search on rheumatoid arthritis (RA) in Saudi Arabia (SA).

A) Systematic literature search in PubMed, OVID, and EBSCO					
Key words	Articles in general	Articles related to RA in Saudi Arabia	Articles in PUBMED	Articles in OVID	Articles EBSCO
1. Rheumatoid arthritis in SA	96	54	96	78	13
2. Rheumatoid factor in SA	28	18	28	23	6
3. Saudi rheumatoid arthritis patients	83	43	83	68	14
4. Prevalence of rheumatoid arthritis in SA	19	13	19	19	4
5. Diagnosis of rheumatoid arthritis in SA	52	25	52	39	8
6. anti-TNF- α in SA	9	3	9	7	1
7. Radiological changes in rheumatoid arthritis in SA	4	2	4	4	1
8. Treatment of rheumatoid arthritis in SA	49	27	49	43	7
B) Electronic search in 3 local journals					
Key words	Articles in Saudi Med J	Articles in Journal of King Abdulaziz University-Medical Science	Articles in Ann Saudi Med		
1. Rheumatoid arthritis in SA	9	2	0		
2. Rheumatoid factor in SA	5	1	0		
3. Saudi rheumatoid arthritis patients	7	2	0		
4. Prevalence of rheumatoid arthritis in SA	5	1	0		
5. Diagnosis of rheumatoid arthritis in SA	3	0	0		
6. Anti-TNF- α in SA	0	0	0		
7. Radiological changes in rheumatoid arthritis in SA	4	0	0		
8. Treatment of rheumatoid arthritis in SA	5	1	0		

TNF- α - tumor necrosis factor-alpha, OVID - Publius Ovidius Naso,

EBSCO - Elton Bryson Stephens Company, Saudi Med J - Saudi Medical Journal, Ann Saudi Med - Annals of Saudi Medicine

of RA patients from various centers. Additionally, there were some reports published by multiple authors from more than one center using either cross-sectional methodologies²⁴ or questionnaire-based studies.²⁵ We also identified several RA-related review articles published by Saudi authors.²⁶⁻²⁹

The epidemiology and clinical features of rheumatoid arthritis in Saudi Arabia. As previously mentioned, most of the identified studies represented single center experiences. One of the earliest reports indicated that 39 out of 194 RA patients displayed less severe findings when compared to RA patients in “the west”, but no specific details were given.¹⁵ In contrast, a later study from the same center, involving 195 patients who were followed over a 5-year period, concluded that the RA disease pattern (rheumatoid factor [RF] positivity) and joint distribution in SA resembled that observed in other developed countries.¹⁶ Notably, the only study of its kind, 5,891 adult subjects were analyzed within the Qassim region of SA to determine the prevalence of RA in SA, which was estimated to be 2.2 per thousand people.³⁰ However, future studies are needed to confirm this relatively low rate of RA in SA. Moreover, it was found that RA in SA was more common in women, increasing with age.³⁰

Although human leukocyte antigen (HLA-DR10) was identified as the most common human leukocyte antigen associated with RA in 91 patients from King Saud University,¹⁷ those with HLA-DR10 showed only limited differences in clinical presentation when compared to those without.¹⁷ However, it must be noted that the study contained no control group. However, a later cross-sectional study among 70 RA patients and 70 controls revealed that HLA-DRB1 *04 was the most frequent allele associated with RA, followed by DRB1 *08, and DRB1 *10.³¹ In addition, further molecular subtyping revealed a statistically significant association between RA and DRB1 *0405.³¹ All studies addressing the clinical features of RA in SA are listed in Table 2. Cross-sectional studies^{24,25} and retrospective case series^{16,18,32,33} represented the most frequently used methodologies. Among 340 RA patients from 3 different centers in western SA, hypertension (35.9%) was observed to be the most common comorbidity, followed by diabetes mellitus (30.9%), osteoporosis (25.8%), and dyslipidemia (19.4%).²⁴ Furthermore, there was one study involving 140 RA patients at King Abdulaziz University hospital, which retrospectively reviewed the incidence of extra-articular manifestations of RA¹⁸ (Table 3). In a highly selected patient group (7 females and 3 males), which acquired retrognathia secondary to RA, 3 patients were found to have

obstructive sleep apnea. Additionally, in 40 patients with early RA, 10% were found to have interstitial lung disease, 27% showed abnormal high resolution computed tomography, and 32.5% displayed abnormal pulmonary function tests.³²

