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ANALYSIS

Serological Association with Extra-articular conditions in Saudi Rheumatoid Arthritis Patients

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ABSTRACT

Objectives: To assess the extra-articular manifestations (EAMs) in Saudi rheumatoid arthritis (RA) patients, and their association with serological markers [rheumatoid factor (RF) and anti-Cyclic Citrullinated Peptide (Anti-CCP)].

Methods: Retrospectively**,** we studied 205 Saudi RA patients at DR Dhia private center (Jeddah, SA) over three years (2/2011-2/2014). Positivity of RF and of anti-CCP, demographic and clinical features were recorded. Disease activity was scored for 28 joints (DAS28).

Results: Prevalence of EAMs was 33%, and was higher in male (45%) than female (32%). EAMs included: Hypertension(HTN) [25 patient (12.5%)], Diabetes Melittus (DM) (22(11%)], Hypothyroidism [15(7.3%)],nodule [8(4%)], low WBC [5(2.4%)], ANA positivity [4(2%)], Gout [3(1.5%)], *Sjögren's syndrome [2(1%)], and one case (0.5%) of each of lung affect, kidney atrophy***,** Sickle cell, high CK, high creatinin and epilepsy. EAMs showed no association with the serological markers, neither with RF nor with anti-CCP. Only hypertension showed significant correlation (P= 0.017) with DAS28.

Conclusion: The low levels of nodules and EAMs in Saudi RA patients are different from European and North American populations. They are similar concerning the higher levels of EAMs in males than females. Only hypertension had correlation with disease activity. EAMs showed no association with the serological markers. Presence of discrepancies in rats of EAMs between centers in Saudi Arabia.

Key-words: Saudi Arabia; Extra-articular ; EAMs; Anti-CCP antibodies; Rheumatoid arthritis; Rheumatoid factor; Association.

Abbreviations: DM-Diabetes Melittus; WBC-White blood cell; ANA-Anti-nuclear antibody; HTN-Hypertension; EAMs-Eextra-articular manifestations; RF-Rheumatoid arthritis; Anti-CCP-anti-Cyclic Citrullinated Peptide; *CRP-C-reactive protein*; ESR-Erythrocyte Sedimentation Rate; RF-Rheumatoid factor; DAS28-Disease Activity Score in 28 Joints.

1. INTRODUCTION

Rheumatoid Arthritis is an autoimmune disease with different autoantibodies (Goodyear CS et al. 2008). It is a systemic inflammatory disease that is manifests in multiple joints of the body, affecting primarily the synovial membrane that lining of the joints, leading to erosions and sometimes joint deformity, but other organs can also be affected (CDC 2014).The prevalence of RA is estimated to range from 0.5-1.0% in the general population (CDC 2014); its incidence is higher in female (CDC 2014); with a higher lifetime risk (3.6%) compared to male (1.7%) (Crowson CS et al. 2011). The prevalence of RA in the US was estimated to be 0.6% among the adults (aged ≥ 18) (Helmick CG et al. 2008, Sacks JJ et al. 2010). The prevalence is higher among women (0.98%) than among men (o.41%) (Myasoedova E et al. 2010); with a higher lifetime risk e (4%) than male (3%) among the Rochester Minnesota Mayo Clinic Population (Crowson CS et al. 2011).

Prior to the 2010, the 1987 criteria of the American College of Rheumatology (ACR) were the standard for diagnosis and study of RA (Arnett FC et al. 1988). Since 2010 RA is diagnosed and classified according to the 2010 American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for rheumatoid arthritis (Aletaha D et al. 2010, Neogi T et al. 2010). The strongest associations have been found between RA and the HLA- DRB1*0401 and DRB1*0404 alleles (Scott DL et al. 2010); and the strongest candidate gene has been found to be the "*PTPN22 gen"*, which is linked to several autoimmune condition (Mielants H and Van den Bosch F 2009).