Finally, although few studies in the literature have addressed work ability among housewives with RA, a cross-sectional study involving 120 patients from 3 different hospitals in SA found that housewives suffered worse work ability outcomes and poorer work satisfaction compared to paid workers with RA.²⁵

Laboratory-related studies. We identified a total of 18 publications concerning laboratory findings in Saudi RA patients (Table 2). However, one laboratory-related article, which focused on cytokine profiling in gingival crevicular fluid from RA patients with chronic periodontitis, was categorized as a review.³⁴ Among the remaining 17 studies, 4 focused on experimental mouse models,³⁵⁻³⁸ whereas the majority were retrospective patient studies. These investigations often described the experiences of single centers and represented specific regions of SA.

In addition, the articles on laboratory findings could be classified as either basic science or experimental results. With regard to the basic science papers, we could further divide them into immunological or genetic studies. Among the immunological studies,³⁹⁻⁴³ the levels of various cytokines were measured in RA patients. However, there was no clear clinical significance for these findings. Most of these articles concluded that cytokines produced by monocytes (interleukin-1 alpha [IL-1 α], IL-6, TNF- α , and granulocyte macrophage colony-stimulating factor [GM-CSF]) and CD4+ T cells (Th2 cytokines: IL-4 and IL-10) played important immunopathologic and immunoregulatory roles in RA patients.^{42,44,45} Among the articles that focused on genetics,^{43,46-48} we identified a case-control study involving 232 Saudi subjects (106 RA patients and 126 matched controls), which was conducted at the Prince Sultan Military Medical City, Riyadh.⁴³ It was found that individuals with the GG genotype at position -308 of TNF- α were susceptible to RA, whereas genotype AA conferred a potentially protective effect with regard to RA susceptibility. In contrast, the GG and AA genotypes of TNF- α at +252 position were suggested to contribute to additive RA susceptibility. Thus, these TNF- α (-308) and TNF- α (+252) polymorphisms may represent pivotal genetic changes that can influence RA susceptibility within the Saudi population. Furthermore, transferrin C (TfC) subtypes were investigated in RA patients, revealing a significant association between TfC2 and RA. Indeed,

Table 2 - Classification of identified studies on rheumatoid arthritis (RA) in Saudi Arabia.

Categories/ reference	Year	Patient number	Center(s)	Duration	Study type	Principal findings	Comments
<i>Epidemiological studies</i>							
Rajapakse ¹⁵	1987	39	KKUH, Riyadh	one year	Retrospective	Rheumatoid arthritis less severe compared to the West	Single center
Al-Dalaan et al ³⁰	1998	5,891 adults studied: 2,674 males and 3,197 females; 13 cases of RA diagnosed according to ACR	King Fahad Hospital, Qassim	NS	House-to- house epidemiological survey	The prevalence of RA in Al Qassim was estimated at 2.2 per thousand people; disease prevalence increased with age and in females	One region in SA; small sample size
Al-Arfaj ¹⁷	2001	91	KSU, Riyadh	NS	Retrospective	Little difference between RA patients with HLA-DR10 compared to those without	HLA-DR10 is the most common in Saudi population
Al-Swailem et al ³¹	2006	140 subjects: 70 RA patients and 70 matched healthy controls	PSMMC, Riyadh	NS	Cross-sectional	HLA-DRB1 *04 was the most frequent allele associated with RA, followed by DRB1 *08 and DRB1 *10	
<i>Clinical features</i>							
Alballa ¹⁶	1995	195	KKUH, Riyadh	5 years	Retrospective	RF was positive in 79.5% of cases; most frequently involved joints were the PIP joints, knees and MCP joints; rheumatoid nodules in 15.9% and keratoconjunctivitis sicca in 14.4% of cases; most patients used second line drugs; the majority of patients (57.4%) were in functional class 1 and 2	Single center
Alamoudi ³³	2006	7 women and 3 men with acquired retrognathia secondary to RA	KAUH, Jeddah	NS	Case series	SDB occurs frequently in non-obese patients with acquired retrognathia secondary to RA; SDB severity is related to the degree of retrognathia and the presence of daytime sleepiness; nasal CPAP therapy is effective and well tolerated	Highly selected groups; small sample size
Al-Ghamdi & Attar ¹⁸	2009	140	KAUH, Jeddah	4 years	Retrospective	The frequency of ExRA was 70% among Saudi RA patients, which is higher than North American populations (40%), but similar to the British population (68%); see Table 3	Single center; short follow-up time
Habib et al ³²	2011	40	Al Ahsa Hospital, Al Ahsa	3 years	Retrospective	10% of patients had ILD, 27% had abnormal HRCT, and 32.5% had abnormal PFT; more evident with active RA, seropositivity, steroid use and anti-TNF- α therapy	Small sample size; conducted on early RA patients
Al-Bishri & Attar ²⁴	2013	340	Al-Hada Hospital, National Guard Hospital and King Abdul-Aziz Hospital, Jeddah	1 year	Cross-sectional	Most RA patients suffered from comorbid conditions, including hypertension, diabetes, osteoporosis, and dyslipidemia that impact treatment regimens; physicians may be forced to prescribe RA medications that worsen comorbidities; comorbidities should be carefully considered and treated in addition to RA	Three centers
Janoudi et al ²⁵	2013	120 RA patients	Dr. Soliman Fakeeh Hospital, Jeddah	9 months	Cross-sectional	Housewives with RA suffer worse work ability outcomes and poorer work satisfaction compared to paid workers with RA	
ACR - American College of Rheumatology, RF - rheumatoid factor, PIP - proximal interphalangeal, MCP - metacarpophalangeal, SDB - sleep-disordered breathing, CPAP - continuous positive air pressure, ExRA - extra-articular manifestations in rheumatoid arthritis, TNF- α - tumor necrosis factor-alpha, ILD - interstitial lung disease, HRCT - high resolution computed tomography, HLA - human leukocyte antigen, KKUH - King Khalid University Hospital, KSU - King Saud University, KAUH - King Abdulaziz University Hospital, PSMMC - Prince Sultan Military Medical City							

Table 2 - Classification of identified studies on rheumatoid arthritis (RA) in Saudi Arabia (continuation)

Categories/ reference	Year	Patient number	Center(s)	Duration	Study type	Principal findings	Comments
<i>Laboratory</i>							
El-Hazmi et al ⁶⁶	1991	128	KSU, Riyadh	NS	Cross-sectional	A significant association between TfC2 and RA was found, whereas TfC1 homozygous phenotype is protective for the development of RA	
Al-Janadi et al ³⁹	1993	NS	KSU, Riyadh	NS	Cross-sectional	The CD4 ⁺ CD29 ⁺ T cell subsets produced elevated levels of IL-4 and IL-6, but deficient levels of IL-2; IL-6 cytokine induced CD4 ⁺ CD29 ⁺ subsets were found to provide effective helper function to B cells in IgG and IgM synthesis	Missing information
Kamel & Serafi ⁷⁹	1995	135 RA patients & 60 healthy controls	Dr. Fakhry Hospital, Dhahran	NS	Case-control	Serum L-fucose was significantly correlated with rheumatoid disease activity, duration, number of involved joints, and bone erosions	No clear clinical application
Al-Janadi et al ⁴¹	1996	NS	KSU, Riyadh	NS	Cross-sectional	Cytokines produced by monocytes (IL-1 α , IL-6, TNF- α , and GM-CSF) and by CD4 ⁺ T cells (Th2 response: IL-4 and IL-10) may exert immunopathologic and immunoregulatory effects in SF, thereby mediating some of the clinical manifestations of RA	Missing information; no control group
Al-Janadi et al ⁴⁰	1996		KSU, Riyadh	NS	Cross-sectional	IL-10 may play an important role in highly disturbed immune systems and B cell-T cell function in RA and SLE	
Sankaran-Kutty et al ⁴⁵	1998	70	KFUH, Al Khobar, SJMC, and USM	5 years	Comparative	Comparing SA to Malaysia, brucellar and tuberculous arthritis were predominantly seen in SA; the incidence of RA, pigmented villonodular synovitis, and acute suppurative arthritis was almost equal in both countries	
Haq et al ¹²	1999	28	KFSH&RC, Riyadh	NS	Case-control	The presence of elevated levels of endothelin-1 in SF and serum samples of patients with RA	
Al-Mobireek et al ⁴⁴	2000	48 adult male guinea pigs aged 4-6 months; divided into 2 groups	KSU, Riyadh	Four animals from each group were sacrificed and examined clinically and radiographically at intervals of 48 hours and 1, 2, 4, 6, and 8 weeks	Experimental	The clinical and radiographic manifestations are comparable with those previously reported in the small joints of humans	RA was induced by inactivated group A Streptococcus pyogenes
Alorainy ¹⁰⁰	2008	40 male rats	Alqassim University, Alqassim	NS	Experimental	Proper management of antioxidant intake may reduce free radical generation and improve antioxidant status in RA; allopurinol and vitamin E may effectively normalize the impaired oxidant/antioxidant system and delay RA complications	Human studies needed to verify findings
Al-Rayes et al ⁴³	2011	232 subjects: 106 RA patients and 126 matched controls	PSMMC, Riyadh	1 year	Case-control	Important role of ethnicity in the association of TNF- α and TNF- α polymorphism in RA; TNF- α (-308) and TNF- α (+252) polymorphisms may work in tandem in the pathogenesis of RA in Saudi patients	