Rheumatoid arthritis is described as systemic, in which inflammation can affect extra-articular tissues/organs in addition to synovial joints (articular) and non-articular muscular structures (tendons, ligaments, and fascia) (Mielants H and Van den Bosch F 2009). In contrast to articular, extra-articular manifestations (EAMs) were considered as diseases and symptoms not directly related to the locomotor system (Bongartz T et al. 2007, Mielants H and Van den Bosch F 2009, Cojocaru M et al. 201010, Aletaha D et al. 2010, Sahatciu-Meka V et al. 2010). The four most common EAMs were cardiovascular disease (CVD), in particular ischemic heart disease (Symmons DP et al. 2011), infections, mostly tuberculosis, that may be responsible for ¼ of deaths among RA patients (Boonen A, and Severens JL 2011), mental conditions (Odegard S et al. 2007) and malignancies, such as leukemia and multiple myeloma that has been reported among patients (MikulsTR et al. 2001). In both early and established rheumatoid arthritis, almost 40% of the patients develop EAMs (Cimmino MA et al. 2000, Hochberg MC et al. 2008). Several predictors for the development of EAMs had been suggested (Gabriel SE et al. 2003), RA patients with high titers of RF are most likely to have EAMs (Kinoshita M et al. 1990, Hochberg MC et al. 2008).Other autoantibodies (as ANA and anti-CCP), male sex, shared MHC genotypes and smoking have been also described as predictors for the development of EAMs (Turesson C et al. 2004, Gossec L et al. 2005, Roudier J 2006, Calgüneri M et al. 2006).

In Rheumatoid arthritis (RA), although females are affected two to three times more than males (Myasoedova E et al. 2010, CDC 2014), never the less EAMs of RA have been described in males more than in females (Cojocaru M et al. 2010). In RA, there is a systemic inflammatory process which lead to high mortality rate (Crostein BN 2007), the major factors for its prediction are the presence of co-existing heart and lung disease, malignancy and dementia (Lindqvist E et al. 2002). Other factors for prediction mortality included active disease (despite medical treatment) and presence of EAMs (Gabriel SE et al. 2003, Carmona L et al. 2003).

Occurrence of EAMs is usually accompanied with severe active disease and increased mortality (Turesson C et al. 2002, Gabriel SE et al. 2003, Carmona L et al. 2003, Young A and Koduri G 2013, Turesson C 2013). Thus, EAMs are serious, that should be aggressively treated and monitored (Young A and Koduri G 2013). The improved overall control of disease activity, has led to less occurance of some EAMs, in particular vasculitis, than previously reported (Turesson C 2013).

However EAMs remain a major diagnostic and therapeutic challenge in some RA patients (Young A and Koduri G 2013). Nevertheless, we find rare reports from Saudi Arabia concerning EAMs, and none concerning EAMs association with serological markers; the aims of the current study.

Objectives

In this study, our aim was to assess the extra-articular conditions in Saudi rheumatoid arthritis (RA) patients, and to evaluate their association with serological markers [rheumatoid factor (RF) and anti-Cyclic Citrullinated Peptide (Anti-CCP)].

2. MATERIALS AND METHODS

This study was conducted in the faculty of Medicine at King AbdulAziz University (KAU), Jeddah, Saudi Arabia; with a written ethical approval, obtained from the Unit of Biomedical Ethics, at the faculty of Medicine. Retrospectively, we studied 205 Saudi RA patients at DR Dhia private center (Jeddah, SA) over a three years period (2/2011-2/2014). Over the three years, demographic and clinical data were collected, at the first visit, from RA patients attended to Dr Dhiya Centre for Rheumatism & Physiotherapy and Acupuncture, Jeddah, Saudi Arabia. This study included all patients that met the American College of Rheumatology (ACR) 1978 classification criteria for RA (Arnett FC et al. 1988), and excluded the non Saudi patients. The recorded data included:1-Demographic data including age, sex and ethnicity; 2- clinical data including disease duration (dd) by years, physician's global assessment (PGA) as 100 mm on scale, a 28 joint count for tenderness (TJ) and for swilling (SJ) 3- laboratory data including erythrocyte sedimentation rate ESR (mm/h), CRP, RF, hemoglobin (Hb) and platelets (Plt). Anti-CCP was measured by Electrochemiluminescence (Elecsys machine from Roche), which is a CE approved second generation assay for anti CCP (anti-CCP2), and was considered positive when the concentration was ≥ 3 IU/ml according to the manufacturer instructions. IgM rheumatoid factor measured by Latex agglutination. Disease activity was assessed using the 28 joint disease activity score (DAS28) (Prevoo ML et al. 1995) which was calculated according to TJ, SJ, ESR and PGA. The current study focuses on extra-articular manifestations EAMs which were considered as diseases and

symptoms not directly related to the locomotor system, (Bongartz T et al. 2007, Mielants H and Van den Bosch F 2009, Cojocaru M et al. 2010, Sahatciu-Meka V et al. 2010) including not only the classic EAMs, but also any non-articular complications of RA (Cojocaru M et al. 2010). *Thus the EAMs in this paper* included the following: Hypertension(HTN), which was diagnosed according to the World Health Organization-International Society of Hypertension (WHO-ISH) guidelines as a diastolic blood pressure above 90 mmHg (1993 guidelines), or when the patient is on antihypertensive agent as known case on treatment; Diabetes Mellitus (DM) which was diagnosed according to the WHO definition increased fasting plasma glucose above 125 mg/dl (7.0 mmol/l) (Alberti KG and Zimmet PZ 1998), or as known case on treatment; Hypothyroidism as a low level of thyroxine and high level of TSH in blood, or as known case on treatment; Nodules that were detected as firm lumps, that appear subcutaneously as single or clustered that were found mainly in elbows and hands; low WBCs when WBCs count was less than 4000 per microliter (mcL); ANA positivity when ANA titre was more than1/80, Gout as known case of high hyperurecimia more than 9 mg/dl with gouty attacks more than 3/year; *Sjögren's syndrome* as indicated by RA plus dry mouth and dry eyes; **L***ung affect* as lung fibrosis; *kidney atrophy ;* Sickle cell as those who had sickle cell disease; high CK as increased more than double normal value, high creatinin as increased more than 50% of normal value .

The collected data were part of retrospective review, thus informed consent was not obtained; however written ethical approval was obtained.

Entrez-PubMed, Advanced search - PubMed - NCBI and Saudi Digital Library (SDL) were used for checking references and prior related research:

-Entrez-PubMed "http://www.ncbi.nlm.nih.gov/entrez/query/static/citmatch.html"
-Advanced search - PubMed - NCBI "http://www.ncbi.nlm.nih.gov/pubmed/advanced"
-Saudi Digital Library (SDL) "http://www.sdl.edu.sa/SDLPortal/AR/Publishers.aspx"

Statistical Analysis

The data were analyzed using statistical package for social science (SPSS Inc), Version 14. Chicago. The results were illustrated in tabulated form showing comparisons and frequencies of variables. Results were considered significant if the p-value was less than 0.05. The association between EAMs and presence of the serological markers (RF and anti-CCP) was analyzed using the Chi-squared test and odds ratio with SPSS version 14. The predictive value disease ac ivity (DAS28) for the various EAMs was analyzed using the multivariate Linear Regression Analysis (Stepwise Model); with a confidence interval 95%.

3. RESULTS

Among the 205 RA patients, extra-articular manifestations (EAMs) were found in 68 patients (33%). Divided as 45 patients (23%) with one condition, 21 patients (9%) with two conditions and two patients (1%) with three conditions (table 1). The recorded extra-articular conditions (Table 1) included: Hypertension(HTN) [25 patient (12.5%)], Diabetes Melittus (DM) (22(11%)] ,Hypothyroidism [15(7.3%)],nodule [8(4%)], low WBC [5(2.4%)],ANA positivity[4(2%)], Gout[3(1.5%)], *Sjögren's syndrome [2(1%)], and one case (0.5%) of each of lung affect, kidney atrophy***,** Sickle cell, high CK, high creatinin and epilepsy.