Khan et al ⁴⁸	2011	NS	KKUH, Riyadh	NS	Case-control	High binding of modified DNA with IgG from RA patients might explain possible antigenic role of 4-hydroxyestradiol (4-OHE)2 -modified DNA in the production of anti-DNA antibodies; these antibodies may be useful for RA diagnosis	
Safi et al ⁶	2012	200 Saudi RF-negative RA patients; 164 females & 36 males	NS	NS	Cross-sectional study	There was no difference in the severity or treatment of RA patients with RF/CCP ⁺ compared to RF-/CCP ⁻ patients. Anti-CCP test was not useful for disease activity or patient management decisions.	Single center
Attar ⁴⁹	2012	100 RA patients (85% women) and 100 controls	KAUH, Jeddah	January 2010 to December 2011	Retrospective	Serum vitamin D levels in RA patients were similar to healthy controls; significantly lower 25-hydroxy vitamin D values were found in poor responders to treatment that were not in disease remission	Single center experience; small sample size; short duration
Arwa et al ⁵	2013	43 patients with plaque psoriasis, 55 RA patients and 40 healthy controls matched for age	PSMMC, Riyadh,	Between March and September 2012	Cross-sectional study	Serum 25-hydroxy vitamin D levels were significantly lower in psoriatic and RA patients than in healthy controls	Single center experience; small sample size; short duration
Ramadan & El-Menshaway ³⁸	2013	AIA rat model	KFU, Al-Hufuf	NS	Experimental	Ginger-turmeric rhizomes mixture may be effective against RA severity and complications	
Ahmad et al ³⁷	2013	AIA rat model	KSU, Riyadh	NS	Experimental	Oral treatment with grape seed proanthocyanidin extract attenuated AIA in mice	
Abd-Allah et al ³⁵	2014	CAIA rat model	KSU, Riyadh	NS	Experimental	Histamine 4 receptor agonist (JNJ) exhibits significant anti-inflammatory and anti-arthritis activities, demonstrating the clear involvement of H4R antagonism in the pathogenesis and progression of RA	
Hussein et al ⁴⁷	2014	160 RA patients & 168 healthy unrelated controls	Eltaiief University, Eltaiief	NS	Case-control	The TGF- α 1 TT genotype may determine the development of osteoporosis and bone erosion in RA	
Ahmad et al ³⁶	2014	NS	KSU, Riyadh	NS	Experimental	3-aminobenzamide, an inhibitor of poly (ADP-ribose) synthetase activity, may represent a therapeutic approach in RA	

RA - rheumatoid arthritis, NS - not specified, AIA - adjuvant-induced arthritis, TfC2 - transferrin C2, TfC1 - transferrin C1, TNF- α - tumor necrosis factor-alpha, GM-CSF - granulocyte macrophage colony-stimulating factor, IL - interleukin, SLE - systemic lupus erythematosus, SF - synovial fluid, SA - Saudi Arabia, CCP - CCP - cyclic citrullinated peptide, JNJ - JNJ7777120, ADP - Adenosine diphosphate ribose, H4R - histamine 4 receptor, KSU - King Saud University, KFUh - King Fahad University Hospital, PSMMC - Prince Sultan Military Medical City, KFU - King Faisal University, KFSH&RC - King Faisal Specialist Hospital & Research Center, SJMC - Subang Jaya Medical Medical Center, USM - University Science Malaysia, KKUH - King Khalid University Hospital, KAUH - King Abdulaziz University Hospital

Table 2 - Classification of identified studies on rheumatoid arthritis (RA) in Saudi Arabia (continuation)