In the total cohort, 81/205 (40%) patients had early RA and 124 (60%) had established RA. As illustrated in Table 2, the 68 patients with extra-articular conditions were divided between early and established RA as 24 (34%) and 44 (66%) respectively, the two patients with EAMs and erosion were divided between early and established RA as Nil (0.0%) and 2 (100%) respectively. The prevalence of extra-articular conditions were slightly higher in established RA than early RA [44/124 (35.5%) and 24/81(30 %) respectively] with no significant difference (P=0.06) (Table 2).

In the total cohort, 185/205 (90%) were females and 20/205 (10%) were male (table 3). As illustrated in Table 3; within the females 59 (31.4%) had EAMs (one EAM with erosion). Within the males 9 had EAMs (one EAM with erosion) (Table 3). Presence of EAMs was higher within male (45 % within male population) than female (32% within female population), with no difference (P>0.05) (Table 3).

Table 4 illustrates prevalence and association of RF in patients with different extra-articular manifestations (EAMs). The 68 patients with EAMs were divided as 20 (30%) with RF and 48 (70%) without RF, with no association between presence of EAMs (total or individually) and RF positivity (Table 4).

Table 5 shows the same illustrations as Table 4 but for anti-CCP positivity instead of R. No association was observed between presence of EAMs (total or individually) and anti-CCP positivity (Table 5). In EAMs positive group, anti-CCP positivity showed higher prevalence 28/68 (41%) than RF Positivity 20/68 (30%) (Table 4 &5) Only HTN, but none of the rest EMAs, showed significant correlation with disease activity as judged by DAS28 (Table 6).

Table 1

Frequency of extra-articular manifestations (EAMs), as alone or combined; in cohort (205)

Condition	Total	Alone	Combined	EAM
Presence One condition Two condition Three condition	68/205(33%) 45 (23%) 21 (9%) 02 (1%)	45 (30%)	23(10%)	
Hypertension(HTN	25/205(12.5%)	9 (4.5%)	16(8%)	EAM
Diabetus Melittus (DM)	22/205(11%)	8(4%)	14 (7%)	EAM
Hypothyroidism	15/205(7.3%)	10 (5.5%)	5 (7%)	EAM
Nodules	8/205(4%)	7 (4.5%)	1 (0.5%)	EAM
Low WBC	5/205(2.4%)	3 (1.5%)	2 (1%)	EAM
ANA positive	4/205(2%)	3 (1,5%)	1 (0.5%)	EAM
Gout	3/205(1.5%)	2 (1%)	1 (0.5%)	EAM
Sjögren's syndrome	2/205(1%)	NIL	2/205(1%)	EAM
Lung effect	1/205(0.5%)	NIL	1 (0.5%)	EAM
Kidney atrophy	1/205(0.5%)	NIL	1 (0.5%)	EAM
Other* *,Sickle cell, high CK, high creatinin, epilepsy	each=1 /205(0.5%) [All=4/205(2.5%)]	3(2.55%)	1	EAM
HTN and DM	11/205(5.4%)	NIL	11/205(5.4%)	EAMs
HTN and Hypothyroid	2/205(1%)	NIL	2/205(1%)	EAMs
HTN and Kidney Atrophy(KA)	1/205(0.5%)	NIL	1/205(0.5%)	EAMs
HTN and gout and high creat	1/205(0.5%)	NIL	1/205(0.5%)	EAMs
HTN and DM and Nodule	1/205(0.5%)	NIL	1/205(0.5%)	EAMs
DM and Hypothyroid	1/205(0.5%)	NIL	1/205(0.5%)	EAMs
Erosion and DM	1/205(0.5%)	NIL	1/205(0.5%)	EAM with erosion
Erosion and Hypothyroid	1/205(0.5%)	NIL	1/205(0.5%)	EAM with erosion
Sjögren's syndrome and Low WBC	*2/205(1%)*	NIL	2/205(0.5%)	EAMs
ANA and Hypothyroid	1/205(0.5%)	NIL	1/205(0.5%)	EAMs
Total		60	23	