Categories/reference	Year	Patient number	Center(s)	Duration	Study type	Principal findings	Comments
<i>Radiological</i>							
Al-Boukai & Al-Arfaj ⁵¹	2003	49	KKUH, Riyadh	3 years	Prospective	Cervical spine changes are common in patients with RA, particularly subluxation, and are non-significantly correlated with disease duration, female gender, and RF	
Noorwali ¹⁹	2004	30	Al-Noor Specialist Hospital, Makkah	9 months	Case-control	A significant decrease in BMD was observed in RA patients compared with healthy controls; impaired functional activity, increased disease activity, and long-term steroid use are major determinants of BMD in both spinal and femoral bones	All patients were females; single center study
Al-Arfaj & Al-Bouki ⁵⁰	2005	56	KKUH, Riyadh	4 months	Prospective	Radiographic changes in hands and feet of Saudi RA patients are less severe than those reported in the West. Differential pattern of effects observed in the feet	
Attar & Ghamdi ²²	2010	57	KAUH, Jeddah	7 months	Prospective	Higher rate of radiological changes in RA patients in West SA compared to central SA, but a lower rate than patients from industrialized countries; hands and feet equally involved	
<i>RA management</i>							
Eleishi et al ⁵³	2009	36	Dr. Soliman Fakeeh Hospital, Jeddah	3 years	Retrospective	Anti-TNF agents effective and well tolerated; financial issues appear to be a major factor interfering with treatment compliance for anti-TNF agents in SA	
Attar ²¹	2010	116	KAUH, Jeddah	3-years	Retrospective	Gastrointestinal disturbances were the most common side effects of methotrexate, while lung involvement was the least; the impact of clinical variables on side effects requires close attention	
Dewedar et al ⁵²	2012	2 groups: 112 RA patients each	Suez Canal University, Egypt & KKUH, Abha	5 years	Prospective	The use of anti-TNF therapy was as safe as traditional DMARDs; long-term follow-up with careful examination is essential to detect adverse effects	
Arafa et al ¹⁰¹	2013	100 rats; acute or chronic arthritis induced by bacterial outer membrane protein	Jazan University, Jazan	15 days	Experimental	Oral administration of either echinacea or genuphil nutraceutical supplements led to decreased rheumatic marker levels compared to controls	
<i>Review articles</i>							
Daba et al ¹⁰²	2004	NA	KSU, Riyadh		Review article	Drug-induced pulmonary fibrosis	
Al-Ahaideb et al ²³	2006	NA	KSU, Riyadh		Review article	Fractional flexor tendon lengthening for advanced metacarpophalangeal flexion contracture in rheumatoid hands	
Al-Ahaideb ²⁰	2008	NA	KSU, Riyadh		Review article	Septic arthritis in patients with RA	
Javed et al ³⁴	2013	NA	KSU, Riyadh		Review article	Cytokine profile in the gingival crevicular fluid of RA patients with chronic periodontitis	
Almoallim et al ²⁷	2012	NA	Umm Alqura University, Makkah		Review article	Anti-TNF- α induced SLE	
Bissar et al ²⁹	2013	NA	KFSH&RC, Jeddah		Review article	Perioperative management of patients with rheumatic diseases	
RA - rheumatoid arthritis, NA - not applicable, RF - rheumatoid factor, TNF - tumor necrosis factor, SLE - systemic lupus erythematosus, BMD, bone mass density, SA - Saudi Arabia, DMARDs - disease-modifying anti-rheumatic agents, KSU - King Saud University, KFSH&RC - King Faisal Specialist Hospital & Research Center, KKUH - King Khalid University Hospital, KAUH - King Abdulaziz University Hospital							

Table 3 - Prevalence of extra-articular manifestations of rheumatoid arthritis among Saudi patients.¹⁸

Extra-articular manifestations among Saudi patients	%	Comments
Anemia (iron deficiency anemia)	61	Most common
Thrombocytosis	16	-
Interstitial lung disease	10	-
Kidney amyloidosis	6	Frequently present late in the disease and related to worse outcomes, including mortality, only a small proportion of the patients (20%) had a routine evaluation of their kidney function, which represents a limitation
Rheumatoid nodules	30	Rheumatoid nodules are reported in 30% of patients, but only 3% was reported, due to the possibility of an under-reporting
<i>Other classical features</i>		
Secondary Sjögren syndrome	3	Least common
Felty syndrome	2	Least common
Neuropathy	1	Least common
Mortality rate	16	The overall mortality rate was observed to be high (16%), with the following predictors: respiratory system involvement, age >50 years, kidney amyloidosis, comparing males with females, gender had a little effect on the disease pattern, severity, or the presence of ExRA, and mortality

RA - rheumatoid arthritis,
ExRA - extra-articular manifestations in rheumatoid arthritis

while the Tfc1 homozygous phenotype was found to protect against the onset of RA, Tfc2 was linked to an increased risk of cellular damage.⁴⁶

Finally, 2 additional laboratory studies found that serum levels of vitamin D in RA patients were similar to those of healthy control subjects, whereas lower levels were detected in patients who responded poorly to treatment and were not in disease remission.^{5,49} Thus, although more research is needed, these laboratory-related findings have yielded important insight into the differences that exist between RA patients.