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Table 2

Prevalence of of extra-articular manifestations (EAMs) in early and established RA

		EAM	EAM with erosion	Presenc of EAMs	Cohort 205
Early RA*	Count	24 30%	0 00%	24 30%	81 100%
	% within early RA	100.0%	.0%	(100.0%)	
	% within extra articular	36.4%	.0%	34%	40%
Established RA **	Count	42	2	44 35.5%	124 100%
	% within early RA	95.5%	4.5%	(100.0%)	
	% within extra articular	63.6%	100.0%	66%	60%
Total	Count	66	2	68	205
	% within early RA	99.0%	1.0%	100%	
	% within extra articular	100.0%	100.0%	100.0%	100.0%

* *Early RA:* When the disease duration (dd) was equal or less than one year.

** *Established RA:* When the disease duration (dd) was more than one year.

Table 3

Presence of extra-aricular manifestations (EAMs) according to gender

		EAMs	EAM with erosion	Presence of EAMs	Total
Female	Count	58	1	59	185
	% within sex	98.0%	2.0%	100.0% (32.0%)	(100.0%)
	% within extra-articular	87.9%	50.0%	90.2%	90.2%
Male	Count	8	1	9	20
	% within sex	89.0%	11.0%	100.0% (45.0%)	(100.0%)
	% within extra-articular	12.1%	50.0%	9.8%	9.8%
Total	Count	66	2	68	205
	% within sex	97.0%	3.0%	100.0%	100.0%
	% within extra-articular	100.0%	100%	100.0%	100.0%

Table 4

Association of RF positivity with different extra-articular manifestations (EAMs)

condition	Total	RF positivity		Association				
		RF positive	RF negative	X^2	DF	Odds ratio (OR)	confidence interval (CI)	P=
Total **EAMs***	**68**	**20 (30%)**	**48 (70%)**	**2.2**	**1**	**0.6; 95%**	**0.3-1.0**	**0.09**
DM with Erosion	1	1	NIL	1.7	1	1**; 95%**	**0.98-1**	**0.2**

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Hypothyroid with Erosion	1	1	NIL	1.7	1	1; 95%	0.98-1	0.2
Different EAMs** as shown in Table 1	As single or combined as shown in Table 1			**All showed no significant association as meanX^2=0.85 (SD=0.7); DF=1, odds ration (OR)<1.5; 95% and P>0.05**				

*Total EAMs whether alone, combined or EAM with erosion
**Different EAMs were tested separately, whether single or combined as shown in Table 1

Table 5
Association of anti- CCP positivity with different extra-articular manifestations (EAMs)

condition	Total	Anti-CCP positivity		Assoiation				
		positive	negative	X^2	DF	Odds ratio (OR)	confidence interval (CI)	P=
Total **EAMs***	**68**	**28 (41%)**	**40 (59%)**	**0.7**	**1**	**0.77; 95%**	**0.4-1.4**	**0.3**
DM with Erosion	1	1	NIL	1.2	1	1; 95%	0.99-1	0.2
Hypothyroid with Erosion	1	1	NIL	1.2	1	1; 95%	0.99-1	0.2
Different EAMs** as shown in Table 1	As single or combined, as shown in Table 1			**All showed no significant association as meanX^2=0.67 (SD=0.47); DF=1, odds ration (OR)<1.5; 95% and P>0.05**				

*Total **EAMs** whether alone, combined or EAM with erosion
**Different EAMs were tested separately, whether single or combined as shown in Table 1

Table 6
Linear Regression Analysis (Stepwise Model) of different factors (EMAs) related to DAS28

Model	Unstandardized Coefficients		Sig.
	B	Std. Error	
HTN	.416	.174	.017

R2= 2.8%
Excluded Variables: Diabetes Melittus (DM), hypothyroidism, nodule , low WBC, ANA positivity, Gout, *Sjögren's syndrome, lung affect, kidney atrophy*, Sickle cell, high CK, high creatinin, epilepsy, DM with HTN, HTN with *kidney atrophy*, DM with HTN and nodule, HTN with gout and high creatinin, erosion with DM, Hypothyroidism with erosion, Hypothyroidism with ANA, Hypothyroidism with HTN, Hypothyroidism with DM, *Sjögren's syndrome* with low WBC.

4. DISCUSSION

In RA, commonly involved are the small joints of hands and feet, but larger joints like the shoulder and knee can also be involved (Colledge NR et al. 2010).This paper considered the extra-articular manifestations (EAMs) of RA. EAMs were considered as diseases and symptoms not directly related to the locomotor system (Gabriel SE et al. 2003, Hochberg MC et al. 2008, Sahatciu-Meka V et al. 2010), only the classic EAMs, but also any non-articular complications of RA (Cojocaru M et al. 2010).The RA patients, in the current study were all Saudi RA patients from a private centre for Rhumatisme & Physiotherapy and Acupuncture, in Jeddah, S.A. According to our literature search concerning comorbidity in RA and extra-articular RA in Saudi Arabia, one study has evaluated the percentage of EAMs in the western region of Saudi Arabia (Al-Ghamdi A

and Attar SM 2009). They studied RA patients from a university hospital in Jeddah, S.A, including 60% Saudis. Another study, evaluated comorbidities and their relation with drugs prescription (Al-Bishri J et al. 2013). In the current study, the rates of EAMs was 33%. This is lower than that reported in other populations from Saudi Arabia (66%) (38Al-Ghamdi A and Attar SM 2009, Al-Bishri J et al. 2013), from Britain (68%) and North America (40%) (Hochberg MC et al. 2008, Young A and Koduri G 2013, Turesson C et al. 2008). However it is similar to Turkish RA population (33.3%) (Filiz E et al. 2012), and higher than 21.5% that has been recently reported by Richman et al. (Richman NC et al. 2013). The discrepancy of EAMs rates in different populations has been reported (Cojocaru M et al. 2010). The absence of several extra-articular conditions in the current Saudi RA cohort makes it different. The two reports from Saudi Arabia (Al-Ghamdi A and Attar SM 2009, Al-Bishri J et al. 2013) (included Saudi and non-Saudi RA patients) reported several conditions that were not seen in the patients of the current study, including Iron deficiency anemia affecting 52%, Normochromic normocytic anemia affected 8%, Thrombocytosis (16%), enlarged lymph nodes (4%), leg ulcer (2%), Vasculitis (2%), Pericardial effusion (1%), Pericardial effusion and Felty syndrome (1%) and TB; malignancies were also absent in our study. In comparison with Alghamdi and Attar (Al-Ghamdi A and Attar SM 2009), the current study found lower Lungs involvements (0.5% / 7%), kidney involvements (0.5% / 6%) and Sjogren syndrome (1% / 2%) but almost similar in detecting leukopenia (5%). The detected rheumatoid nodules were almost the same (4% / 3%), these low levels of nodules in populations from Saudi Arabia are different from that was reported in other populations (30%) (Young A and Koduri G 2013). In the current study, Hypertension (HTN), Diabetes mellitus (DM) and hypothyroidism were the main EAMs conditions ,the frequency of which were 25/205 (12.5%), 22/205 (11%) and 15/205(7.3%) respectively; these rates were higher than 5% (for HT) , 4% (for DM) and nil (for hypothyroidism) which were reported by Alghamdi and Attar from Saudi Arabia (Al-Ghamdi A and Attar SM 2009); but lower than that reported by Al-Bishri J et al. (Al-Bishri J et al. 2013), which were 36% for HTN, 31% for DM and 9% for hypothyroidism indicating presence of discrepancies in rats of EAMs between centers in Saudi Arabia.