Radiological studies in rheumatoid arthritis patients.

There were 4 articles focusing on the radiological manifestations of RA patients in SA (Table 2), including a 7-month prospective study among 57 RA patients from King Abdul-Aziz University Hospital. This study reported that RA patients from the Western region of SA had a higher rate of radiological changes than those from the Central region, but a lower rate than those from industrialized countries. Notably, the hands and the feet were found to be equally involved.

Moreover, no significant associations were observed between radiological findings and RF or smoking history.²² Also, a 4-month study conducted at King Khalid University Hospital revealed similar results with regard to radiographic changes in the hands and feet, demonstrating that Saudi RA patients were less severe than those reported in the West. Moreover, a differential radiological pattern was observed, with lower effects in the feet of RA patients in SA.⁵⁰ Furthermore, a study conducted at AlNoor Specialist Hospital (Makkah) examined bone mineral density (BMD) in female RA patients, observing a significant decrease in BMD in RA patients compared to healthy controls, which was suggested to stem from impaired functional activity, increased disease activity, and long-term use of steroids.¹⁹ Finally, a study assessing radiographic changes in the cervical spine of RA patients concluded that they were common in RA patients, particularly subluxation in the upper cervical spine. However, these changes were somewhat less prevalent than reported, and non-significantly correlated with disease duration, female sex, and RF.⁵¹

Studies on rheumatoid arthritis management. We did not identify any randomized controlled trials on the management of RA in SA. Nevertheless, one study that compared 112 RA patients receiving anti-TNF- α therapy to 112 RA patients treated with traditional DMARDs found no significant difference with regard to side effects.⁵² Moreover, a retrospective study involving 116 RA patients described the presence of methotrexate-related side effects.²¹ Finally, financial issues were found to be the major factor interfering with compliance related to anti-TNF- α therapy in a study of 36 RA patients at Dr. Soliman Fakeeh Hospital in Jeddah.⁵³

Patient support programs. One national patient support program exists in SA, which was developed and implemented by AbbVie Biopharmaceuticals. The general objective of the program is to improve the quality of care for patients with arthritis, with a particular emphasis on those with RA. It supplies trained ultrasonographers to large rheumatology clinics in SA based on the requests of those clinics. These highly skilled individuals, some of them with medical degrees, provide ultrasonographic findings obtained from RA patients to treating rheumatologists (with the consent of both rheumatologists and patients). In addition, they contribute additional information, including Disease Activity Score in 28 Joints (DAS-28) and Health Assessment Questionnaire (HAQ) scores.

Patient counseling regarding the use of biological agents represents another aspect of the support program that is helpful in busy rheumatology clinics. This support team has participated in various studies on arthritis⁵⁴ and RA.²⁵

Discussion. This review highlights the current status of RA in SA. There have been great initiatives from various researchers and centers in SA to conduct RA studies. However, our analysis revealed that the majority of findings reported in the literature resulted from descriptive investigations, representing only one or a few centers rather than the national experience. Thus, these studies may not provide an accurate picture of the present state of RA management in SA. We found that biological therapies were introduced early in SA for almost all practicing rheumatologists in both government and private sectors. Moreover, there are no national guidelines on the proper management of RA based on local needs and regulations. In addition, although efforts have been made to establish data registry programs for RA, to date they have not been successful. Nevertheless, improvements in RA care seem imminent, as the number of rheumatologists is increasing in SA. Indeed, the Saudi Commission for Health Specialists has even established a local training program in rheumatology.

Overall, our analysis has revealed that promoting future collaboration between researchers from different centers is essential for increasing the number of patients enrolled in studies and improving the validity of results. In addition, collaborative investigations, which are not limited to one or a few centers, should result in longer follow-up periods and the use of more stringent methodologies. Furthermore, there is a fundamental need to establish a national data registry in SA to unify data from different researchers, which can improve the power and reliability of analyses regarding RA.

Currently, epidemiological results found in the literature regarding RA in SA are suboptimal. In fact, the exact prevalence of RA in the Saudi population remains uncertain. Indeed, the only study to examine the rate of RA in SA was published in 1998, involving a single Saudi region, small sample size, and simple methodology. Therefore, conducting a nation wide study on the prevalence of RA in SA is fundamentally important for developing effective management strategies for disease control.

Over the last decade, several investigations have highlighted the value of ultrasound technology for both clinical and research purposes in rheumatology. Ultrasound is a non-invasive, inexpensive, and non-ionizing radiation imaging technique that provides quick

and useful information for the management of RA.⁴ Access to musculoskeletal ultrasonography (MSKUS) findings by treating rheumatologists within clinics in SA has improved the care of RA patients. Indeed, based on musculoskeletal (MSK) examination alone, it can be difficult to distinguish whether palpable fullness, warmth over a joint, or tenderness on palpation is due to subcutaneous edema, tenosynovitis, paratenonitis [inflamed tissue adjacent to tendons without sheath,⁵⁵ joint effusion, or synovial proliferation⁵⁶]. In this regard, MSKUS was demonstrated to be more sensitive than MSK examination for the detection of joint swelling^{54,57-60} and better than conventional radiography for identifying erosions.^{61,62} This increased sensitivity of ultrasound has been shown to result in diagnostic benefit for patients with early synovitis.^{56,62} Moreover, MSKUS has been employed in the differential diagnosis of early RA.⁵⁶ In this regard, there are multiple ultrasonographic features that can be used to distinguish different diseases in early inflammatory arthritic disorders. These characteristics have previously been reviewed in detail.⁵⁶

Since MSKUS is widely used in rheumatology clinics in SA, we believe that it is time to conduct a national study comparing ultrasonographic findings to other outcome measures in RA. In fact, concern has been raised by several studies concerning the validity of the different disease activity measures currently in use. It is true that there is no single gold standard that is applicable for rheumatic disease assessment for all individual patients in clinical trials, clinical research, and clinical care.⁶³ A principal concern is that disease activity measures reflect the sum of several variables rather than a single objective variable, like blood pressure for patients with hypertension or glycated hemoglobin for diabetic patients. Moreover, some of these measures depend on self-reporting by patients, which can be a significant source of bias. Additionally, measures that depend on laboratory values, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), may not necessarily be specific for RA. There is also a major concern regarding the reliability and validity of joint assessment methods, involving the measurement of swollen and tender joint counts by rheumatologists. However, the ability to implement improved outcome measures is limited by practicality, motivation, and resources. Nevertheless, we propose that SA has the capability to incorporate MSKUS findings into busy rheumatology clinics in order to allow for comparative study of these various outcome measures.

Recent treatment recommendations for RA have advocated early introduction of DMARD therapy to

preserve joint function, maintain optimal quality of life, and minimize RA-associated comorbid conditions.^{64,65} In order to achieve these goals a new initiative, called “Treat to Target”,⁶⁶ was implemented for RA patients in SA. This plan aimed to treat RA patients to the state of remission or low disease activity. However, due to the significant impact of RA on the work ability, it was later recommended that the focus of treatment goals should shift from “Treat to Target” to “Treat to Work”.²⁸ This suggestion resulted from findings obtained from a study examining work ability among RA patients with an emphasis on housewives.²⁵ Thus, it is believed that work ability should also be considered as a valid outcome measure. Therefore, routine use of both MSKUS and work ability as outcome measures in RA could improve the ability to quickly and efficiently achieve treatment targets.

It is known that RA imposes a significant burden on patients, caregivers, employers, and the government.^{67,68} In fact, work disability often arises early in the course of the disease. According to several prospective studies, 20-35% of individuals ceased working within 2-3 years of disease onset.⁶⁹⁻⁷¹ After 5-10 years, the reported work disability rates are approximately 40%.^{70,72} In this respect, aggressive therapy has been shown to help preserve the work ability of RA patients. In a study of Klimes et al,⁷³ it was reported that patients on biological therapy displayed less reduction in their daily activities (39.8%) compared to patients on DMARDs (50.5%), reflecting approximately 53.6% higher productivity costs related to patients on DMARDs. Moreover, it was recently observed in a cross-sectional study of RA patients in SA that 55% of RA patients suffered from a greater than 50% drop in their work quantity, and 65.8% described a more than 50% effect on their work ability.²⁵ Mau et al⁷⁴ found that the fastest decline in employment rate among RA patients could be observed within the first 3 years of disease onset, with the 3-year employment rate reduced to 73±5%. Puolakka et al⁷⁵ supported this finding, concluding that prompt remission translated into the maintenance of work capacity. Taken together, these results reflect the importance of early and aggressive management of RA for preserving work ability.