The mortality rate among the current Saudi patients was nil, compared to 15-29% in other populations (Turesson C et al. 1999, Carmona L et al. 2003, Sokka T 2008) and 16% in a RA patients from Saudi Arabia that included 60% Saudis (Al-Ghamdi AA 2009). Mortality in RA were described to be secondary to cardiovascular, lung diseases and malignancy (Lindqvist E et al. 2002); thus, the low level of affected lungs (0.5%) in the current study, together with absence of cardiac complaints and malignancies may explain the absence of mortality among this cohort. Another explanation for the absence of mortality in the current study could be the absence of infections [either in the form of sepsis or as tuberculosis (TB)]; these two infections were found to be predictors for mortality in RA patients from Saudi Arabia (Al-Ghamdi AA 2009); their rates were 12% and 7% respectively (Al-Ghamdi AA 2009). The reason for this discrepancies between our result and these rates could be attributed to the difference in the socioeconomic status and the activity of the disease which are also important factors for increased risk of premature mortality in RA patients (Kinoshita M et al. 1990, Carmona L et al. 2003, Roman et al. 2006), keeping in mind that the cohort of the current study were attending at private center, compared to hospitalized patients in governmental university teaching hospital which provides health care to a multinational population of mixed socioeconomic status (Al-Ghamdi AA 2009).

In the current study, among the 68 patients with total EAMs (including EAM alone, combined extracellular conditions and EAMs plus erosion), 30% were with RF and 40% with anti-CCP antibodies. These were lower than in other previous studies for RF (Prevoo ML et al. 1995, Al-Ghamdi A and Attar SM 2009). This lower level of RF in the current study goes well with the lower rate of EAMs, keeping in mind that patients with RA, who have high titers of rheumatoid factor are most likely to have EAMs, including cardiovascular, vasculitis, and pulmonary, digestive, neurologic, ocular, haematologic and cutaneous complications (Kinoshita M et al. 1990, Gabriel SE et al. 2003, Hochberg MC et al. 2008), Most of which were not found among the patients of the current study, or found at low rat such as rheumatoid nodules and lung involvement.

The current study found no association between presence of EAMs and the serological markers (RF and anti-CCP). The data are conflict regarding the association of anti-CCP with the presence of EAMs (Richman NC et al. 2013). However we are in concordance with the several results (DeRycke et al. 2004, Korkmaz C et al. 2006, Richman NC et al. 2013) who found no association between the presence of anti-CCP and the presence of EAMs. On the other hand, Richman NC et al. 2013, in contrast to our results, found strong association between the presences of serum RF with the development of EAMS.

In RA , although women are affected 2-3 times more than men, (Myasoedova E et al. 2010, CDC 2014), EAMs of RA are more common in males (Cojocaru M et al. 2010, Richman NC et al. 2013). With this in mind, we found similar results in the current study, as RA was higher in female (90%); while EAMs were higher within male than within females.

We found that only hypertension showed significant correlation (P=0.017) with disease activity as judged by DAS28. Similarly, Turkish RA patients (Filiz E et al. 2012), also showed no directly associated between disease activity and presence of EAMs that included pulmonary involvement (28.7%), rheumatoid nodules (14.7%), Sicca Syndrome (8%), peripheral neuropathy (2.7%), and atlantoaxial subluxation (0.7%), but not hupertension.

5. CONCLUSION

HTN, DM, and Hypothyroidism were the most common Extra-articular conditions. The low levels of nodules and extra-articular conditions were different from European and North American populations. We were similar to these populations concerning the higher levels of EAMs in males than females. Only hypertension showed significant correlation (P= 0.017) with disease activity as judged by DAS28. Extra-articular conditions showed no association with the serological markers (RF and anti-CCP). The prevalence of extra-articular conditions were slightly higher in established RA than early RA, with no significant difference (P=0.06). Finally, the mortality rate in the current study was nil. Our findings were compared with the previous studies from Saudi Arabia, namely Al-Ghamdi AA 2009, Al-Ghamdi A and Attar SM 2009 and Al-Bishri J et al. 2013.

DISCLOSURES

The work was not supported or funded by any funding agency or any drug company. Ethical approval was obtained before commencing the study. All authors have read and approve this manuscript. The authors declare no conflict of interests that exist.

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