As outlined in the literature,⁷⁶ there are several important limitations to identifying promising genetic factors that can predict responses in RA. Indeed, a major challenge in human genetics is to devise a systematic strategy to integrate disease-associated variants with diverse genomic and biological data sets in order to provide insight into disease pathogenesis and/or guide drug discovery for complex traits such

as RA.⁷⁷ Nevertheless, researchers have worked to evaluate approximately 10 million single-nucleotide polymorphisms at the genome-wide level in RA patients, discovering 42 novel RA risk loci, which brings the current total to 101 significant loci.⁷⁷ These analyses have shed light on fundamental genes, pathways, and cell types that contribute to RA pathogenesis and have provided empirical evidence that the study of genetics in RA patients can provide important information related to drug discovery. In this respect, it is hoped that such genetic studies can also help predict RA predisposition as well as therapeutic responses for patients in SA. So far, laboratory studies have already begun to focus on genetic predisposition to RA⁴³ and the association of RA with specific HLA-DR antigens⁵ in the Saudi population. As discussed, these findings also have the potential to contribute to the development of specialized drugs for individualized therapy for RA patients in SA.

Regarding the management of RA in SA, recent efforts have been made to identify limitations in RA patient care. In fact, there are reports on the status of MSK examination skills and the education of physicians in SA.^{54,78,79} Among 296 internal medicine residents in SA, the majority considered themselves incompetent in performing MSK examinations (published in abstract form EULAR 2012).⁷⁸ Also, MSK procedures currently lack standardization.^{54,80} In this regard, there has been limited progress in defining and validating simple bedside skills that can aid in the diagnosis of arthritis.⁵⁴ Furthermore, in general, there have been many international reports addressing the perceived difficulties and inadequate training with regard to performing MSK examination among clinicians and medical students.⁸⁰⁻⁹¹ Although several factors have been suggested to contribute to poor MSK examination skills,⁹²⁻⁹⁶ inadequate training represents an unacceptable explanation considering that physical examination is the most common diagnostic test used by doctors and continues to be an essential tool in modern practice.⁹⁷ However, despite this body of evidence, there has been very little intervention in SA to address this concern. Thus, dedicated programs for undergraduate and postgraduate education are needed to enhance the competency of rheumatologists. Indeed, improvements in training have the potential to increase the rate of early diagnosis, thereby promoting early treatment of RA. Notably, this simple correlation may not have been previously appreciated among educational leaders in SA.

In addition to programs aimed at enhancing the training of rheumatologists, patient-centered education programs are also essential. In this regard, establishing

and implementing initiatives to educate patients about their disease and encourage therapeutic maintenance among patients can complement the improvements made in clinical care within SA. Indeed, these programs are likely to dramatically improve the efficacy of existing drug therapies since recent analysis of the literature has suggested that medication adherence in patients with RA is low, varying from 30-80%.⁹⁸ In this regard, investigations are needed to specifically assess patient adherence to treatment in SA, including study of the factors contributing to inconsistent treatment as well as analysis of the effect of programs that might promote improved adherence. Indeed, it was already suggested that financial issues represented a major factor interfering with compliance related to anti-TNF-alpha therapy.⁵³ Thus, addressing such issues related to adherence could enhance RA care in SA. For this reason, future discussion and action among rheumatologists regarding patient adherence may be fundamental.

In conclusions, taken together, our thorough analysis of the literature not only highlights the status of current RA management in SA, but also has the potential to contribute to the development of future directives for improving RA care in SA. In this regard, we have identified several topics in RA research that currently require further investigation, including the benefit of ultrasound technology, the genetics of RA, and current RA patient management trends. In addition, evolution of both clinician and patient education programs is fundamental for improving the care of RA patients in SA. Collectively, information obtained from studies on RA in SA can contribute to solving the many obstacles in RA management, at both the national and international levels.

Acknowledgment. *This work was supervised and supported by the Alzaidi Chair of Research in Rheumatic Diseases, Umm Alqura University, Makkah, Kingdom of Saudi Arabia.*

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